# Australian guidelines for the clinical care of people with COVID-19

## Drug treatments not recommended outside of clinical trials

NATIONAL COVID-19 CLINICAL EVIDENCE TASKFORCE

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# Summary of recommendations

## 1. Drug treatments not recommended outside of clinical trials

**Info Box**

The Taskforce has reviewed high quality evidence for a number of therapeutics used to treat COVID-19 for which there is insufficient evidence to determine whether they are safe and/or effective. The Taskforce recommends that use of these treatments be limited to clinical trials with appropriate ethical approval.

This guideline is supplementary to the primary guideline, '***Australian guidelines for the clinical care of people with COVID-19***'. The primary guideline contains information specific to drug treatments that are recommended and not recommended for use, pregnant and breastfeeding patients, paediatric and adolescent patients, respiratory support and other supportive recommendations.

The primary guideline contains additional information specific to methods and processes, and information on how to read and interpret the various components of each recommendation can be found within the reading guide. Details regarding our member organisations, purpose, scope and NHMRC approval status can be found within the Introduction section.

## 2. All populations

### 2.1 Antiandrogens

#### 2.1.1 Dutasteride

**Only in research settings**

Do not use dutasteride for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Dutasteride should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use dutasteride to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.2 Antineoplastics

#### 2.2.1 Angiotensin 2 receptor agonist (C21)

**Only in research settings**

Do not use the angiotensin 2 receptor agonist C21 for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

C21 should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people

living with frailty and those receiving palliative care. Until further evidence is available, do not use C21 to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.2.2 Camostat mesilate

**Only in research settings**

Do not use camostat mesilate for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Camostat mesilate should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use camostat mesilate to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.2.3 Opaganib

**Only in research settings** New

Do not use opaganib for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use opaganib to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

## 2.3 Antiparasitic, antifungals and other anti-infective agents

### 2.3.1 Chloroquine

**Only in research settings**

Do not use chloroquine for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:

***Additional information***

Chloroquine should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use chloroquine to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.3.2 Doxycycline

**Only in research settings**

Do not use doxycycline for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Doxycycline should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in older people living with frailty and those receiving palliative care. Until further evidence is available, do not use doxycycline to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

Trials are not recommended in pregnant and breastfeeding patients, as doxycycline is contra-indicated in this group.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.3.3 Ivermectin plus doxycycline

**Only in research settings**

Do not use ivermectin plus doxycycline for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Ivermectin plus doxycycline should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use ivermectin plus doxycycline to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

### 2.3.4 Nitazoxanide

**Only in research settings**

Do not use nitazoxanide for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Nitazoxanide should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use nitazoxanide to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

## 2.4 Antihypertensives

### 2.4.1 Telmisartan

**Only in research settings**

Do not use telmisartan for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Telmisartan should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use telmisartan to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

## 2.5 Antithrombotic, antiplatelets and related therapies

### 2.5.1 Sulodexide

**Only in research settings**

Do not use sulodexide for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Sulodexide should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use sulodexide to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

## 2.6 Antivirals

### 2.6.1 Baloxavir marboxil

**Only in research settings**

Do not use baloxavir marboxil for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Baloxavir marboxil should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use baloxavir marboxil to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.6.2 Darunavir-cobicistat

**Only in research settings**

Do not use darunavir-cobicistat for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Darunavir-cobicistat should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use darunavir-cobicistat to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.6.3 Enisamium

**Only in research settings**

Do not use enisamium for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Enisamium should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use enisamium to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.6.4 Ensovibep

**Only in research settings** New

Do not use ensovibep for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use ensovibep to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.6.5 Sofosbuvir-daclatasvir

**Only in research settings**

Do not use sofosbuvir-daclatasvir for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Sofosbuvir-daclatasvir should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use sofosbuvir-daclatasvir to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.6.6 Triazavirin

**Only in research settings**

Do not use triazavirin for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Triazavirin should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use triazavirin for the treatment of COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.6.7 Umifenovir

**Only in research settings**

Do not use umifenovir for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Umifenovir should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use umifenovir for the treatment of COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

## 2.7 Human and blood derived products

### 2.7.1 Human umbilical cord mesenchymal stem cells

**Only in research settings**

Do not use human umbilical cord mesenchymal stem cells for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Human umbilical cord mesenchymal stem cells should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use human umbilical cord mesenchymal stem cells (hUC-MSCs) to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.7.2 Intravenous immunoglobulin

**Only in research settings**

Do not use immunoglobulin for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:

***Additional information***

Intravenous immunoglobulin should still be considered for other evidence-based indications in people who have COVID-19.

This recommendation does not apply to the use of immunoglobulin in children and adolescents when managing paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS), Kawasaki disease or toxic shock syndrome related to COVID-19 (see section for specific guidance). The Taskforce is currently developing recommendations for the management of these conditions in children and adolescents with COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use combination immunoglobulin plus methylprednisolone to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.7.3 Intravenous immunoglobulin plus methylprednisolone

**Only in research settings**

Do not use immunoglobulin plus methylprednisolone for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Intravenous immunoglobulin plus methylprednisolone should still be considered for other evidence-based indications in people who have COVID-19.

This recommendation does not apply to the use of immunoglobulin plus methylprednisolone in children and adolescents when managing paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS), Kawasaki disease or toxic shock syndrome related to COVID-19 (see section for specific guidance). The Taskforce is currently developing recommendations for the management of these conditions in children and adolescents with COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use combination immunoglobulin plus methylprednisolone to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

## 2.8 Immunomodulating drugs

### 2.8.1 Anakinra

**Only in research settings**

Do not use anakinra for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Anakinra should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people

living with frailty and those receiving palliative care. Until further evidence is available, do not use anakinra to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

### 2.8.2 CD24Fc

**Only in research settings**

Do not use CD24Fc for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use CD24Fc to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

### 2.8.3 Lenzilumab

**Only in research settings**

Do not use lenzilumab for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use lenzilumab for the treatment of COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.8.4 Ruxolitinib

**Only in research settings**

Do not use ruxolitinib for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Ruxolitinib should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use ruxolitinib to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.8.5 Tofacitinib

**Only in research settings**

Do not use tofacitinib for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Tofacitinib should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use tofacitinib for the treatment of COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

## 2.9 Interferons

### 2.9.1 Interferon beta-1a (inhaled)

**Only in research settings**

Do not use inhaled interferon beta-1a for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Inhaled interferon β-1a should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use inhaled interferon β-1a to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.9.2 Interferon beta-1b

**Only in research settings**

Do not use interferon beta-1b for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:

***Additional information***

Interferon β-1b should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use interferon β-1b to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.9.3 Interferon gamma

**Only in research settings**

Do not use interferon gamma for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Interferon gamma should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use interferon gamma to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.9.4 Interferon kappa plus trefoil factor 2 (IFN-κ plus TFF2)

**Only in research settings**

Do not use interferon kappa plus trefoil factor 2 for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Interferon kappa plus trefoil factor 2 (IFN-κ plus TFF2) should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use IFN-κ plus TFF2 to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.9.5 Peginterferon lambda

**Only in research settings**

Do not use peginterferon lambda for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Peginterferon lambda should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use peginterferon lambda to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

## 2.10 Other antibody related therapies

### 2.10.1 Bamlanivimab

**Only in research settings**

Do not use bamlanivimab for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use bamlanivimab to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.10.2 Bamlanivimab plus etesevimab

**Only in research settings**

Do not use bamlanivimab plus etesevimab for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Bamlanivimab plus etesevimab should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use bamlanivimab plus etesevimab to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.10.3 Bebtelovimab

**Only in research settings**

Do not use bebtelovimab for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use bebtelovimab to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a high priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

## 2.11 Other therapies

**Only in research settings** New

Do not use aprepitant for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Sabizabulin should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use sabizabulin to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.11.1 Almitrine

**Only in research settings** New

Do not use almitrine for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Almitrine should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use almitrine to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.11.2 Aprepitant

**Only in research settings**

Do not use aprepitant for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Aprepitant should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use aprepitant to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.11.3 Bromhexine hydrochloride

**Only in research settings**

Do not use bromhexine hydrochloride for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Bromhexine hydrochloride should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use bromhexine hydrochloride for the treatment of COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.11.4 Fluvoxamine

**Only in research settings**

Do not use fluvoxamine for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Fluvoxamine should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people

living with frailty and those receiving palliative care. Until further evidence is available, do not use fluvoxamine to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.11.5 Metformin

**Only in research settings**

Do not use metformin for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use metformin to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.11.6 Recombinant human granulocyte colony-stimulating factor (rhG-CSF)

**Only in research settings**

Do not use rhG-CSF for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Recombinant human granulocyte colony-stimulating factor should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use rhG-CSF to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.11.7 Sabizabulin

**Only in research settings** New

Do not use sabizabulin for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Sabizabulin should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use sabizabulin to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a moderate priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

## 2.12 Vitamins, supplements and cofactors

### 2.12.1 Combined metabolic activators (CMA)

**Only in research settings**

Do not use combined metabolic activators (CMA) for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Combined metabolic activators (CMA) should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use CMA to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.12.2 N-acetylcysteine

**Only in research settings**

Do not use N-acetylcysteine for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

N-acetylcysteine should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use N-acetylcysteine to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.12.3 Vitamin C

**Only in research settings**

Do not use vitamin C for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Vitamin C should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use vitamin C to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.12.4 Vitamin D analogues (calcifediol/cholecalciferol)

**Only in research settings**

Do not use vitamin D analogues for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Vitamin D analogues should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use vitamin D analogues to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.12.5 Zinc

**Only in research settings**

Do not use zinc for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Zinc should still be considered for other evidence-based indications in people who have COVID-19.

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use zinc to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### 2.13 Other drug treatments

## 3. Pregnant and breastfeeding women

### 3.1 Baricitinib for pregnant or breastfeeding women

**Only in research settings**

Do not use baricitinib for the treatment of COVID-19 in pregnant or breastfeeding women outside randomised trials with appropriate ethical approval.

Remark:
***Additional information***

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

## 3.2 Molnupiravir (Lagevrio) for pregnant or breastfeeding women

**Only in research settings**

Do not use molnupiravir for the treatment of COVID-19 in pregnant or breastfeeding women outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Currently, there is no direct evidence for the use of molnupiravir (Lagevrio) in pregnant or breastfeeding women. Trials are needed in special populations, including pregnant or breastfeeding women. Until further evidence is available, do not use molnupiravir for the treatment of COVID-19 in pregnant or breastfeeding women unless they are eligible to be enrolled in trials.

There are no clinical data on the use of molnupiravir in pregnant or breastfeeding women. It is unknown whether molnupiravir is present in human or animal milk, and the effects on the breastfed newborn/infant, or the effects on milk production. A risk to the newborn/infant cannot be excluded.

There are no clinical data on the effects of molnupiravir against the SARS-CoV-2 Omicron variant.

Animal reproductive studies indicate that molnupiravir may have embryo-fetal development effects at high doses, which could include embryofetal lethality, teratogenicity, and reduced fetal growth. Animal studies have also shown potential deleterious effects on cartilage and bone growth and it is unclear if these effects are reversible. (TGA Product Information)

*This is a high priority recommendation and will be updated as soon as new evidence becomes available.*

## 3.3 Nirmatrelvir plus ritonavir (Paxlovid) for pregnant or breastfeeding women

**Only in research settings**

Do not use nirmatrelvir plus ritonavir in pregnant or breastfeeding women outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Currently, there is no direct evidence for the use of nirmatrelvir plus ritonavir (Paxlovid) in pregnant or breastfeeding women. Trials are needed in special populations, including pregnant or breastfeeding women. Until further evidence is available, do not use nirmatrelvir plus ritonavir for the treatment of COVID-19 in pregnant or breastfeeding women unless they are eligible to be enrolled in trials.

There are no clinical data on the use of nirmatrelvir plus ritonavir in pregnant or breastfeeding women. It is unknown whether nirmatrelvir plus ritonavir is present in human or animal milk, and the effects on the breastfed newborn/infant, or the effects on milk production. A risk to the newborn/infant cannot be excluded.

There are no clinical data on the effects of nirmatrelvir plus ritonavir against the SARS-CoV-2 Omicron variant.

Use of ritonavir may reduce the efficacy of combined hormonal contraceptives.

Animal reproductive studies indicate that nirmatrelvir plus ritonavir may have embryo-fetal development effects at high doses, which could include early resorptions, decreased fetal body weight and ossification delays and developmental variations (TGA Product Information).

*This is a high priority recommendation and will be updated as soon as new evidence becomes available.*

## 3.4 Regdanvimab (Regkirona) for pregnant or breastfeeding women

**Only in research settings** New

Do not use regdanvimab for the treatment of COVID-19 in pregnant or breastfeeding women outside randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Currently there is no direct evidence evaluating the effectiveness of regdanvimab (Regkirona) in pregnant and breastfeeding women. Until further evidence is available, do not use regdanvimab for the treatment of COVID-19 in pregnant and breastfeeding women unless they are eligible to be enrolled in trials.

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

## 3.5 Sarilumab for pregnant or breastfeeding women

**Only in research settings**

Do not use sarilumab for the treatment of COVID-19 in pregnant or breastfeeding women outside randomised trials with appropriate ethical approval.

Remark:
***Additional information***

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

## 3.6 Tixagevimab plus cilgavimab (Evusheld) for pregnant or breastfeeding women

**Only in research settings**

Do not use tixagevimab plus cilgavimab for the treatment of COVID-19 in pregnant or breastfeeding women outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Currently, there is no direct evidence for the use of tixagevimab plus cilgavimab (Evusheld) in pregnant or breastfeeding women. Trials are needed in special populations, including pregnant or breastfeeding women. Until further evidence is available, do not routinely use tixagevimab plus cilgavimab for the treatment of COVID-19 in pregnant or breastfeeding women unless they are eligible to be enrolled in trials.

*This is a high priority recommendation and will be updated as soon as new evidence becomes available.*

# 4. Children and adolescents

## 4.1 All children and adolescents

### 4.1.1 Casirivimab plus imdevimab (Ronapreve) for children and adolescents

**Only in research settings**

Do not use casirivimab plus imdevimab in children under 12 years of age without risk factors for deterioration who have **mild or asymptomatic COVID-19** outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

*Please note: Two consensus recommendations for the use of casirivimab plus imdevimab in children and adolescents are available in the primary Taskforce guideline (children who do not require oxygen; children who require oxygen)*

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

### 4.1.2 Molnupiravir (Lagevrio) for children and adolescents

**Only in research settings**

Do not use molnupiravir for the treatment of COVID-19 in children and adolescents outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

Currently, there is no direct evidence for the use of molnupiravir (Lagevrio) in children and adolescents. Trials are needed in special populations, including children and adolescents. Until further evidence is available, do not routinely use molnupiravir for the treatment of COVID-19 in children and adolescents unless they are eligible to be enrolled in trials.

Animal studies have shown potential deleterious effects on cartilage and bone growth, and it is unclear if these effects are reversible.

Currently molnupiravir is not approved for use in people under 18 years of age.

*This is a high priority recommendation and will be updated as soon as new evidence becomes available.*

### 4.1.3 Regdanvimab (Regkirona) for children and adolescents

**Only in research settings** New

Do not use regdanvimab for the treatment of COVID-19 in children and adolescents outside of randomised trials with appropriate ethical approval.

Remark:

***Additional information***

Currently, there is no direct evidence evaluating the effectiveness of regdanvimab (Regkirona) in children and adolescents. Until further evidence is available, do not use regdanvimab for the treatment of COVID-19 in children and adolescents unless they are eligible to be enrolled in trials.

Currently regdanvimab is not approved for use in people under 18 years of age.

*This is a high priority recommendation and will be updated as soon as new evidence becomes available.*

### 4.1.4 Sarilumab for children and adolescents

**Only in research settings**

Do not use sarilumab for the treatment of COVID-19 in children and adolescents outside randomised trials with appropriate ethical approval.

Remark:
***Additional information***

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

## 4.2 Children aged < 12 years weighing < 40 kg

### 4.2.1 Nirmatrelvir plus ritonavir (Paxlovid) for children and adolescents

**Only in research settings**

Do not use nirmatrelvir plus ritonavir for the treatment of COVID-19 in children under 12 years of age without risk factors for deterioration who do not require oxygen, outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

*Please note: A consensus recommendation for the use of nirmatrelvir plus ritonavir in children and adolescents is available in the primary Taskforce guideline.*

*This is a high priority recommendation and will be updated as soon as new evidence becomes available.*

### 4.2.2 Sotrovimab (Xevudy) for children and adolescents

**Only in research settings**

Do not routinely use sotrovimab outside of randomised trials with appropriate ethical approval for the treatment of COVID-19 in children and adolescents under 12 years of age and without high risk factors for deterioration.

Where infection with Omicron BA.2 is confirmed or considered likely, use of sotrovimab should only be considered where other treatments are not suitable or available.

Remark:

***Additional information***

*Please note: A consensus recommendation for the use of sotrovimab in children and adolescents is available in the primary Taskforce guideline.*

*Where infection with Omicron BA.2 is confirmed or considered likely, use of sotrovimab in children and adolescents should only be considered where other treatments are not suitable or available. There are limited evidence-based alternatives for children and adolescents currently (e.g. inhaled corticosteroids)*

*While the clinical evidence supports use of sotrovimab to treat mild COVID-19 (in adults at high risk of severe disease), there is no clinical evidence to evaluate its effectiveness against the Omicron variant or BA.1 or BA.2 sub-variants. The Taskforce is aware of* in vitro *data that suggest potentially reduced efficacy against these variants and while the clinical implications of this are not certain, given the availability of other treatments, where infection with Omicron BA.2 is confirmed or considered likely, use of sotrovimab should not be considered unless other treatments are unsuitable or unavailable.*

Children and adolescents were not included in the COMET-ICE trial. However trials are underway in which children over 12 years of age are eligible for inclusion (OPTIMISE-C19, NCT04913675).

The efficacy of sotrovimab (Xevudy) in vaccinated or immunocompromised patients is unknown.

### 4.2.3 Tixagevimab plus cilgavimab (Evusheld) for children and adolescents

**Only in research settings**

Do not use tixagevimab plus cilgavimab for the treatment of COVID-19 in children under 12 years of age without risk factors for deterioration who do not require oxygen outside of randomised trials with appropriate ethical approval.

Remark:
***Additional information***

*Please note: A consensus recommendation for the use of tixagevimab plus cilgavimab in children and adolescents is available in the primary Taskforce guideline.*

*This is a high priority recommendation and will be updated as soon as new evidence becomes available.*

# 1. Drug treatments not recommended outside of clinical trials

Info Box

The Taskforce has reviewed high quality evidence for a number of therapeutics used to treat COVID-19 for which there is insufficient evidence to determine whether they are safe and/or effective. The Taskforce recommends that use of these treatments be limited to clinical trials with appropriate ethical approval.

This guideline is supplementary to the primary guideline, 'Australian guidelines for the clinical care of people with COVID-19'. The primary guideline contains information specific to drug treatments that are recommended and not recommended for use, pregnant and breastfeeding patients, paediatric and adolescent patients, respiratory support and other supportive recommendations.

The primary guideline contains additional information specific to methods and processes, and information on how to read and interpret the various components of each recommendation can be found within the reading guide. Details regarding our member organisations, purpose, scope and NHMRC approval status can be found within the Introduction section.

# 2. All populations

## 2.1 Antiandrogens

### 2.1.1 Dutasteride

Only in research settings

Do not use dutasteride for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Dutasteride should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use dutasteride to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

**Evidence to decision**

**Benefits and harms**

Important harms

**General adult population**
In addition to uncertainty around benefits for patients with COVID-19, there are common side effects and harms associated with dutasteride, including impotence, altered libido and breast disorders.

**Children and adolescents**
Dutasteride is contraindicated in children as its use not been studied in this population.

**Pregnant and breastfeeding women**
Dutasteride is contraindicated for use in women as it has not been studied in this population. In pregnant women, pre-clinical data suggest that the suppression of circulating levels of dihydrotestosterone may inhibit the development of a male fetus carried by a woman exposed to dutasteride.

**Certainty of the evidence**

Very low

**General adult population**
Certainty of the evidence for each outcome is very low due to serious risk of bias and very serious imprecision (low number of patients and/or observed events and reliance on a single study).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel

believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, the use of dutasteride is contraindicated for pregnant and breastfeeding women.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

**General adult population**
There is currently limited evidence about the impact of dutasteride on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that dutasteride should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of dutasteride for the treatment of COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Dutasteride
**Comparator:** Standard Care

### Summary

There remains significant uncertainty whether dutasteride is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial that compared dutasteride with placebo in 130 adult males hospitalised with mild COVID-19 *[1]*.

Note: the study authors have confirmed the randomisation process and use of a matching placebo tablet, and that no hospitalisations occurred.

**Study characteristics**
Mean age of participants was 42 years; no women were included in the study. Patients received dutasteride 0.5 mg or placebo once a day for 30 days or until full remission of COVID-19 symptoms. Both groups also received nitazoxanide 500 mg twice a day for six days and azithromycin 500 mg a day for five days.

**What are the main results?**
No patients in either arm required hospitalisation. It is unclear whether dutasteride increases or decreases time to clinical recovery.

**Our confidence in the results**
Certainty of the evidence is very low for all outcomes due to serious risk of bias and very serious imprecision (reliance on a single study with low patient numbers and few events).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness due to the absence of these populations in the included studies.

**Additional information**
Dutasteride is contraindicated in **children** as its use not been studied in this population *[5]*.

Dutasteride has not been studied in **women**. As a result, the safety profile is unknown in this population and its use should be avoided. Furthermore, dutasteride is contraindicated in breastfeeding women because pre-clinical data suggest that the suppression of circulating levels of dihydrotestosterone may inhibit the development of a male fetus carried by a woman exposed to dutasteride *[5]*.

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Standard Care | **Intervention** Dutasteride | **Certainty of the evidence** (Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Hospitalisation** End of Follow-up 9 Critical | Based on data from 87 participants in 1 studies. [1] | | | 2 | No patients required hospitalisation. |
| **Time to recovery** Remission of all symptoms 6 Important | Based on data from 87 participants in 1 studies. [3] | 9.2 (Mean) | 16.3 (Mean) CI 95% | **Very low** Due to serious risk of bias and very serious imprecision 4 | We are uncertain whether dutasteride increases or decreases time to recovery. |

1. Systematic review [3] with included studies: Cadegiani 2020.
2. **Risk of Bias: serious.** Selective outcome reporting. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Only data from one study, Low number of patients. **Publication bias: no serious.**
3. Systematic review [3]
4. **Risk of Bias: serious.** Selective outcome reporting. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Low number of patients, Only data from one study. **Publication bias: no serious.**

**References**

1. Cadegiani FA, McCoy J, Wambier CG, Goren A. Early antiandrogen therapy with dutasteride reduces viral shedding, inflammatory responses, and time-to-remission in males with COVID-19: a randomized, double-blind, placebo-controlled interventional trial (EAT-DUTA AndroCoV Trial – Biochemical). Cureus 2021;13(2):e13047 Journal

3. Dutasteride for [COVID-19].

5. Therapeutic Goods Administration. Australian Product Information: APO-Dutasteride (Dutasteride) Soft Capsules. 24 September 2020. Website

## 2.2 Antineoplastics

### 2.2.1 Angiotensin 2 receptor agonist (C21)

Only in research settings

Do not use the angiotensin 2 receptor agonist C21 for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*C21 should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use C21 to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

## Evidence to decision

**Benefits and harms**

**General adult population**
As the safety profile for C21 is incompletely characterised in humans, there is uncertainty around the benefits and harms for patients with COVID-19.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There are additional concerns regarding harms as C21 has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

**Certainty of the evidence**

Very low

Certainty of the evidence is very low for death due to very serious imprecision (wide confidence intervals, few events and reliance on a single study) and serious publication bias (the study was commercially funded). Certainty for the remaining outcomes is also very low due to the above factors with the addition of serious risk of bias (insufficient information regarding randomisation).

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

## Rationale

**General adult population**
There is currently limited evidence about the impact of C21 on patient-relevant outcomes in the treatment of COVID-19. The panel has

significant concerns regarding the potential harms of unproven treatments. We therefore recommend that C21 should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of C21 to treat COVID-19 in these populations should be avoided until evidence becomes available.

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### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** C21
**Comparator:** Placebo

### Summary

There remains significant uncertainty whether angiotensin 2 receptor agonist (C21) is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial that compared C21 with placebo in 106 adults hospitalised with COVID-19 *[4]*.

**Study characteristics**
Mean age of participants was 53 years and 25% were women. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
Insufficient patients received supplemental oxygen, invasive mechanical ventilation or died to determine whether C21 makes a difference to these outcomes.

**Our confidence in the results**
Certainty of the evidence is very low for all outcomes. This judgement is based on very serious imprecision (low patient numbers, wide confidence intervals and reliance on a single study with few events), serious risk of bias (randomisation process) and serious publication bias (commercially funded).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
As of 28 May 2021, angiotensin II receptor agonist C21 is not listed in the Australian Register of Therapeutic Goods and is not approved for use in Australia. The safety profile for C21 is incompletely characterised in humans.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>C21 | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Day 14<br><br>9 Critical | Relative risk 0.36<br>(CI 95% 0.04 — 3.35)<br>Based on data from 106 participants in 1 studies. [1]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision and serious publication bias [2] | We are uncertain whether angiotensin 2 receptor agonist (C21) increases or decreases mortality (4 deaths). |
| **Invasive mechanical ventilation**<br>End of follow-up<br><br>9 Critical | Relative risk 0.27<br>(CI 95% 0.03 — 2.33)<br>Based on data from 106 participants in 1 studies. [3]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision and serious publication bias [4] | We are uncertain whether angiotensin 2 receptor agonist (C21) increases or decreases invasive mechanical ventilation (5 events). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>C21 | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Supplemental oxygen**<br>End of follow-up<br><br>6 Important | Relative risk 0.1<br>(CI 95% 0.01 — 0.73)<br>Based on data from 106 participants in 1 studies. [5]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision and serious publication bias [6] | We are uncertain whether angiotensin 2 receptor agonist (C21) increases or decreases supplemental oxygen (12 events). |

1, 3, 5. Systematic review [2] with included studies: Tornling 2021.
2. **Risk of Bias: no serious.** No information on concealment of allocation during randomization process, resulting in potential for selection bias. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias: serious.** Mostly commercially funded studies, due to preprint.
4. **Imprecision: very serious.** Low number of patients, Wide confidence intervals, Only data from one study. **Publication bias: serious.** Mostly commercially funded studies, due to [reason].
6. **Risk of Bias: no serious.** No information on concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias: serious.** Mostly commercially funded studies, due to preprint.

### References

2. [Intervention] for [COVID-19].

4. Tornling G, Batta R, Porter JC, Williams B, Bengtsson T, Parmar K, et al. Seven days treatment with the angiotensin II type 2 receptor agonist C21 in hospitalized COVID-19 patients; a placebo-controlled randomised multi-centre double-blind phase 2 trial. EClinicalMedicine 2021;41:101152 Pubmed Journal

## 2.2.2 Camostat mesilate

Only in research settings

Do not use camostat mesilate for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Camostat mesilate should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use camostat mesilate to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

## Evidence to decision

### Benefits and harms

**General adult population**
As the safety profile for camostat mesilate is incompletely characterised in humans, there is uncertainty around the benefits and harms for patients with COVID-19

**Children an adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There are additional concerns regarding harms as camostat mesilate has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

### Certainty of the evidence

Very low

Certainty of the evidence is low for death due to very serious imprecision (wide confidence intervals, few events and reliance on a single study). In addition to the above factors, certainty is very low for all remaining outcomes due to serious risk of bias (insufficient information regarding randomisation and allocation concealment).

### Values and preferences

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

### Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Equity

Important issues, or potential issues not investigated

**General adult population**
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Children and adolescents, pregnant and breastfeeding women**
Because the benefit-to-harm ratio is uncertain, this recommendation protects these more vulnerable populations.

**People requiring palliative care and older people living with frailty or cognitive impairment**
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit-to-harm ratio, this recommendation protects these more vulnerable populations.

### Acceptability

Important issues, or potential issues not investigated

**General adult population, children and adolescents, pregnant and breastfeeding women**
We have no systematically collected evidence regarding acceptability. Substantial variability is expected as some patients would accept the treatment and others not.

**People requiring palliative care and older people living with frailty or cognitive impairment**

Because the benefit-to-harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

**Feasibility** Important issues, or potential issues not investigated

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

### Rationale

**General adult population**
There is currently limited evidence about the impact of camostat mesilate on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that camostat mesilate should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of camostat mesilate to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Camostat mesilate
**Comparator:** Placebo

### Summary

There remains significant uncertainty whether camostat mesilate is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial that compared camostat mesilate with standard care in 208 adults hospitalised with COVID-19 *[6]*.

**Study characteristics**
Median age of participants was 61 years and 40% were women. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
Insufficient patients required intensive care admission, invasive mechanical ventilation or died to determine whether camostat mesilate makes a difference to these outcomes. It is uncertain if camostat mesilate increases or decreases requirement for supplemental oxygen or increases adverse or serious adverse events.

**Our confidence in the results**
Certainty of the evidence is very low for all outcomes. This judgement is based on very serious imprecision (low patient numbers, wide confidence intervals and reliance on a single study with few events) and serious risk of bias (no information on concealment of allocation).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
As of 28 May 2021, camostat mesilate is not listed in the Australian Register of Therapeutic Goods and is not approved for use in Australia. The safety profile for camostat mesilate is incompletely characterised in humans.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Camostat mesilate | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Day 28<br>9 Critical | Relative risk 0.99<br>(CI 95% 0.31 — 3.18)<br>Based on data from 205 participants in 1 studies. [1]<br>(Randomized controlled) | **59**<br>per 1000<br>Difference: | **58**<br>per 1000<br>**1 fewer per 1000**<br>41 fewer — 129 more | **Low**<br>Due to very serious imprecision [2] | We are uncertain whether camostat mesilate increases or decreases mortality (12 deaths). |
| **Invasive mechanical ventilation**<br>End of follow-up<br>9 Critical | Relative risk 2.15<br>(CI 95% 0.63 — 7.29)<br>Based on data from 205 participants in 1 studies. [3]<br>(Randomized controlled) | **44**<br>per 1000<br>Difference: | **95**<br>per 1000<br>**51 more per 1000**<br>16 fewer — 277 more | **Low**<br>Due to very serious imprecision [4] | We are uncertain whether camostat mesilate increases or decreases invasive mechanical ventilation (16 events). |
| **Supplemental oxygen**<br>End of follow-up<br>6 Important | Relative risk 0.98<br>(CI 95% 0.84 — 1.16)<br>Based on data from 205 participants in 1 studies. [5]<br>(Randomized controlled) | **765**<br>per 1000<br>Difference: | **750**<br>per 1000<br>**15 fewer per 1000**<br>122 fewer — 122 more | **Low**<br>Due to very serious imprecision [6] | We are uncertain whether camostat mesilate increases or decreases supplemental oxygen (155 events). |
| **Serious adverse events**<br>End of follow-up<br>6 Important | Relative risk 1.68<br>(CI 95% 0.8 — 3.49)<br>Based on data from 205 participants in 1 studies. [7]<br>(Randomized controlled) | **118**<br>per 1000<br>Difference: | **198**<br>per 1000<br>**80 more per 1000**<br>24 fewer — 294 more | **Low**<br>Due to very serious imprecision [8] | We are uncertain whether camostat mesilate increases serious adverse events (38 events). |
| **Adverse events**<br>End of follow-up<br>6 Important | Relative risk 0.86<br>(CI 95% 0.55 — 1.33)<br>Based on data from 205 participants in 1 studies. [9]<br>(Randomized controlled) | **324**<br>per 1000<br>Difference: | **279**<br>per 1000<br>**45 fewer per 1000**<br>146 fewer — 107 more | **Low**<br>Due to very serious imprecision [10] | We are uncertain whether camostat mesilate increases adverse events (60 events). |
| **ICU admission**<br>End of follow-up<br>6 Important | Relative risk 0.87<br>(CI 95% 0.38 — 1.97)<br>Based on data from 205 participants in 1 studies. [11]<br>(Randomized controlled) | **118**<br>per 1000<br>Difference: | **103**<br>per 1000<br>**15 fewer per 1000**<br>73 fewer — 114 more | **Low**<br>Due to very serious imprecision [12] | We are uncertain whether camostat mesilate increases or decreases ICU admission (22 events). |

1, 3, 5, 7, 9, 11. Systematic review [8] with included studies: Gunst 2021.

2, 4, 6, 10. **Risk of Bias: no serious.** No information on concealment of allocation during randomization process, resulting in potential for selection bias. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study.

8. **Risk of Bias: no serious.** No information on concealment of allocation during randomization process, resulting in potential for selection bias. **Imprecision: very serious.** Low number of patients, Only data from one study, Wide confidence intervals.

12. **Risk of Bias: no serious.** No information on concealment of allocation during randomization process, resulting in potential for selection bias. **Imprecision: very serious.** Low number of patients, Wide confidence intervals, Only data from one study.

### References

6. Gunst JD, Staerke NB, Pahus MH, Kristensen LH, Bodilsen J, Lohse N, et al. Efficacy of the TMPRSS2 inhibitor camostat mesilate in patients hospitalized with Covid-19-a double-blind randomized controlled trial. EClinicalMedicine 2021;35:100849 Pubmed Journal

8. [Intervention] for [COVID-19].

## 2.2.3 Opaganib

Only in research settings

New

Do not use opaganib for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use opaganib to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### Evidence to decision

**Benefits and harms**

Small net benefit, or little difference between alternatives

We are uncertain whether opaganib impacts all-cause mortality, the need for invasive mechanical ventilation, serious adverse events or discharge from hospital. Opaganib may decrease supplemental oxygen slightly and increase clinical improvement slightly, however further evidence is required.

**Certainty of the evidence**

Low

Certainty of the evidence is low for all six outcomes reported (all-cause mortality, invasive mechanical ventilation, supplemental oxygen, serious adverse events, discharge from hospital and clinical improvement), due to very serious imprecision (reliance on a single study and wide confidence intervals).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of ensovibep in pregnancy are unknown.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit.

### Rationale

**General adult population**
There is currently limited evidence about the impact of opaganib on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that opaganib should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of opaganib for the treatment of COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Patients with Covid-19
**Intervention:** Opaganib
**Comparator:** Placebo

### Summary

There remains uncertainty whether opaganib is more effective and safer than placebo in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial that compared opaganib with placebo in 463 adults with moderate to severe COVID-19 *[226]*.

**Study characteristics**
Median age of participants was 56 years and approximately 35% of participants were female. The majority of participants (99%) required oxygen but not mechanical ventilation at baseline, and the majority also received concomitant corticosteroids (94%). Children and adolescents, and pregnant and breastfeeding women were ineligible.

**What are the main results?**
We are uncertain whether opaganib impacts all-cause mortality, the need for invasive mechanical ventilation, serious adverse events or discharge from hospital. Opaganib may decrease supplemental oxygen slightly and increase clinical improvement slightly, however further evidence is required.

**Our confidence in the results**
Certainty of the evidence is low for all six outcomes reported (all-cause mortality, invasive mechanical ventilation, supplemental oxygen, serious adverse events, discharge from hospital and clinical improvement), due to very serious imprecision (reliance on a single study and wide confidence intervals).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
Opaganib is an experimental antineoplastic and is currently not approved for use in Australia.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Opaganib | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Invasive Mechanical Ventilation**<br>Within 42 days of commencing treatment<br>9 Critical | Relative risk 0.94<br>(CI 95% 0.68 — 1.31)<br>Based on data from 463 participants in 1 studies. [1]<br>(Randomized controlled) | **245**<br>per 1000<br>Difference: | **230**<br>per 1000<br>**15 fewer per 1000**<br>( CI 95% 78 fewer — 76 more ) | **Low**<br>Due to very serious imprecision [2] | Opaganib may have little impact on invasive mechanical ventilation (110 events). |
| **All cause mortality**<br>Within 42 days of commencing treatment<br>9 Critical | Relative risk 0.95<br>(CI 95% 0.66 — 1.37)<br>Based on data from 463 participants in 1 studies. [3]<br>(Randomized controlled) | **202**<br>per 1000<br>Difference: | **192**<br>per 1000<br>**10 fewer per 1000**<br>( CI 95% 69 fewer — 75 more ) | **Low**<br>Due to very serious imprecision [4] | Opaganib may have little impact on death (91 events). |
| **Supplemental oxygen**<br>Within 14 days of commencing treatment<br>6 Important | Relative risk 0.91<br>(CI 95% 0.73 — 1.13)<br>Based on data from 463 participants in 1 studies. [5]<br>(Randomized controlled) | **433**<br>per 1000<br>Difference: | **394**<br>per 1000<br>**39 fewer per 1000**<br>( CI 95% 117 fewer — 56 more ) | **Low**<br>Due to very serious imprecision [6] | Opaganib may decrease requirement of supplemental oxygen slightly (192 events). |
| **Serious adverse events**<br>End of follow-up<br>6 Important | Relative risk 1.05<br>(CI 95% 0.75 — 1.49)<br>Based on data from 463 participants in 1 studies. [7]<br>(Randomized controlled) | **210**<br>per 1000<br>Difference: | **220**<br>per 1000<br>**10 more per 1000**<br>( CI 95% 53 fewer — 103 more ) | **Low**<br>Due to very serious imprecision [8] | Opaganib may have little impact on serious adverse events (100 events). |
| **Discharge from hospital**<br>Within 14 days of commencing treatment<br>6 Important | Relative risk 0.98<br>(CI 95% 0.84 — 1.15)<br>Based on data from 463 participants in 1 studies. [9]<br>(Randomized controlled) | **567**<br>per 1000<br>Difference: | **556**<br>per 1000<br>**11 fewer per 1000**<br>( CI 95% 91 fewer — 85 more ) | **Low**<br>Due to very serious imprecision [10] | Opaganib may have little impact on discharge from hospital (260 events). |

| Outcome<br>Timeframe | Study results and measurements | Comparator<br>Placebo | Intervention<br>Opaganib | Certainty of the evidence<br>(Quality of evidence) | Summary |
|---|---|---|---|---|---|
| **Clinical improvement** [11]<br>End of follow-up<br><br>6 Important | Relative risk 1.06<br>(CI 95% 0.92 — 1.23)<br>Based on data from 463 participants in 1 studies. [12]<br>(Randomized controlled) | 592<br>per 1000<br><br>Difference: | 628<br>per 1000<br><br>**36 more per 1000**<br>( CI 95% 47 fewer — 136 more ) | **Low**<br>Due to very serious imprecision [13] | Opaganib may increase clinical improvement slightly (283 events). |

1, 3, 5, 7, 9, 12. Systematic review [224] with included studies: Neuenschwander 2022.
2, 4, 6, 8, 10, 13. **Imprecision: very serious.** Wide confidence intervals, Only data from one study.
11. 2 or more WHO ordinal scale

**References**

224. Opaganib for Covid-19.

## 2.3 Antiparasitic, antifungals and other anti-infective agents

### 2.3.1 Chloroquine

Only in research settings

Do not use chloroquine for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Chloroquine should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use chloroquine to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

**Evidence to decision**

**Benefits and harms**

Important harms

**General adult population**
In addition to uncertainty around benefits for patients with COVID-19, there are well-known harms with potentially severe adverse events. Although most of the information on side effects and harms associated with chloroquine is derived from long-term use, potential acute harms include prolonged QT interval and lowered convulsive

threshold.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There are additional concerns regarding harms as chloroquine has not been sufficiently tested in these populations. Chloroquine is used in pregnant and breastfeeding women for the treatment of malaria and autoimmune diseases in some countries. The available evidence is limited, though chloroquine use is not associated with pregnancy loss, stillbirth or neonatal death *[211]*. For people requiring palliative care, the benefits for symptom management are uncertain.

**Certainty of the evidence**

Very low

**General adult population**
Certainty of the evidence for each outcome is very low. This is based on serious risk of bias due to non-blinding of participants and personnel and incomplete outcome data, and very serious imprecision due to the low number of patients and/or events for some outcomes and the reliance on a single study.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is additionally considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of chloroquine in pregnancy are unknown.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit.

### Rationale

**General adult population**
There is currently limited evidence about the impact of chloroquine on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that chloroquine should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of chloroquine to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Special populations with COVID-19
**Intervention:** Chloroquine
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether chloroquine is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from a single randomised trial that compared chloroquine with standard care in 30 adults hospitalised with moderate COVID-19 *[10]*.

We have found one new study comparing chloroquine administered as nasal drops with standard care (Thakar et al. Indian J Med Res doi: 10.4103/ijmr.IJMR_3665_20). This study is currently under review and an updated recommendation will be included in a future version of the guideline.

**Publication status**
The study is only available as a preprint paper (posted to medRxiv on 22 June 2020) and has therefore not been peer reviewed.

**Study characteristics**
Mean age was 45 years in the chloroquine group and 51 years in the control group; the proportion of women was 61% and 42% respectively. It is unclear if pregnant and breastfeeding women were eligible.

**What are the main results?**
No patients in either arm died, progressed to severe or critical disease, or experienced a serious adverse event. We are uncertain whether chloroquine increases or decreases time to clinical recovery, time to termination of oxygen therapy or the likelihood of experiencing adverse events. The study did not report results for respiratory failure or requirement for mechanical ventilation.

**Our confidence in the results**
Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias (patients, personnel and outcome assessors not blinded, and incomplete reporting of data), serious indirectness (limited inclusion of these populations) and very serious imprecision (low patient numbers, few observed events and reliance on a single study).

**Additional information**
Although listed on the Australian Register of Therapeutic Goods, chloroquine is not marketed in Australia and is not available for general use.

Paediatricians have considerable experience with using chloroquine in **children and adolescents** for other indications. To date, no specific information on benefits or harms for children and adolescents with COVID-19 has been collected.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Chloroquine | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 28 days after commencing treatment<br><br>9 Critical | Based on data from 30 participants in 1 studies. [1]<br>(Randomized controlled) | | | 2 | There were no deaths. |
| **Progression to severe or critical disease**<br>Within 28 days | Based on data from 30 participants in 1 studies. [3] | | | 4 | No patients progressed to severe or critical disease. |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Chloroquine | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| after commencing treatment<br>6 Important | (Randomized controlled) | | | | |
| **Adverse events**<br>Within 28 days after commencing treatment<br>6 Important | Relative risk 2.67<br>(CI 95% 0.68 — 10.46)<br>Based on data from 30 participants in 1 studies. [5]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias, serious indirectness and very serious imprecision [6] | We are uncertain whether chloroquine increases or decreases adverse events (10 events). |
| **Serious adverse events**<br>Within 28 days after commencing treatment<br>6 Important | Based on data from 30 participants in 1 studies.<br>(Randomized controlled) | | | [7] | There were no serious adverse events. |
| **Time to clinical recovery**<br>Median time to clinical recovery (Days)<br>6 Important | Measured by: Median time to clinical recovery; chloroquine: 5.5 days (IQR 3.25-7.5), control: 7.5 days (IQR 5.0-16.25)<br>Lower better<br>(Randomized controlled) | **7.5**<br>(Median) | **5.5**<br>(Median)<br>CI 95% | **Very low**<br>Due to serious risk of bias, serious indirectness and very serious imprecision [8] | We are uncertain whether chloroquine increases or decreases time to clinical recovery. |
| **Time to termination of oxygen therapy**<br>Median time from randomisation to termination of oxygen therapy (Days)<br>6 Important | Measured by: Median time to termination of oxygen therapy; chloroquine: 8.5 days (IQR 0-9.25); control: 8 days (IQR 3.25-14)<br>Lower better<br>(Randomized controlled) | **8**<br>(Median) | **8.5**<br>(Median)<br>CI 95% | **Very low**<br>Due to serious risk of bias, serious indirectness and very serious imprecision [9] | We are uncertain whether chloroquine increases or decreases time to termination of oxygen therapy. |

1, 3, 5. Systematic review [7] with included studies: Chen L 2020.
2, 9. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up. **Indirectness: serious. Imprecision: very serious.** Low number of patients, Only data from one study.
4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up. **Indirectness: serious. Imprecision: very serious.** Low number of patients, Only data from one study.
6, 8. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Indirectness: serious. Imprecision: very serious.** Low number of patients, Only data from one study.
7. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up, Inadequate/lack of blinding of outcome assessors, resulting in

potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Indirectness: serious. Imprecision: very serious.** Only data from one study, Low number of patients.

### References

7. Chloroquine for COVID-19.

9. Sridharan K, Sivaramakrishnan G, Kanters S. Adverse pregnancy outcomes between the anti-malarial drugs: Is there a difference between the drugs recommended by World Health Organization? Results of a mixed treatment comparison analysis of randomized clinical trials and cohort studies. International Journal of Risk & Safety in Medicine 2019;30(2):73-89 Pubmed Journal

10. Chen L, Zhang Z-Y, Fu J-G. Efficacy and safety of chloroquine or hydroxychloroquine in moderate type of COVID-19: a prospective open-label randomized controlled study. medRxiv 2020. Journal Website

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Chloroquine
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether chloroquine is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from a single randomised trial that compared chloroquine with standard care in 30 adults hospitalised with moderate COVID-19 *[10]*.

We have found one new study comparing chloroquine administered as nasal drops with standard care (Thakar et al. Indian J Med Res doi: 10.4103/ijmr.IJMR_3665_20). This study is currently under review and an updated recommendation will be included in a future version of the guideline.

**Publication status**
The study is only available as a preprint (posted to medRxiv on 22 June 2020) and has therefore not been peer reviewed.

**Study characteristics**
Mean age was 45 years in the chloroquine group and 51 years in the control group; the proportion of women was 61% and 42% respectively. It is unclear if pregnant and breastfeeding women were eligible.

**What are the main results?**
No patients in either arm died, progressed to severe or critical disease, or experienced a serious adverse event. We are uncertain whether chloroquine increases or decreases time to clinical recovery, time to termination of oxygen therapy or the likelihood of experiencing adverse events. The study did not report results for respiratory failure or requirement for mechanical ventilation.

**Our confidence in the results**
Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias (patients, personnel and outcome assessors not blinded, and incomplete reporting of data) and very serious imprecision (low patient numbers, few observed events and reliance on a single study).

**Additional information**
Although listed on the Australian Register of Therapeutic Goods, chloroquine is not marketed in Australia and is not available for general use.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Chloroquine | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 28 days after commencing treatment<br>9 Critical | Based on data from 30 participants in 1 studies. [1]<br>(Randomized controlled) | | | 2 | There were no deaths. |
| **Progression to severe or critical disease**<br>Within 28 days after commencing treatment<br>6 Important | Based on data from 30 participants in 1 studies. [3]<br>(Randomized controlled) | | | 4 | No patients progressed to severe or critical disease. |
| **Adverse events**<br>Within 28 days after commencing treatment<br>6 Important | Relative risk 2.67<br>(CI 95% 0.68 — 10.46)<br>Based on data from 30 participants in 1 studies. [5]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision<br>6 | We are uncertain whether chloroquine increases or decreases adverse events (10 events). |
| **Serious adverse events**<br>Within 28 days after commencing treatment<br>6 Important | Based on data from 30 participants in 1 studies.<br>(Randomized controlled) | | | 7 | There were no serious adverse events. |
| **Time to clinical recovery**<br>Median time to clinical recovery (Days)<br>6 Important | Measured by: Median time to clinical recovery; chloroquine: 5.5 days (IQR 3.25-7.5), control: 7.5 days (IQR 5.0-16.25)<br>Lower better<br>(Randomized controlled) | **7.5**<br>(Median) | **5.5**<br>(Median)<br>CI 95% | **Very low**<br>Due to serious risk of bias and very serious imprecision<br>8 | We are uncertain whether chloroquine increases or decreases time to clinical recovery. |
| **Time to termination of oxygen therapy**<br>Median time from randomisation to termination of oxygen therapy (Days)<br>6 Important | Measured by: Median time to termination of oxygen therapy; chloroquine: 8.5 days (IQR 0-9.25); control: 8 days (IQR 3.25-14)<br>Lower better<br>(Randomized controlled) | **8**<br>(Median) | **8.5**<br>(Median)<br>CI 95% | **Very low**<br>Due to serious risk of bias and very serious imprecision<br>9 | We are uncertain whether chloroquine increases or decreases time to termination of oxygen therapy. |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Chloroquine | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| 6 Important | | | | | |

1, 3, 5. Systematic review [7] with included studies: Chen L 2020.
2, 9. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Incomplete data and/or large loss to follow up. **Imprecision: very serious.** Low number of patients, Only data from one study.
4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up. **Imprecision: very serious.** Low number of patients, Only data from one study.
6, 8. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: very serious.** Low number of patients, Only data from one study.
7. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: very serious.** Only data from one study, Low number of patients.

### References

7. Chloroquine for COVID-19.

9. Sridharan K, Sivaramakrishnan G, Kanters S. Adverse pregnancy outcomes between the anti-malarial drugs: Is there a difference between the drugs recommended by World Health Organization? Results of a mixed treatment comparison analysis of randomized clinical trials and cohort studies. International Journal of Risk & Safety in Medicine 2019;30(2):73-89 Pubmed Journal

10. Chen L, Zhang Z-Y, Fu J-G. Efficacy and safety of chloroquine or hydroxychloroquine in moderate type of COVID-19: a prospective open-label randomized controlled study. medRxiv 2020. Journal Website

## 2.3.2 Doxycycline

Only in research settings

Do not use doxycycline for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Doxycycline should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in older people living with frailty and those receiving palliative care. Until further evidence is available, do not use doxycycline to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*Trials are not recommended in pregnant and breastfeeding patients, as doxycycline is contra-indicated in this group.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

## Evidence to decision

**Benefits and harms**

**General adult population**
Evidence indicates no difference between doxycycline and standard care for death, requirement for invasive mechanical ventilation, admission to hospital and mortality, intensive care admission, use of supplemental oxygen and serious adverse events. It is uncertain if doxycycline reduces recovery from COVID-19 compared with standard care.

**Certainty of the evidence**

Low

**General adult population**
Certainty of the evidence is moderate for death due to serious imprecision (reliance on a single study, wide confidence intervals, and few events).

Certainty is low for invasive mechanical ventilation, hospitalisation and death, intensive care admission, supplemental oxygen, self-reported recovery and serious adverse events due to serious imprecision and serious risk of bias (reliance on a single study, wide confidence intervals, and lack of blinding of participants and outcome assessors).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as this treatment has shown no clear benefits, most informed patients would prefer not to use it, while some patients may choose to participate in clinical trials of this treatment.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

There is currently limited evidence about the impact of doxycycline on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that doxycycline should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Doxycycline
**Comparator:** Standard care

### Summary

Evidence indicates that doxycycline is no more effective than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from a single randomised trial (PRINCIPLE) that compared doxycycline with standard care in 1792 adults with mild

COVID-19 *[12]*.

**Study characteristics**
Patients were 65 years and older (or 50 years and older with comorbidities) and not admitted to hospital at trial entry. Mean age of participants was 61 years and 56% were women. Comorbidities included COPD, asthma or lung disease (37%), diabetes (37%), hypertension (42%) and cardiovascular disease (14%).

**What are the main results?**
Doxycycline probably has no impact on risk of death (4 more per 1000; RR 3.11, CI 95% 0.61 to 16.01; 1792 patients in 1 study) or invasive mechanical ventilation (4 fewer per 1000; RR 0.49, CI 95% 0.12 to 2.05; 1378 patients in 1 study). There is probably little difference between doxycycline and standard care for the composite outcome of death or hospitalisation.

Although self-reported recovery was greater in the doxycycline group (31 more per 1000; RR 1.05, CI 95% 0.97 to 1.13), the open-label design makes this outcome at high risk of bias.

**Our confidence in the results**
Certainty of the evidence is moderate for mortality due to serious imprecision (reliance on a single study, wide confidence intervals and few events). Certainty is low for all other outcomes due to serious imprecision and risk of bias (reliance on single study, wide confidence intervals, lack of blinding of participants and outcome assessors).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Doxycycline | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 28 days of commencing treatment<br>9 Critical | Relative risk 3.11<br>(CI 95% 0.61 — 16.01)<br>Based on data from 1,792 participants in 1 studies. [1]<br>(Randomized controlled) | **2**<br>per 1000<br>Difference: | **6**<br>per 1000<br>**4 more per 1000**<br>( CI 95% 1 fewer — 30 more ) | **Low**<br>Due to very serious imprecision [2] | There were too few who died to determine whether doxycycline makes a difference (7 events). |
| **Invasive mechanical ventilation**<br>Within 28 days of commencing treatment<br>9 Critical | Relative risk 0.49<br>(CI 95% 0.12 — 2.05)<br>Based on data from 1,378 participants in 1 studies. [3]<br>(Randomized controlled) | **8**<br>per 1000<br>Difference: | **4**<br>per 1000<br>**4 fewer per 1000**<br>( CI 95% 7 fewer — 8 more ) | **Low**<br>Due to very serious imprecision [4] | There were too few who required invasive mechanical ventilation to determine whether doxycycline makes a difference (8 events). |
| **Mortality or hospitalisation**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 1.19<br>(CI 95% 0.78 — 1.8)<br>Based on data from 1,792 participants in 1 studies. [5]<br>(Randomized controlled) | **43**<br>per 1000<br>Difference: | **51**<br>per 1000<br>**8 more per 1000**<br>( CI 95% 9 fewer — 34 more ) | **Low**<br>Due to serious risk of bias and serious imprecision [6] | Doxycycline may have little or no difference on mortality or hospitalisation (84 events). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Doxycycline | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **ICU admission**<br>Within 28 days of commencing treatment<br><br>6 Important | Relative risk 0.55<br>(CI 95% 0.16 — 1.93)<br>Based on data from 1,375 participants in 1 studies. [7]<br>(Randomized controlled) | **10**<br>per 1000<br><br>Difference: | **6**<br>per 1000<br><br>**4 fewer per 1000**<br>( CI 95% 8 fewer — 9 more ) | **Low**<br>Due to serious risk of bias and serious imprecision [8] | There were too few who required ICU admission to determine whether doxycycline makes a difference (10 events). |
| **Supplemental oxygen**<br>Within 28 days of commencing treatment<br><br>6 Important | Relative risk 0.98<br>(CI 95% 0.55 — 1.76)<br>Based on data from 1,378 participants in 1 studies. [9]<br>(Randomized controlled) | **32**<br>per 1000<br><br>Difference: | **31**<br>per 1000<br><br>**1 fewer per 1000**<br>( CI 95% 14 fewer — 24 more ) | **Moderate**<br>Due to serious imprecision [10] | Doxycycline probably has little impact on requirement for supplemental oxygen (44 events). |
| **Serious adverse events**<br>Within 28 days of commencing treatment<br><br>6 Important | Relative risk 0.11<br>(CI 95% 0.01 — 2.04)<br>Based on data from 1,792 participants in 1 studies. [11]<br>(Randomized controlled) | **5**<br>per 1000<br><br>Difference: | **1**<br>per 1000<br><br>**4 fewer per 1000**<br>( CI 95% 5 fewer — 5 more ) | **Low**<br>Due to serious risk of bias and serious imprecision [12] | There were too few who experienced a serious adverse event to determine whether doxycycline makes a difference (5 events). |
| **Recovery (self-reported)**<br>End of follow-up<br><br>6 Important | Relative risk 1.05<br>(CI 95% 0.97 — 1.13)<br>Based on data from 1,424 participants in 1 studies. [13]<br>(Randomized controlled) | **615**<br>per 1000<br><br>Difference: | **646**<br>per 1000<br><br>**31 more per 1000**<br>( CI 95% 18 fewer — 80 more ) | **Low**<br>Due to serious risk of bias and serious imprecision [14] | Doxycycline may improve self-reported recovery slightly (898 events). |

1, 3, 5, 7, 9, 11, 13. Systematic review [11] with included studies: PRINCIPLE 2021.
2. **Risk of Bias: no serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals, Only data from one study, due to few events. **Publication bias: no serious.**
4. **Risk of Bias: no serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Only data from one study, Wide confidence intervals. **Publication bias: no serious.**
6, 12, 14. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals, Only data from one study. **Publication bias: no serious.**
8. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals, Only data from one study. **Publication bias: no serious.**
10. **Risk of Bias: no serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals, Only data from one study. **Publication bias: no serious.**

**References**

11. [Intervention] for [health problem].

12. Butler CC, Yu L-M, Dorward J, Gbinigie O, Hayward G, Saville BR, et al. Doxycycline for community treatment of suspected COVID-19 in people at high risk of adverse outcomes in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. Lancet Respiratory Medicine 2021;9(9):1010-1020 Pubmed Journal

## 2.3.3 Ivermectin plus doxycycline

Only in research settings

Do not use ivermectin plus doxycycline for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Ivermectin plus doxycycline should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use ivermectin plus doxycycline to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

**Evidence to decision**

**Benefits and harms**

**General adult population**
In addition to uncertainty around benefits for patients with COVID-19, there are well-known side effects and harms associated with both ivermectin and doxycycline including gastrointestinal disorders (such as diarrhoea, vomiting, nausea and abdominal pain), rash, fever, headache and photosensitivity.

**Certainty of the evidence**

Very low

**General adult population**
Certainty of the evidence is very low for all outcomes due to very serious imprecision (low patient numbers, few events and the reliance on a single study) and serious risk of bias (incomplete outcome data).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

**General adult population**
There is currently limited evidence about the impact of ivermectin plus doxycycline on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that ivermectin plus doxycycline should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of ivermectin plus doxycycline to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Ivermectin plus doxycycline
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether ivermectin plus doxycycline is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from two randomised trials that compared ivermectin plus doxycycline with standard care in 447 adults with COVID-19 *[14][17]*.

**Study characteristics**
Mean age of participants ranged from 42 to 48 years and the proportion of women ranged from 48 to 54%. Patients received ivermectin 12 mg on day one and doxycycline 100 mg twice daily for five days. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
There were too few who died (three deaths) to determine whether ivermectin plus doxycycline makes a difference. We are uncertain if ivermectin plus doxycycline increases or decreases adverse or serious adverse events, negative polymerase chain reaction, clinical improvement or clinical deterioration.

**Our confidence in the results**
Certainty of the evidence is very low for all outcomes due to very serious risk of bias and very serious imprecision (reliance on a single study, low patient numbers and few events).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
Common side effects and harms associated with ivermectin are diarrhoea, nausea and dizziness *[16]*. Common side effects and harms associated with doxycycline are nausea, vomiting, diarrhoea, epigastric burning, tooth discolouration, enamel dysplasia and photosensitivity *[13]*.

Limited information suggests that ivermectin is not associated with an increased risk of congenital abnormalities when administered to **pregnant women**. Ivermectin may be used in **women who are breastfeeding** *[22]*. Doxycycline is safe if used during the first 18 weeks of pregnancy. After 16 weeks post-conception, doxycycline use is contraindicated as it can inhibit bone growth in the fetus *[22]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Ivermectin plus doxycycline | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Day 28<br><br>9 Critical | Relative risk 0.14<br>(CI 95% 0.01 — 2.7)<br>Based on data from 363 participants in 1 studies. [1]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [2] | There were too few who died to determine whether ivermectin plus doxycycline makes a difference (3 deaths). |
| **Serious adverse events**<br>End of treatment<br><br>6 Important | Relative risk 4.92<br>(CI 95% 0.24 — 101.74)<br>Based on data from 411 participants in 2 studies. [3]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [4] | There were too few who experienced serious adverse events to determine whether ivermectin plus doxycycline makes a difference (2 events). |
| **Adverse events**<br>End of treatment<br><br>6 Important | Relative risk 14.76<br>(CI 95% 0.85 — 256.46)<br>Based on data from 363 participants in 1 studies. [5]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [6] | There were too few who experienced adverse events to determine whether ivermectin plus doxycycline makes a difference (7 events). |
| **Virological clearance (negative PCR)**<br>End of treatment<br><br>6 Important | Relative risk 1.15<br>(CI 95% 1.06 — 1.26)<br>Based on data from 363 participants in 1 studies. [7]<br>(Randomized controlled) | **800**<br>per 1000<br><br>Difference: | **920**<br>per 1000<br><br>**120 more per 1000**<br>( CI 95% 48 more — 208 more ) | **Very low**<br>Due to serious risk of bias and very serious imprecision [8] | We are uncertain whether ivermectin plus doxycycline increases or decreases virological clearance (negative PCR). |
| **Clinical improvement**<br>End of treatment<br><br>6 Important | Relative risk 1.36<br>(CI 95% 1.12 — 1.67)<br>Based on data from 363 participants in 1 studies. [9]<br>(Randomized controlled) | **444**<br>per 1000<br><br>Difference: | **604**<br>per 1000<br><br>**160 more per 1000**<br>( CI 95% 53 more — 297 more ) | **Very low**<br>Due to serious risk of bias and very serious imprecision [10] | We are uncertain whether ivermectin plus doxycycline increases or decreases clinical improvement. |
| **Clinical deterioration**<br>End of treatment | Relative risk 0.49<br>(CI 95% 0.28 — 0.86)<br>Based on data from 363 participants in 1 studies. [11]<br>(Randomized controlled) | **177**<br>per 1000<br><br>Difference: | **97**<br>per 1000<br><br>**80 fewer per 1000** | **Very low**<br>Due to serious risk of bias and very serious imprecision [12] | We are uncertain whether ivermectin plus doxycycline improves or worsens clinical deterioration. |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Standard care | **Intervention** Ivermectin plus doxycycline | **Certainty of the evidence** (Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| 6 Important | | | ( CI 95% 112 fewer — 22 fewer ) | | |

1, 5, 7, 9, 11. Systematic review [15] with included studies: Reaz 2020.
2. **Risk of Bias: serious.** the large loss to follow up. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals, Only data from one study, Low number of patients. **Publication bias: no serious.**
3. Systematic review [15] with included studies: Reaz 2020, Ahmed 2020.
4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up. **Imprecision: very serious.** Wide confidence intervals, Wide confidence intervals, Only data from one study, due to few events.
6. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up. **Imprecision: very serious.** Wide confidence intervals, Only data from one study.
8. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up. **Imprecision: very serious.** Wide confidence intervals, Only data from one study, Wide confidence intervals.
10. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up. **Imprecision: very serious.** Only data from one study, Wide confidence intervals.
12. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Incomplete data and/or large loss to follow up. **Imprecision: very serious.** Only data from one study, Wide confidence intervals.

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13. Therapeutic Goods Administration. Australian Product Information - APO-Doxycycline (Doxycycline monohydrate) tablets. 14 September 2020. Website

14. Ahmed S, Karim MM, Ross AG, Hossain MS, Clemens JD, Sumiya MK, et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. International Journal of Infectious Diseases 2020;103:214-216 Pubmed Journal

15. [Intervention] for [COVID-19].

16. Therapeutic Goods Administration. Australian Product Information: Stromectol (ivermectin). August 2020. Website

17. Mahmud R, Rahman MM, Alam I, Ahmed KGU, Kabir AKMH, Sayeed SKJB, et al. Ivermectin in combination with doxycycline for treating COVID-19 symptoms: a randomized trial. The Journal of international medical research 2021;49(5):3000605211013550 Pubmed Journal

22. Australian Medicines Handbook 2020 (online). 2020. Website

## 2.3.4 Nitazoxanide

Only in research settings

Do not use nitazoxanide for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Nitazoxanide should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use nitazoxanide to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### Evidence to decision

**Benefits and harms**

**General adult population**
As the safety profile for nitazoxanide is incompletely characterised in humans, there is uncertainty around the benefits and harms for patients with COVID-19.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There are additional concerns regarding harms as nitazoxanide has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

**Certainty of the evidence**

Very low

**General adult population**
Certainty of the evidence is low for all-cause mortality, ICU admission, adverse and serious adverse events, hospital discharge and clinical improvement due to serious risk of bias and/or serious imprecision (wide confidence intervals, few events), and very low for all outcomes due to very serious risk of bias and very serious imprecision (reliance on a single study, low patient numbers and few events).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of nitazoxanide in pregnancy are unknown.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

**General adult population**
There is currently limited evidence about the impact of nitazoxanide on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that nitazoxanide should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of nitazoxanide to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Nitazoxanide
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether nitazoxanide is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from five randomised trials that compared nitazoxanide with placebo in 1818 adults with mild or moderate COVID-19 *[25][18][24][34][23]*.

**Publication status**
One study is only available as a preprint (Silva et al. posted to medRxiv on 5 March 2021) and has therefore not been peer reviewed.

**Study characteristics**
Median age of participants ranged from 37 to 53 years and 28 to 55% were women. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
Nitazoxanide may have little impact on all-cause mortality, adverse events or serious adverse events, however it may decrease ICU admission slightly and improve clinical improvement slightly.

**Our confidence in the results**
Certainty of the evidence is low for all-cause mortality, adverse events and serious adverse events (based on serious risk of bias and serious imprecision, due to wide confidence intervals), and ICU admission, hospital discharge and clinical improvement (based on very serious imprecision due to wide confidence intervals and reliance on a single study). Certainty is very low for all remaining outcomes due to very serious risk of bias and very serious imprecision (low patient numbers and few events).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
In Australia nitazoxanide is only available under the special access scheme for the treatment of giardiasis, cryptosporidiosis and blastocystis. Common side effects and harms associated with nitazoxanide are stomach pain, headache, vomiting and discoloured urine.

Limited information suggests that nitazoxanide is not associated with an increased risk of congenital abnormalities when administered to **pregnant women**.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Nitazoxanide | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Adverse events**<br>End of follow-up<br>6 Important | Relative risk 0.95<br>(CI 95% 0.81 — 1.13)<br>Based on data from 1,732 participants in 3 studies. [1]<br>(Randomized controlled) | **237**<br>per 1000<br>Difference: | **225**<br>per 1000<br>**12 fewer per 1000**<br>( CI 95% 45 fewer — 31 more ) | **Low**<br>Due to serious risk of bias and serious imprecision [2] | Nitazoxanide may have little impact on adverse events. |
| **Serious adverse events**<br>End of follow-up<br>6 Important | Relative risk 0.38<br>(CI 95% 0.1 — 1.5)<br>Based on data from 1,732 participants in 3 studies. [3]<br>(Randomized controlled) | **9**<br>per 1000<br>Difference: | **3**<br>per 1000<br>**6 fewer per 1000**<br>( CI 95% 8 fewer — 5 more ) | **Low**<br>Due to serious risk of bias and serious imprecision [4] | Nitazoxanide may have little impact on serious adverse events (11 events). |
| **ICU admission**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 0.67<br>(CI 95% 0.39 — 1.14)<br>Based on data from 405 participants in 1 studies. [5]<br>(Randomized controlled) | **148**<br>per 1000<br>Difference: | **99**<br>per 1000<br>**49 fewer per 1000**<br>( CI 95% 90 fewer — 21 more ) | **Low**<br>Due to very serious imprecision [6] | Nitazoxanide may decrease ICU admission slightly (50 events). |
| **All-cause mortality**<br>End of treatment<br>9 Critical | Relative risk 1.09<br>(CI 95% 0.43 — 2.77)<br>Based on data from 1,818 participants in 5 studies. [7]<br>(Randomized controlled) | **9**<br>per 1000<br>Difference: | **10**<br>per 1000<br>**1 more per 1000**<br>( CI 95% 5 fewer — 16 more ) | **Low**<br>Due to serious risk of bias and serious imprecision [8] | Nitazoxanide may have little impact on death (18 events). |
| **Discharge from hospital**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 1.01<br>(CI 95% 0.92 — 1.11)<br>Based on data from 405 participants in 1 studies. [9]<br>(Randomized controlled) | **798**<br>per 1000<br>Difference: | **806**<br>per 1000<br>**8 more per 1000**<br>( CI 95% 64 fewer — 88 more ) | **Low**<br>Due to very serious imprecision [10] | Nitazoxanide may have little impact on discharge from hospital (325 events). |
| **Discontinuation due to an adverse event**<br>End of follow-up<br>6 Important | Relative risk 6.12<br>(CI 95% 0.74 — 50.4)<br>Based on data from 392 participants in 1 studies. [11]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [12] | We are uncertain whether nitazoxanide increases or decreases discontinuation due to an adverse event (7 events). |
| **Hospitalisation**<br>End of follow up | Relative risk 0.21<br>(CI 95% 0.02 — 1.8)<br>Based on data from 379 | | | **Very low**<br>Due to serious risk of bias and very serious imprecision | We are uncertain whether nitazoxanide increases or decreases hospitalisation (6 events). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Nitazoxanide | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| 6 Important | participants in 1 studies. [13] | | | | |
| **Clinical deterioration**<br>End of follow-up<br>6 Important | Relative risk 0.15<br>(CI 95% 0.02 — 1.22)<br>Based on data from 379 participants in 1 studies. [14] | | | **Very low**<br>Due to serious risk of bias and very serious imprecision | We are uncertain whether nitazoxanide increases or decreases clinical deterioration (8 events). |
| **Clinical recovery**<br>End of follow-up<br>6 Important | Relative risk 1.02<br>(CI 95% 0.95 — 1.1)<br>Based on data from 797 participants in 2 studies. [15]<br>(Randomized controlled) | **780**<br>per 1000<br>Difference: | **796**<br>per 1000<br>**16 more per 1000**<br>( CI 95% 39 fewer — 78 more ) | **Very low**<br>Due to serious risk of bias and very serious imprecision [16] | We are uncertain whether nitazoxanide increases or decreases clinical recovery (281 events). |
| **Clinical improvement** | Relative risk 1.06<br>(CI 95% 0.97 — 1.15)<br>Based on data from 405 participants in 1 studies. [17]<br>(Randomized controlled) | **823**<br>per 1000<br>Difference: | **872**<br>per 1000<br>**49 more per 1000**<br>( CI 95% 25 fewer — 123 more ) | **Low**<br>Due to very serious imprecision [18] | Nitazoxanide may improve clinical improvement slightly. |

1. Systematic review [20] with included studies: Rossignol 2021, RoccoPRM 2021, Rocco 2022.
2. **Risk of Bias: serious. Imprecision: serious.** Wide confidence intervals.
3. Systematic review [20] with included studies: RoccoPRM 2021, Rocco 2022, Rossignol 2021.
4, 8. **Risk of Bias: serious. Imprecision: serious.** due to few events.
5, 9, 17. Systematic review [20] with included studies: Rocco 2022.
6, 10, 18. **Imprecision: very serious.** Wide confidence intervals, Only data from one study.
7. Systematic review [20] with included studies: RoccoPRM 2021, Blum 2021, Rocco 2022, Rossignol 2021, Silva 2021.
11. Systematic review [29] with included studies: RoccoPRM 2021.
12. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting. **Imprecision: very serious.** Low number of patients, Only data from one study, Wide confidence intervals.
13, 14. Systematic review [19] with included studies: Rossignol 2021.
15. Systematic review [21] with included studies: Rocoo 2022, RoccoPRM 2021.
16. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting. **Imprecision: very serious.** Low number of patients, Only data from one study.

### References

18. Silva M, Espejo A, Pereyra M. Efficacy of nitazoxanide in reducing the viral load in COVID-19 patients. medRxiv 2021. Journal Website

19. [Nitazoxanide] for [COVID-19].

20. [Nitazoxanide] for [COVID-19].

21. [Nitazoxanide] for [COVID-19].

23. Rocco PRM, Silva PL, Cruz FF, Tierno PFGMM, Rabello E, Junior JC, et al. Nitazoxanide in patients hospitalized with COVID-19 pneumonia: A multicentre, randomized, double-blind, placebo-controlled trial. Frontiers in Medicine 2022;9:844728 Pubmed Journal

24. Rossignol J-F, Bardin MC, Fulgencio J, Mogelnicki D, Bréchot C. A randomized double-blind placebo-controlled clinical trial of nitazoxanide for treatment of mild or moderate COVID-19. EClinicalMedicine 2022;45:101310 Pubmed Journal

25. Rocco PRM, Silva PL, Cruz FF, Junior MACM, Tierno PFGMM, Moura MA, et al. Early use of nitazoxanide in mild Covid-19 disease: randomised, placebo-controlled trial. European Respiratory Journal 2021. Pubmed Journal

29. [Nitazoxanide] for [COVID-19].

34. Blum VF, Cimerman S, Hunter JR, Tierno P, Lacerda A, Soeiro A, et al. Nitazoxanide superiority to placebo to treat moderate COVID-19 - A Pilot prove of concept randomized double-blind clinical trial. EClinicalMedicine 2021;37:100981 Pubmed Journal

## 2.4 Antihypertensives

### 2.4.1 Telmisartan

Only in research settings

Do not use telmisartan for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Telmisartan should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use telmisartan to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

**Evidence to decision**

**Benefits and harms**

**General adult population**
Although there are no significant harms associated with telmisartan, there is uncertainty around the benefits and harms for patients with COVID-19.

**Certainty of the evidence**

Low

**General adult population**
Certainty of the evidence is low for all outcomes due to serious imprecision (low patient numbers and the reliance on a single study).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

**General adult population**
There is currently limited evidence about the impact of telmisartan on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that telmisartan should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of telmisartan for the treatment of COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Special populations with COVID-19
**Intervention:** Telmisartan
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether telmisartan is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from a single randomised trial that compared telmisartan with standard care in 78 adults hospitalised with confirmed COVID-19 *[36]*.

**Publication status**
The study is only available as a preprint paper (posted to medRxiv on 13 August 2020) and has therefore not been peer reviewed.

**Study characteristics**
Median age of participants was 62 years and 38% were women. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
For the outcomes of death, invasive mechanical ventilation and admission to intensive care, there were too few events (six deaths, four who required invasive ventilation and nine who were admitted to intensive care unit) to determine whether telmisartan makes a difference. Telmisartan may increase the likelihood of patients being discharged from hospital and may reduce the time to discharge. No adverse events related to telmisartan were reported.

**Our confidence in the results**
Certainty of the evidence is very low for all outcomes due to very serious imprecision (low patient numbers and reliance on a single study) and serious indirectness (limited inclusion of these populations).

**Additional information**

According to the Therapeutic Goods Administration, common adverse effects related to telmisartan use include pain, fatigue, headache and upper respiratory tract infections. However, the incidence of these adverse effects was equivalent in patients receiving placebo *[37]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Telmisartan | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>15 days after commencing treatment<br><br>9 Critical | Relative risk 0.95<br>(CI 95% 0.14 — 6.41)<br>Based on data from 78 participants in 1 studies. [1]<br>(Randomized controlled) | **53**<br>per 1000<br><br>Difference: | **50**<br>per 1000<br><br>**3 fewer per 1000**<br>( CI 95% 46 fewer — 287 more ) | **Very low**<br>Due to very serious imprecision and serious indirectness [2] | There were too few who had died by day 15 to determine whether telmisartan makes a difference (4 events). |
| **All-cause mortality**<br>30 days after commencing treatment<br><br>9 Critical | Relative risk 0.48<br>(CI 95% 0.09 — 2.44)<br>Based on data from 78 participants in 1 studies. [3]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision and serious indirectness [4] | There were too few who had died by day 30 to determine whether telmisartan makes a difference (6 events). |
| **Mechanical ventilation**<br>15 days after commencing treatment<br><br>9 Critical | Relative risk 0.32<br>(CI 95% 0.03 — 2.91)<br>Based on data from 78 participants in 1 studies. [5]<br>(Randomized controlled) | **79**<br>per 1000<br><br>Difference: | **25**<br>per 1000<br><br>**54 fewer per 1000**<br>( CI 95% 77 fewer — 151 more ) | **Very low**<br>Due to very serious imprecision and serious indirectness [6] | There were too few who required mechanical ventilation at day 15 to determine whether telmisartan makes a difference (4 events). |
| **Mechanical ventilation**<br>30 days after commencing treatment<br><br>9 Critical | Relative risk 0.32<br>(CI 95% 0.03 — 2.91)<br>Based on data from 78 participants in 1 studies. [7]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision and serious indirectness [8] | There were too few who required mechanical ventilation at day 30 to determine whether telmisartan makes a difference (4 events). |
| **ICU admission**<br>30 days after commencing treatment<br><br>6 Important | Relative risk 0.76<br>(CI 95% 0.22 — 2.62)<br>Based on data from 78 participants in 1 studies. [9]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision and serious indirectness [10] | There were too few who were admitted to intensive care to determine whether telmisartan makes a difference (9 events). |
| **Discharge from hospital** | Relative risk 1.43<br>(CI 95% 1.01 — 2.02) | | | **Very low**<br>Due to very serious | We are uncertain whether telmisartan may increase |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Telmisartan | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| 15 days after commencing treatment<br><br>6 Important | Based on data from 68 participants in 1 studies. [11] (Randomized controlled) | | | imprecision and serious indirectness [12] | discharge from hospital (47 events). |
| **Time to discharge from hospital**<br>Days<br><br>6 Important | Based on data from 78 participants in 1 studies. [13] (Randomized controlled) | **15**<br>(Median) | **9**<br>(Median)<br><br>CI 95% | **Very low**<br>Due to very serious imprecision and serious indirectness [14] | We are uncertain whether telmisartan decreases time to discharge from hospital. |

1, 3, 5, 7, 9, 11. Systematic review [40] with included studies: Duarte 2020.
2, 4, 6, 8, 10, 12, 14. **Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: very serious.** Low number of patients, Only data from one study.
13. Systematic review [40]

### References

36. Duarte M, Pelorosso F, Nicolosi L. Telmisartan for treatment of Covid-19 patients: an open randomized clinical trial. Preliminary report. medRxiv 2020. Journal Website

37. Therapeutic Goods Administration. Australian Product Information: Alkem Telmisartan (telmisartan). 27 March 2020. Website

40. Telmisartan for COVID-19.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Telmisartan
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether telmisartan is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from a single randomised trial that compared telmisartan with standard care in 78 adults hospitalised with confirmed COVID-19 *[36]*.

**Publication status**
The study is only available as a preprint paper (posted to medRxiv on 13 August 2020) and has therefore not been peer reviewed.

**Study characteristics**
Median age of participants was 62 years and 38% were women. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
For the outcomes of death, invasive mechanical ventilation and admission to intensive care, there were too few events (six deaths, four who

required invasive ventilation and nine who were admitted to intensive care unit) to determine whether telmisartan makes a difference. Telmisartan may increase the likelihood of patients being discharged from hospital and may reduce the time to discharge. No adverse events related to telmisartan were reported.

**Our confidence in the results**
Certainty of the evidence is low for all outcomes due to very serious imprecision (low patient numbers and reliance on a single study).

**Additional information**
According to the Therapeutic Goods Administration, common adverse effects related to telmisartan use include pain, fatigue, headache and upper respiratory tract infections. However, the incidence of these adverse effects was equivalent in patients receiving placebo *[37]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Telmisartan | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>15 days after commencing treatment<br><br>9 Critical | Relative risk 0.95<br>(CI 95% 0.14 — 6.41)<br>Based on data from 78 participants in 1 studies. [1]<br>(Randomized controlled) | **53**<br>per 1000<br><br>Difference: | **50**<br>per 1000<br><br>**3 fewer per 1000**<br>( CI 95% 46 fewer — 287 more ) | **Low**<br>Due to very serious imprecision [2] | There were too few who had died by day 15 to determine whether telmisartan makes a difference (4 events). |
| **All-cause mortality**<br>30 days after commencing treatment<br><br>9 Critical | Relative risk 0.48<br>(CI 95% 0.09 — 2.44)<br>Based on data from 78 participants in 1 studies. [3]<br>(Randomized controlled) | **105**<br>per 1000<br><br>Difference: | **50**<br>per 1000<br><br>**55 fewer per 1000**<br>( CI 95% 96 fewer — 151 more ) | **Low**<br>Due to very serious imprecision [4] | There were too few who had died by day 30 to determine whether telmisartan makes a difference (6 events). |
| **Invasive mechanical ventilation**<br>15 days after commencing treatment<br><br>9 Critical | Relative risk 0.32<br>(CI 95% 0.03 — 2.91)<br>Based on data from 78 participants in 1 studies. [5]<br>(Randomized controlled) | **79**<br>per 1000<br><br>Difference: | **25**<br>per 1000<br><br>**54 fewer per 1000**<br>( CI 95% 77 fewer — 151 more ) | **Low**<br>Due to very serious imprecision [6] | There were too few who required mechanical ventilation at day 15 to determine whether telmisartan makes a difference (4 events). |
| **Invasive mechanical ventilation**<br>30 days after commencing treatment<br><br>9 Critical | Relative risk 0.32<br>(CI 95% 0.03 — 2.91)<br>Based on data from 78 participants in 1 studies. [7]<br>(Randomized controlled) | **79**<br>per 1000<br><br>Difference: | **25**<br>per 1000<br><br>**54 fewer per 1000**<br>( CI 95% 77 fewer — 151 more ) | **Low**<br>Due to very serious imprecision [8] | There were too few who required invasive mechanical ventilation at day 30 to determine whether telmisartan makes a difference (4 events). |
| **ICU admission** | Relative risk 0.76 | **132** | **100** | **Low** | There were too few who |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Telmisartan | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| 30 days after commencing treatment<br><br>6 Important | (CI 95% 0.22 — 2.62)<br>Based on data from 78 participants in 1 studies. [9]<br>(Randomized controlled) | per 1000<br><br>Difference: | per 1000<br><br>**32 fewer per 1000**<br>( CI 95% 103 fewer — 214 more ) | Due to very serious imprecision [10] | were admitted to intensive care to determine whether telmisartan makes a difference (9 events). |
| **Discharge from hospital**<br>15 days after commencing treatment<br><br>6 Important | Relative risk 1.43<br>(CI 95% 1.01 — 2.02)<br>Based on data from 68 participants in 1 studies. [11]<br>(Randomized controlled) | **563**<br>per 1000<br><br>Difference: | **805**<br>per 1000<br><br>**242 more per 1000**<br>( CI 95% 6 more — 574 more ) | **Low**<br>Due to very serious imprecision [12] | Telmisartan may increase discharge from hospital (47 events). |
| **Time to discharge from hospital**<br>Days<br><br>6 Important | Based on data from 78 participants in 1 studies. [13]<br>(Randomized controlled) | **15**<br>(Median) | **9**<br>(Median)<br><br>CI 95% | **Low**<br>Due to very serious imprecision [14] | Telmisartan may decrease time to discharge from hospital. |

1, 3, 5, 7, 9, 11. Systematic review [40] with included studies: Duarte 2020.
2, 4, 6, 8, 10, 12, 14. **Imprecision: very serious.** Low number of patients, Only data from one study.
13. Systematic review [40]

**References**

36. Duarte M, Pelorosso F, Nicolosi L. Telmisartan for treatment of Covid-19 patients: an open randomized clinical trial. Preliminary report. medRxiv 2020. Journal Website

37. Therapeutic Goods Administration. Australian Product Information: Alkem Telmisartan (telmisartan). 27 March 2020. Website

40. Telmisartan for COVID-19.

## 2.5 Antithrombotic, antiplatelets and related therapies

### 2.5.1 Sulodexide

Only in research settings

Do not use sulodexide for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Sulodexide should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use sulodexide to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

## Evidence to decision

**Benefits and harms**

There is uncertainty around the benefits and harms associated with the use of sulodexide in patients with COVID-19. As of 16 February 2021, sulodexide is not approved for use in Australia.

**Certainty of the evidence**

Low

Certainty of the evidence is low for all outcomes due to very serious imprecision (reliance on a single study, wide confidence intervals and few events for the outcomes of death, invasive mechanical ventilation and discontinuation due to adverse events).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

## Rationale

**General adult population**
There is currently limited evidence about the impact of sulodexide on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that sulodexide should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of sulodexide for the treatment of COVID-19 in these populations should be avoided until evidence becomes available.

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### Clinical question/ PICO

**Population:** Sulodexide for COVID-19
**Intervention:** Sulodexide
**Comparator:** Placebo

### Summary

There remains significant uncertainty whether sulodexide is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial that compared sulodexide with placebo in 243 adult outpatients with mild COVID-19, who were at high risk of severe clinical progression due to chronic comorbidities *[26]*.

**Study characteristics**
Mean age of participants was 55 years and the proportion of women was 53%. Of note, the minimum age at enrolment was 40 years. Patients received either sulodexide 500 mg twice daily (4 x 250 mg capsules) or placebo equivalent for 3 weeks. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
It is unclear whether sulodexide increases or decreases incidence of death, requirement of invasive mechanical ventilation, supplemental oxygen or duration of supplemental oxygen, number of patients who require hospitalisation and duration of hospitalisation, adverse events, or number of patients who discontinued due to adverse events.

**Our confidence in the results**
Certainty of the evidence is low for all outcomes due to very serious imprecision (reliance on a single study, wide confidence intervals and few events for the outcomes of death, invasive mechanical ventilation and discontinuation due to adverse events).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
As the safety profile for sulodexide is incompletely characterised in humans, there is uncertainty around the benefits and harms for patients with COVID-19. As of 16 February 2021, sulodexide is not approved for use in Australia.

There are additional concerns regarding harms, as sulodexide has not been sufficiently tested in **pregnant and breastfeeding women**.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Sulodexide | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 21 days of commencing treatment<br><br>9 Critical | Relative risk 0.41<br>(CI 95% 0.11 — 1.55)<br>Based on data from 243 participants in 1 studies. [1]<br>(Randomized controlled) | 59<br>per 1000<br><br>Difference: | 24<br>per 1000<br><br>**35 fewer per 1000**<br>( CI 95% 53 fewer — 32 more ) | **Very low**<br>Due to very serious imprecision and serious risk of bias [2] | We are uncertain whether sulodexide impacts death (10 events). |
| **Invasive mechanical ventilation**<br>Within 21 days of commencing | Relative risk 0.48<br>(CI 95% 0.12 — 1.87)<br>Based on data from 243 participants in 1 studies. [3]<br>(Randomized controlled) | 50<br>per 1000<br><br>Difference: | 24<br>per 1000<br><br>**26 fewer per 1000** | **Very low**<br>Due to very serious imprecision and serious risk of bias [4] | We are uncertain whether sulodexide increases or decreases need for invasive mechanical ventilation (9 events). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Sulodexide | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| treatment<br><br>9 Critical | | | ( CI 95% 44 fewer — 44 more ) | | |
| **Supplemental oxygen**<br>Within 21 days of commencing treatment<br><br>6 Important | Relative risk 0.71<br>(CI 95% 0.5 — 1)<br>Based on data from 243 participants in 1 studies. [5]<br>(Randomized controlled) | **420**<br>per 1000<br><br>Difference: | **298**<br>per 1000<br><br>**122 fewer per 1000**<br>( CI 95% 210 fewer — 0 fewer ) | **Very low**<br>Due to very serious imprecision and serious risk of bias [6] | We are uncertain whether sulodexide increases or decreases need for supplemental oxygen (87 events). |
| **Hospitalisation**<br>Within 21 days of commencing treatment<br><br>6 Important | Relative risk 0.6<br>(CI 95% 0.38 — 0.97)<br>Based on data from 243 participants in 1 studies. [7]<br>(Randomized controlled) | **294**<br>per 1000<br><br>Difference: | **176**<br>per 1000<br><br>**118 fewer per 1000**<br>( CI 95% 182 fewer — 9 fewer ) | **Very low**<br>Due to very serious imprecision and serious risk of bias [8] | We are uncertain whether sulodexide increases or decreases need for hospitalisation (57 events) |
| **Adverse events**<br>Within 21 days of commencing treatment<br><br>6 Important | Relative risk 1.08<br>(CI 95% 0.93 — 1.26)<br>Based on data from 243 participants in 1 studies. [9]<br>(Randomized controlled) | **714**<br>per 1000<br><br>Difference: | **771**<br>per 1000<br><br>**57 more per 1000**<br>( CI 95% 50 fewer — 186 more ) | **Very low**<br>Due to very serious imprecision and serious risk of bias [10] | We are uncertain whether sulodexide increases or decreases adverse events (181 events). |
| **Discontinuation due to adverse events**<br>Within 21 days of commencing treatment<br><br>6 Important | Relative risk 1.28<br>(CI 95% 0.46 — 3.58)<br>Based on data from 243 participants in 1 studies. [11]<br>(Randomized controlled) | **50**<br>per 1000<br><br>Difference: | **64**<br>per 1000<br><br>**14 more per 1000**<br>( CI 95% 27 fewer — 129 more ) | **Very low**<br>Due to very serious imprecision and serious risk of bias [12] | We are uncertain whether sulodexide increases or decreases discontinuation due to adverse events (14 events). |
| **Duration of supplemental oxygen**<br>Days<br><br>6 Important | Based on data from 243 participants in 1 studies. [13]<br>(Randomized controlled) | **11.5**<br>(Mean)<br><br>Difference: | **9**<br>(Mean)<br><br>**MD 2.5 lower**<br>( CI 95% 4.64 lower — 0.36 lower ) | **Very low**<br>Due to very serious imprecision and serious risk of bias [14] | We are uncertain whether sulodexide increases or decreases duration of supplemental oxygen. |
| **Duration of hospitalisation**<br>Days | Based on data from 243 participants in 1 studies. [15] | **7.8**<br>(Mean)<br><br>Difference: | **6.2**<br>(Mean) | **Very low**<br>Due to very serious imprecision and serious risk of bias | We are uncertain whether sulodexide increases or decreases duration of hospitalisation. |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Placebo | **Intervention** Sulodexide | **Certainty of the evidence** (Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| 6 Important | (Randomized controlled) | | **MD 1.6 lower** ( CI 95% 2.68 lower — 0.52 lower ) | 16 | |

1, 3, 5, 7, 9, 11, 13, 15. Systematic review [27] with included studies: Gonzalez Ochoa 2020.
2, 4. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up. **Imprecision: very serious.** Wide confidence intervals, Only data from one study, due to few events.
6. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up. **Imprecision: very serious.** Only data from one study, Low number of patients.
8, 10, 12, 14, 16. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up. **Imprecision: very serious.** Wide confidence intervals, Only data from one study.

### References

26. Gonzalez Ochoa AJ, Raffetto J, Hernandez Ibarra AG, Zavala N, Gutierrez O, Vargas A, et al. Sulodexide in the treatment of patients with early stages of COVID-19: a randomized controlled trial. Thrombosis and Haemostasis 2021. Pubmed Journal

27. Sulodexide for COVID-19.

## 2.6 Antivirals

### 2.6.1 Baloxavir marboxil

Only in research settings

Do not use baloxavir marboxil for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Baloxavir marboxil should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use baloxavir marboxil to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### Evidence to decision

**Benefits and harms**

**General adult population**
In addition to uncertainty around benefits for patients with COVID-19, there are well-known side effects and harms associated with baloxavir marboxil, including diarrhoea, bronchitis, nausea, sinusitis and headache.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There are additional concerns regarding harms as baloxavir marboxil has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

**Certainty of the evidence**

Very low

**General adult population**
Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias due to lack of blinding, and very serious imprecision due to the low number of patients and/or observed events and the reliance on a single study.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of baloxavir marboxil in pregnancy are unknown.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

**General adult population**
There is currently limited evidence about the impact of baloxavir marboxil on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that baloxavir marboxil should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of baloxavir marboxil to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Baloxavir marboxil
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether baloxavir marboxil is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial that compared baloxavir marboxil with standard care in 20 adults hospitalised with COVID-19 *[32]*.

**Study characteristics**
Mean age of participants was 50 years and 30% were women. It is unclear whether pregnant and breastfeeding women were eligible. Patients concomitantly used lopinavir-ritonavir, darunavir-cobicistat and/or arbidol.

**What are the main results?**
For the critical outcomes of death and mechanical invasive ventilation there were too few events (one death and one requiring ventilation) to determine whether baloxavir marboxil makes a difference. We are uncertain whether baloxavir marboxil increases or decreases respiratory support or likelihood of clinical improvement after 14 days. No data were reported on adverse or serious adverse events.

**Our confidence in the results**
Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias due to lack of blinding and very serious imprecision due to low patient numbers, few observed events and reliance on a single study.

**Additional information**
The Therapeutic Goods Administration highlights several mild side effects associated with baloxavir marboxil, including diarrhoea, bronchitis, nausea, sinusitis and headache. In addition, post-marketing surveillance has identified cases of anaphylactic reactions, angioedema, vomiting and other gastrointestinal and skin/subcutaneous tissue disorders *[28]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Baloxavir marboxil | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Mortality**<br>During treatment (14 days)<br>9 Critical | Based on data from 20 participants in 1 studies. [1] | | | | There were no deaths in the study. |
| **Respiratory support and ARDS**<br>During treatment (14 days)<br>9 Critical | Odds ratio 2.25<br>(CI 95% 0.38 — 13.47)<br>Based on data from 20 participants in 1 studies. [2]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [3] | We are uncertain whether baloxavir marboxil increases or decreases respiratory support and ARDS (10 events). |
| **Invasive mechanical ventilation or ECMO**<br>During treatment (14 days)<br>9 Critical | Odds ratio 3.32<br>(CI 95% 0.12 — 91.6)<br>Based on data from 20 participants in 1 studies. [4]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [5] | There were too few who required invasive mechanical ventilation or ECMO to determine whether baloxavir marboxil makes a difference (1 event). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Baloxavir marboxil | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Serious adverse events**<br>During treatment (14 days)<br>9 Critical | 6 | | | | Data for number of patients experiencing one or more events were not reported. |
| **Adverse events**<br>During treatment (14 days)<br>6 Important | 7 | | | | Data for number of patients experiencing one or more events were not reported. |
| **Clinical improvement**<br>End of treatment (14 days)<br>6 Important | Odds ratio 1.5<br>(CI 95% 0.26 — 8.82)<br>Based on data from 20 participants in 1 studies. [8]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [9] | We are uncertain whether baloxavir marboxil increases or decreases clinical improvement (11 events). |

1, 2, 4, 8. Systematic review [30] with included studies: Lou 2020.
3, 5, 9. **Risk of Bias: serious. Imprecision: very serious.** Low number of patients, Only data from one study.
6, 7. Systematic review [30] with included studies: [31].

### References

28. Therapeutic Goods Administration. Australian Product Information: Xofluza (baloxavir marboxil) tablets. 2020. Website

30. Baloxavir Marboxil for COVID-19.

31. Lou Y, Yao H, Hu Z. Clinical outcomes and plasma concentrations of baloxavir marboxil and favipiravir in COVID-19 patients: an exploratory randomized, controlled trial. medRxiv 2020. Journal Website

32. Lou Y, Liu L, Yao H, Hu X, Su J, Xu K, et al. Clinical outcomes and plasma concentrations of baloxavir marboxil and favipiravir in COVID-19 patients: an exploratory randomized, controlled trial. European Journal of Pharmaceutical Sciences 2020;105631 Pubmed Journal

### Clinical question/ PICO

**Population:** Special populations with COVID-19
**Intervention:** Baloxavir marboxil
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether baloxavir marboxil is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial that compared baloxavir marboxil with standard care in 20 adults hospitalised with COVID-19 *[32]*.

**Study characteristics**
Mean age of participants was 50 years and 30% were women. It is unclear whether pregnant and breastfeeding women were eligible. Patients concomitantly used lopinavir-ritonavir, darunavir-cobicistat and/or arbidol.

**What are the main results?**
For the critical outcomes of death and mechanical ventilation there were too few events (one death and one requiring ventilation) to determine whether baloxavir marboxil makes a difference. We are uncertain whether baloxavir marboxil increases or decreases respiratory support or likelihood of clinical improvement after 14 days. No data were reported on adverse or serious adverse events.

**Our confidence in the results**
Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias due to lack of blinding, serious indirectness due to limited inclusion of these populations, and very serious imprecision due to low patient numbers, few observed events and reliance on a single study.

**Additional information**
The Therapeutic Goods Administration highlights several mild side effects associated with baloxavir marboxil, including diarrhoea, bronchitis, nausea, sinusitis and headache. In addition, post-marketing surveillance has identified cases of anaphylactic reactions, angioedema, vomiting and other gastrointestinal and skin/subcutaneous tissue disorders *[28]*.

There is insufficient safety data on the use of baloxavir marboxil in **children or adolescents** for other indications.

No studies pertained to the safety of baloxavir marboxil (for any indication) when used in **pregnant or breastfeeding women**.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Baloxavir marboxil | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Mortality**<br>During treatment (14 days)<br>9 Critical | Based on data from 20 participants in 1 studies. [1] | | | | There were no deaths in the study. |
| **Respiratory support and ARDS**<br>During treatment (14 days)<br>9 Critical | Odds ratio 2.25<br>(CI 95% 0.38 — 13.47)<br>Based on data from 20 participants in 1 studies. [2]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias, serious indirectness and very serious imprecision [3] | We are uncertain whether baloxavir marboxil increases or decreases respiratory support and ARDS (10 events). |
| **Invasive mechanical ventilation or ECMO**<br>During treatment (14 days)<br>9 Critical | Odds ratio 3.32<br>(CI 95% 0.12 — 91.6)<br>Based on data from 20 participants in 1 studies. [4]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias, serious indirectness and very serious imprecision [5] | There were too few who required mechanical ventilation or ECMO (1 event) to determine whether baloxavir marboxil makes a difference. |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Baloxavir marboxil | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Serious adverse events**<br>During treatment (14 days)<br>9 Critical | 6 | | | | Data for number of patients experiencing one or more events were not reported. |
| **Adverse events**<br>During treatment (14 days)<br>6 Important | 7 | | | | Data for number of patients experiencing one or more events were not reported. |
| **Clinical improvement**<br>End of treatment (14 days)<br>6 Important | Odds ratio 1.5<br>(CI 95% 0.26 — 8.82)<br>Based on data from 20 participants in 1 studies. [8]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias, serious indirectness and very serious imprecision [9] | We are uncertain whether baloxavir marboxil increases or decreases clinical improvement (11 events). |

1, 2, 4, 8. Systematic review [30] with included studies: Lou 2020.
3, 5, 9. **Risk of Bias: serious. Indirectness: serious. Imprecision: very serious.** Low number of patients, Only data from one study.
6, 7. Systematic review [30] with included studies: [31].

### References

28. Therapeutic Goods Administration. Australian Product Information: Xofluza (baloxavir marboxil) tablets. 2020. Website

30. Baloxavir Marboxil for COVID-19.

31. Lou Y, Yao H, Hu Z. Clinical outcomes and plasma concentrations of baloxavir marboxil and favipiravir in COVID-19 patients: an exploratory randomized, controlled trial. medRxiv 2020. Journal Website

32. Lou Y, Liu L, Yao H, Hu X, Su J, Xu K, et al. Clinical outcomes and plasma concentrations of baloxavir marboxil and favipiravir in COVID-19 patients: an exploratory randomized, controlled trial. European Journal of Pharmaceutical Sciences 2020;105631 Pubmed Journal

## 2.6.2 Darunavir-cobicistat

Only in research settings

Do not use darunavir-cobicistat for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Darunavir-cobicistat should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use darunavir-cobicistat to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### Evidence to decision

**Benefits and harms**

Important harms

**General adult population**
In addition to uncertainty around benefits for patients with COVID-19, there are well-known short-term harms associated with darunavir-cobicistat including severe skin reactions. There are several known and potential interactions with drugs that inhibit CYP3A4 and anti-arrhythmic drugs.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
The benefits and harms associated with darunavir-cobicistat in pregnant women and young children with COVID-19 are not well established. Darunavir plus cobicistat is not recommended for the treatment of HIV in pregnant women because of inadequate safety data for cobicistat. Caution should be taken when prescribing darunavir-cobicistat to children, adolescents or elderly patients.

**Certainty of the evidence**

Very low

**General adult population**
Certainty of the evidence for each outcome is very low due to serious risk of bias and very serious imprecision (low number of patients and/or observed events and reliance on a single study).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values.The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values

for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of darunavir-cobicistat in pregnancy are unknown.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

**General adult population**
There is currently limited evidence about the impact of darunavir-cobicistat on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that darunavir-cobicistat should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of darunavir-cobicistat to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Special populations with COVID-19
**Intervention:** Darunavir-cobicistat
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether darunavir-cobicistat is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from a single randomised trial that compared darunavir-cobicistat with standard care in 30 adults hospitalised with mild-to-moderate symptoms of laboratory-confirmed COVID-19 *[33]*.

**Study characteristics**
Mean age was 47 years and 40% were women. Patients considered unlikely to complete the study (e.g. severely or critically ill) or deemed not suitable by the investigators were excluded. It is unlikely that pregnant and breastfeeding women were eligible.

**What are the main results?**
There were no deaths and only one patient progressed to critical illness. We are uncertain whether darunavir-cobicistat makes a difference to viral clearance (days 3, 5 or 7) or to the likelihood of patients experiencing adverse events.

**Our confidence in the results**
Certainty of the evidence for viral clearance and adverse events is very low. This judgement is based on very serious imprecision (low patient numbers, few observed events and reliance on a single study), serious indirectness (limited inclusion of these populations) and serious risk of bias (patients, personnel and outcome assessors not blinded).

**Additional information**
Paediatricians have limited experience of darunavir-cobicistat in **children and adolescents** for other indications. To date, no specific information on its benefits or harms for children and adolescents has been collected for treating COVID-19 in this population.

Darunavir plus cobicistat is not recommended for the treatment of HIV in **pregnant wome**n because of inadequate safety data for cobicistat *[35]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Darunavir-cobicistat | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>14 days after commencing treatment<br>9 Critical | Based on data from 30 participants in 1 studies. [1]<br>(Randomized controlled) | | | 2 | There were no deaths in the study. |
| **Progression to critical illness**<br>14 days after commencing treatment<br>9 Critical | Based on data from 30 participants in 1 studies. [3]<br>(Randomized controlled) | | | 4 | There were too few who experienced progression to critical illness to determine whether darunavir-cobicistat makes a difference (1 event). |
| **Adverse events**<br>Within 14 days of commencing treatment<br>6 Important | Odds ratio 1.31<br>(CI 95% 0.31 — 5.48)<br>Based on data from 30 participants in 1 studies. [5]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias, serious indirectness and very serious imprecision [6] | We are uncertain whether darunavir-cobicistat increases or decreases adverse events within 14 days (15 events). |
| **Viral clearance**<br>Day 7 of treatment<br>6 Important | Relative risk 0.78<br>(CI 95% 0.39 — 1.54)<br>Based on data from 30 participants in 1 studies. [7]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias, serious indirectness and very serious imprecision [8] | We are uncertain whether darunavir-cobicistat increases or decreases viral clearance at day 7 (16 events). |
| **Viral clearance**<br>Day 5 of treatment<br>6 Important | Odds ratio 1.45<br>(CI 95% 0.26 — 8.01)<br>Based on data from 30 participants in 1 studies. [9]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias, serious indirectness and very serious imprecision [10] | We are uncertain whether darunavir-cobicistat increases or decreases viral clearance at day 5 (5 events). |
| **Viral clearance**<br>Day 3 of treatment<br>6 Important | Odds ratio 1<br>(CI 95% 0.17 — 5.98)<br>Based on data from 30 participants in 1 studies. [11]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias, serious indirectness and very serious imprecision [12] | We are uncertain whether darunavir-cobicistat increases or decreases viral clearance at day 3 (6 events). |

1, 3, 7, 9, 11. Systematic review [38] with included studies: Chen J 2020.

2. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: no serious. Indirectness: serious. Imprecision: very serious.** Low number of patients, Only data from one study, due to no events. **Publication bias: no serious.**

4, 6, 10, 12. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias.

**Inconsistency: no serious. Indirectness: serious. Imprecision: very serious.** Low number of patients, Only data from one study. **Publication bias: no serious.**
5. [33].
8. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: no serious. Indirectness: serious. Imprecision: very serious.** Low number of patients, Only data from one study.

### References

33. Chen J, Xia LU, Liu LI, Xu Q, Ling Y, Huang D, et al. Antiviral activity and safety of darunavir/cobicistat for the treatment of COVID-19. Open Forum Infectious Diseases 2020;7(7):ofaa241 Pubmed Journal

35. Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. 2020. Website

38. Darunavir/Cobicistat for COVID-19.

### Clinical question/ PICO

**Population:** Darunavir-cobicistat for COVID-19
**Intervention:** Darunavir-cobicistat
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether darunavir-cobicistat is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from a single randomised trial that compared darunavir-cobicistat with standard care in 30 adults hospitalised with mild-to-moderate symptoms of laboratory-confirmed COVID-19 *[33]*.

**Study characteristics**
Mean age was 47 years and 40% were women. Patients considered unlikely to complete the study (e.g. severely or critically ill) or deemed not suitable by the investigators were excluded. It is unlikely that pregnant and breastfeeding women were eligible.

**What are the main results?**
There were no deaths and only one patient progressed to critical illness. We are uncertain whether darunavir-cobicistat makes a difference to viral clearance (days 3, 5 or 7) or to the likelihood of patients experiencing adverse events.

**Our confidence in the results**
Certainty of the evidence for viral clearance and adverse events is very low. This judgement is based on very serious imprecision (low patient numbers, few observed events and reliance on a single study) and serious risk of bias (patients, personnel and outcome assessors not blinded).

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Darunavir-cobicistat | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>14 days after commencing treatment<br><br>9 Critical | Based on data from 30 participants in 1 studies. [1]<br>(Randomized controlled) | | | 2 | There were no deaths in the study. |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Darunavir-cobicistat | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Progression to critical illness**<br>14 days after commencing treatment<br>9 Critical | Based on data from 30 participants in 1 studies. [3]<br>(Randomized controlled) | | | [4] | There were too few who experienced progression to critical illness to determine whether darunavir-cobicistat makes a difference (1 event). |
| **Adverse events**<br>Within 14 days of commencing treatment<br>6 Important | Odds ratio 1.31<br>(CI 95% 0.31 — 5.48)<br>Based on data from 30 participants in 1 studies. [5]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [6] | We are uncertain whether darunavir-cobicistat increases or decreases adverse events within 14 days (15 events). |
| **Viral clearance**<br>Day 7 of treatment<br>6 Important | Relative risk 0.78<br>(CI 95% 0.39 — 1.54)<br>Based on data from 30 participants in 1 studies. [7]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [8] | We are uncertain whether darunavir-cobicistat increases or decreases viral clearance at day 7 (16 events). |
| **Viral clearance**<br>Day 5 of treatment<br>6 Important | Odds ratio 1.45<br>(CI 95% 0.26 — 8.01)<br>Based on data from 30 participants in 1 studies. [9]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [10] | We are uncertain whether darunavir-cobicistat increases or decreases viral clearance at day 5 (5 events). |
| **Viral clearance**<br>Day 3 of treatment<br>6 Important | Odds ratio 1<br>(CI 95% 0.17 — 5.98)<br>Based on data from 30 participants in 1 studies. [11]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [12] | We are uncertain whether darunavir-cobicistat increases or decreases viral clearance at day 3 (6 events). |

1, 3, 7, 9, 11. Systematic review [38] with included studies: Chen J 2020.
2. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Low number of patients, Only data from one study, due to no events. **Publication bias: no serious.**
4, 6, 10, 12. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Low number of patients, Only data from one study. **Publication bias: no serious.**
5. [33].
8. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Low number of patients, Only data from one study.

## References

33. Chen J, Xia LU, Liu LI, Xu Q, Ling Y, Huang D, et al. Antiviral activity and safety of darunavir/cobicistat for the treatment of COVID-19. Open Forum Infectious Diseases 2020;7(7):ofaa241 Pubmed Journal

35. Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission. 2020. Website

38. Darunavir/Cobicistat for COVID-19.

## 2.6.3 Enisamium

Only in research settings

Do not use enisamium for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Enisamium should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use enisamium to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### Evidence to decision

**Benefits and harms**

**General adult population**
As the safety profile for enisamium is incompletely characterised in humans, there is uncertainty around the benefits and harms for patients with COVID-19.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There are additional concerns regarding harms as enisamium has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

**Certainty of the evidence**

Very low

**General adult population**
Certainty of the evidence is very low for time to recovery due to very serious risk of bias (issues with randomisation, blinding and loss to follow-up) and serious imprecision (reliance on a single study, wide confidence intervals and few events).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of enisamium in pregnancy are unknown.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

## Rationale

**General adult population**
There is currently limited evidence about the impact of enisamium on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that enisamium should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of enisamium to treat COVID-19 in these populations should be avoided until evidence becomes available.

## Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Enisamium
**Comparator:** Placebo

## Summary

There remains significant uncertainty whether enisamium is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial that compared enisamium with standard care in 373 adults with moderate COVID-19 *[39]*.

**Publication status**
The included study is only available as a preprint (posted to medRxiv on 21 January 2021) and has therefore not been peer reviewed.

**Study characteristics**
Median age of participants was not reported, nor was the proportion of female patients. Patients received either 500 mg enisamium iodide or matching placebo 4 times daily every 6 hours for 7 days. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
The study primarily focused on pharmacokinetic analyses and the only reported clinical outcome of relevance was time to recovery, in which we are uncertain whether enisamium makes a difference.

**Our confidence in the results**
Certainty of the evidence is very low for time to recovery due to very serious risk of bias (issues with randomisation, blinding and loss to follow-up) and serious imprecision (reliance on a single study, wide confidence intervals and few events).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited

inclusion of these populations in the included studies).

**Additional information**
Enisamium is not approved for use in Australia and, as of 16 March 2021, there are no reliable safety data to inform treatment.

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Placebo | **Intervention** Enisamium | **Certainty of the evidence** (Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| Time to recovery<br>Days<br>6 Important | Lower better<br>Based on data from 373 participants in 1 studies.<br>(Randomized controlled) | 13.9<br>(Mean) | 11.1<br>(Mean)<br>CI 95% | Very low<br>Due to very serious risk of bias and serious imprecision [1] | We are uncertain whether enisamium increases or decreases time to recovery. |

1. **Risk of Bias: very serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up. **Imprecision: serious.** Only data from one study.

### References

39. Holubovska O, Bojkova D, Elli S. Enisamium is an inhibitor of the SARS-CoV-2 RNA polymerase and shows improvement of recovery in COVID-19 patients in an interim analysis of a clinical trial. medRxiv 2021. Journal Website

## 2.6.4 Ensovibep

Only in research settings

New

Do not use ensovibep for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use ensovibep to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

## Evidence to decision

**Benefits and harms**

Small net benefit, or little difference between alternatives

Although results demonstrate slightly reduced incidence of death and requirement of mechanical ventilation, and slightly higher incidence of clinical recovery and discharge from hospital, these did not meet the threshold for clinical significance. As a result, we are uncertain whether ensovibep is safer or more effective than placebo in treating patients with moderate to severe COVID-19.

**Certainty of the evidence**

Low

Certainty of the evidence is low for all four outcomes reported (all-cause mortality, invasive mechanical ventilation, clinical recovery and discharge from hospital), due to very serious imprecision (reliance on a single study and wide confidence intervals).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of ensovibep in pregnancy are unknown.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit.

### Rationale

**General adult population**
There is currently limited evidence about the impact of ensovibep on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that ensovibep should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of ensovibep for the treatment of COVID-19 in these populations should be avoided until evidence becomes available.

## Clinical question/ PICO

**Population:** Patients with Covid-19
**Intervention:** Ensovibep
**Comparator:** Placebo

### Summary

There remains uncertainty whether ensovibep is more effective and safer than placebo in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial that compared ensovibep with placebo in 485 adults with moderate to severe COVID-19 *[225]*.

**Study characteristics**
Median age of participants was 56 years and approximately 43% of participants were female. Approximately 60% of participants had one or comorbidities, with almost half having a BMI of over 30 kg/$m^2$. Almost two thirds of participants required either low-flow or high-flow oxygen at baseline, with 20% requiring no oxygen and 20% requiring either high flow nasal oxygenation or non-invasive ventilation. Thirty percent of individuals had received one or more doses of vaccine, and the majority also received concomitant remdesivir (69%) and/or corticosteroids (72%). Pregnant and breastfeeding women were ineligible.

**What are the main results?**
Although results demonstrate slightly reduced incidence of death and requirement of mechanical ventilation, and slightly higher incidence of clinical recovery and discharge from hospital, these did not meet the threshold for clinical significance. As a result, we are uncertain whether ensovibep is safer or more effective than placebo in treating patients with moderate to severe COVID-19.

**Our confidence in the results**
Certainty of the evidence is low for all four outcomes reported (all-cause mortality, invasive mechanical ventilation, clinical recovery and discharge from hospital), due to very serious imprecision (reliance on a single study and wide confidence intervals).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
Ensovibep is an experimental antiviral developed to treat COVID-19 and is currently not approved for use in Australia.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Ensovibep | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 28 days of treatment<br>9 Critical | Relative risk 0.83<br>(CI 95% 0.52 — 1.3)<br>Based on data from 485 participants in 1 studies. [1]<br>(Randomized controlled) | **147**<br>per 1000<br>Difference: | **122**<br>per 1000<br>**25 fewer per 1000**<br>( CI 95% 71 fewer — 44 more ) | **Low**<br>Due to very serious imprecision [2] | Ensovibep may have little impact on death (65 events). |
| **Invasive Mechanical Ventilation**<br>Within 28 days of treatment<br>9 Critical | Relative risk 0.58<br>(CI 95% 0.26 — 1.3)<br>Based on data from 447 participants in 1 studies. [3]<br>(Randomized controlled) | **68**<br>per 1000<br>Difference: | **39**<br>per 1000<br>**29 fewer per 1000**<br>( CI 95% 50 fewer — 20 more ) | **Low**<br>Due to very serious imprecision [4] | Ensovibep may have little impact on invasive mechanical ventilation (24 events). |
| **Clinical Recovery**<br>Within 28 days of treatment<br>6 Important | Relative risk 1.03<br>(CI 95% 0.94 — 1.12)<br>Based on data from 485 participants in 1 studies. [5]<br>(Randomized controlled) | **798**<br>per 1000<br>Difference: | **822**<br>per 1000<br>**24 more per 1000**<br>( CI 95% 48 fewer — 96 more ) | **Low**<br>Due to very serious imprecision [6] | Ensovibep may have little impact on clinical recovery (393 events). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Ensovibep | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Discharge from Hospital**<br>Within 28 days of treatment<br><br>6 Important | Relative risk 1.03<br>(CI 95% 0.97 — 1.11)<br>Based on data from 485 participants in 1 studies. [7]<br>(Randomized controlled) | **857**<br>per 1000<br><br>Difference: | **883**<br>per 1000<br><br>**26 more per 1000**<br>( CI 95% 26 fewer — 94 more ) | **Low**<br>Due to very serious imprecision [8] | Ensovibep may have little impact on discharge from hospital (423 events). |

1, 3, 5, 7. Systematic review [223] with included studies: ACTIV-3/TICO study group, 2022.
2, 4, 6, 8. **Imprecision: very serious.** Wide confidence intervals, Only data from one study.

### References

223. Ensovibep for Covid-19.

## 2.6.5 Sofosbuvir-daclatasvir

Only in research settings

Do not use sofosbuvir-daclatasvir for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Sofosbuvir-daclatasvir should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use sofosbuvir-daclatasvir to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### Evidence to decision

**Benefits and harms**

Important harms

**General adult population**
In addition to uncertainty around benefits for patients with COVID-19, there are well-known side effects and harms associated with sofosbuvir, including fatigue, insomnia, anaemia and irritability, and with daclatasvir, including fatigue, diarrhoea, nausea and headache.

**Certainty of the evidence**

Low

Certainty of the evidence is low for mechanical ventilation, adverse events, clinical recovery, time to hospital discharge, incidence of hospitalisation and dyspnoea due to very serious imprecision (low patient numbers, wide confidence intervals and/or reliance on a single study). Certainty is very low for mortality (days 14 and 28) and ICU admission due to very serious imprecision (based on aforementioned reasons with the addition of few events).

For children & adolescents and pregnant & breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

**General adult population**
There is currently limited evidence about the impact of sofosbuvir-daclatasvir on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that sofosbuvir-daclatasvir should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of combination sofosbuvir-daclatasvir to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Sofosbuvir-daclatasvir
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether sofosbuvir-daclatasvir is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from two randomised trials that compared sofosbuvir-daclatasvir with standard care in 66 adults hospitalised with moderate or severe COVID-19 *[47]* and 89 adults hospitalised with mild to severe COVID-19 *[48]*. A third study compared sofosbovir-daclatasvir plus hydroxychloroquine with hydroxychloroquine alone in 55 adult outpatients with confirmed COVID-19 *[46]*.

We have found one new study comparing sofosbuvir-daclatasvir with placebo (Mobarak et al. J Antimicrob Chemother doi: 10.1093/jac/dkab433). This study is currently under review and an updated recommendation will be included in a future version of the guideline

**Publication status**
One study is only available as a preprint (Yakoot et al. posted to SSRN on 6 October 2020 *[48]*) and has therefore not been peer reviewed.

**Study characteristics**
Across the studies, median age of participants ranged from 43 to 58 years, and the proportion of women ranged from 48 to 56%. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
There were too few deaths (eight deaths at 14 days and seven deaths at 28 days) to determine whether sofosbuvir-daclatasvir makes a difference. We are uncertain if sofosbuvir-daclatasvir decreases the requirement for invasive mechanical ventilation, increases or decreases admission to hospital or intensive care unit, or whether it impacts adverse events or dyspnoea. However, sofosbuvir-daclatasvir may improve clinical recovery slightly (154 more recover per 1000 patients; RR 1.21 95% CI 1.04 to 1.41; 155 patients in 2 studies).

**Our confidence in the results**
Certainty of the evidence is low for mechanical ventilation, adverse events, clinical recovery, time to hospital discharge, incidence of hospitalisation and dyspnoea due to very serious imprecision (low patient numbers, wide confidence intervals and/or reliance on a single study). Certainty is very low for mortality (days 14 and 28) and ICU admission due to very serious imprecision (based on the aforementioned reasons with the addition of few events).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
According to the Therapeutic Goods Administration, known acute harms for sofosbuvir include fatigue, insomnia, anaemia and irritability *[67]*, and known acute harms for daclatasvir include fatigue, diarrhoea, nausea and headache. There are several known and potential interactions with other drugs *[49]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Sofosbuvir-daclatasvir | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 28 days of commencing treatment<br><br>9 Critical | Relative risk 0.41<br>(CI 95% 0.08 — 2)<br>Based on data from 89 participants in 1 studies. [1]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision [2] | We are uncertain whether sofosbuvir-daclatasvir increases or decreases risk of dying (7 deaths). |
| **All-cause mortality**<br>Within 14 days of commencing treatment<br><br>9 Critical | Relative risk 0.6<br>(CI 95% 0.16 — 2.31)<br>Based on data from 66 participants in 1 studies. [3]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision [4] | We are uncertain whether sofosbuvir-daclatasvir increases or decreases risk of dying (8 deaths). |
| **Mechanical ventilation**<br>Within 14 days of commencing treatment<br><br>9 Critical | Relative risk 0.42<br>(CI 95% 0.16 — 1.13)<br>Based on data from 155 participants in 2 studies. [5]<br>(Randomized controlled) | **154**<br>per 1000<br><br>Difference: | **65**<br>per 1000<br><br>**89 fewer per 1000**<br>( CI 95% 129 fewer — 20 more ) | **Low**<br>Due to very serious imprecision [6] | We are uncertain whether sofosbuvir-daclatasvir decreases mechanical ventilation (17 events). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Sofosbuvir-daclatasvir | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **ICU admission**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 1.02<br>(CI 95% 0.15 — 6.94)<br>Based on data from 89 participants in 1 studies. [7]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision [8] | We are uncertain whether sofosbuvir-daclatasvir increases or decreases ICU admission (4 events). |
| **Adverse events**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 1.02<br>(CI 95% 0.36 — 2.93)<br>Based on data from 89 participants in 1 studies. [9]<br>(Randomized controlled) | **133**<br>per 1000<br>Difference: | **136**<br>per 1000<br>**3 more per 1000**<br>( CI 95% 85 fewer — 257 more ) | **Low**<br>Due to very serious imprecision [10] | We are uncertain whether sofosbuvir-daclatasvir increases or decreases adverse events (12 events). |
| **Clinical recovery**<br>Within 14 days of commencing treatment<br>6 Important | Relative risk 1.21<br>(CI 95% 1.04 — 1.41)<br>Based on data from 155 participants in 2 studies. [11]<br>(Randomized controlled) | **731**<br>per 1000<br>Difference: | **885**<br>per 1000<br>**154 more per 1000**<br>( CI 95% 29 more — 300 more ) | **Low**<br>Due to very serious imprecision [12] | Sofosbuvir-daclatasvir may improve clinical recovery slightly (126 events). |
| **Hospitalisation**<br>End of follow-up<br>6 Important | Relative risk 0.26<br>(CI 95% 0.03 — 2.17)<br>Based on data from 55 participants in 1 studies. [13]<br>(Randomized controlled) | **143**<br>per 1000<br>Difference: | **37**<br>per 1000<br>**106 fewer per 1000**<br>( CI 95% 139 fewer — 167 more ) | **Low**<br>Due to very serious imprecision [14] | We are uncertain whether sofosbuvir-daclatasvir decreases incidence of hospitalisation (5 events). |
| **Dyspnoea**<br>End of follow-up<br>6 Important | Relative risk 0.38<br>(CI 95% 0.14 — 1.04)<br>Based on data from 55 participants in 1 studies. [15]<br>(Randomized controlled) | **393**<br>per 1000<br>Difference: | **149**<br>per 1000<br>**244 fewer per 1000**<br>( CI 95% 338 fewer — 16 more ) | **Low**<br>Due to very serious imprecision [16] | We are uncertain whether sofosbuvir-daclatasvir improves dyspnoea (15 events). |
| **Time to hospital discharge**<br>Days<br>6 Important | Based on data from 66 participants in 1 studies.<br>(Randomized controlled) | In Sadeghi 2020 time to clinical recovery was lower in the sofosbuvir-daclatasvir group (median 6 days, IQR 4-10 days) than the control group (median 11 days, IQR 6-17 days). | | **Low**<br>Due to very serious imprecision [17] | We are uncertain whether sofosbuvir-daclatasvir increases or decreases time to hospital discharge. |

1, 7, 9. Systematic review [65] with included studies: Yakoot 2020.
2, 8. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study, due to few events.
3. Systematic review [65] with included studies: Sadeghi 2020.
4, 17. **Imprecision: very serious.** Low number of patients, Wide confidence intervals, Only data from one study.

5. Systematic review [65] with included studies: Sadeghi 2020, Yakoot 2020.
6, 12. **Imprecision: very serious.** Low number of patients, Wide confidence intervals.
10. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study.
11. Systematic review [65] with included studies: Yakoot 2020, Sadeghi 2020.
13, 15. Systematic review [50] with included studies: Roozbeh 2020.
14. **Imprecision: very serious.** Low number of patients, Only data from one study, Wide confidence intervals.
16. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study, due to [reason].

### References

46. Roozbeh F, Saeedi M, Alizadeh-Navaei R, Hedayatizadeh-Omran A, Merat S, Wentzel H, et al. Sofosbuvir and daclatasvir for the treatment of COVID-19 outpatients: a double-blind, randomized controlled trial. Journal of Antimicrobial Chemotherapy 2020;76(3):753-757 Pubmed Journal

47. Sadeghi A, Ali Asgari A, Norouzi A, Kheiri Z, Anushirvani A, Montazeri M, et al. Sofosbuvir and daclatasvir compared with standard of care in the treatment of patients admitted to hospital with moderate or severe coronavirus infection (COVID-19): a randomized controlled trial. Journal of Antimicrobial Chemotherapy 2020. Pubmed Journal

48. Yakoot M, Eysa B, Gouda E. Efficacy and safety of sofosbuvir/daclatasvir in the treatment of COVID-19: a randomized, controlled study. SSRN preprint 2020. Journal Website

49. Therapeutic Goods Administration. Australian Product Information: Daklinza (daclatasvir). April 2019. Website

50. Sofosbuvir/daclatasvir for COVID-19.

65. Sofosbuvir/daclatasvir for COVID-19.

67. Therapeutic Goods Administration. Australian Product Information: Sovaldi (sofosbuvir). August 2020. Website

## 2.6.6 Triazavirin

Only in research settings

Do not use triazavirin for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Triazavirin should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use triazavirin for the treatment of COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### Evidence to decision

| | |
|---|---|
| **Benefits and harms** | **General adult population**<br>As the safety profile for triazavirin is incompletely characterised in humans, there is uncertainty around the benefits and harms for patients with COVID-19. |

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There are additional concerns regarding harms as triazavirin has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

**Certainty of the evidence**

Very low

**General adult population**
Certainty of the evidence is very low for all outcomes due to very serious imprecision (reliance on a single study with low patient numbers and wide confidence intervals) and very serious risk of bias.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is further considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the effects of triazavirin during pregnancy and breastfeeding are unknown in the context of COVID-19.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

**General adult population**
There is currently limited evidence about the impact of triazavirin on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that triazavirin should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of triazavirin for the treatment of COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Triazavirin
**Comparator:** Placebo

### Summary

There remains significant uncertainty whether triazavirin is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial that compared triazavirin with placebo in 52 adults hospitalised with mild, severe or critical COVID-19 *[51]*.

**Study characteristics**
Mean age of participants was 58 years and 50% were women. Patients received 250 mg triazavirin three times a day (mild patients) or four times a day (severe or critical patients) for seven days. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
There were too few who died (one death) or suffered adverse or serious adverse events to determine whether triazavirin makes a difference. It is unclear whether triazarivin increases or decreases viral clearance at day 28 or time to clinical improvement.

**Our confidence in the results**
Certainty of the evidence is very low for all outcomes due to very serious risk of bias (trial stopped early, selective outcome reporting) and very serious imprecision (reliance on a single study with low patient numbers and few events).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
As the safety profile for triazavirin is incompletely characterised in humans, there is uncertainty around the benefits and harms for patients with COVID-19.

There are additional concerns regarding harms, as triazavirin has not been sufficiently tested in **pregnant and breastfeeding women**.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Triazavirin | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 28 days of commencing treatment<br><br>9 Critical | Relative risk 0.33<br>(CI 95% 0.01 — 7.82)<br>Based on data from 52 participants in 1 studies. [1]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious risk of bias and very serious imprecision [2] | There were too few who died to determine whether triazavirin makes a difference (1 death). |
| **Invasive mechanical ventilation**<br>Within 28 days of commencing treatment<br><br>9 Critical | | | | | Data for patients requiring mechanical ventilation were not reported. |
| **Serious adverse events**<br>Within 28 days of commencing treatment | Relative risk 0.8<br>(CI 95% 0.24 — 2.65)<br>Based on data from 52 participants in 1 studies. [3]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious risk of bias and very serious imprecision [4] | There were too few who experienced one or more serious adverse events to determine whether triazavirin makes a |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Triazavirin | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| 9 Critical | | | | | difference (9 events). |
| **Adverse events**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 0.6<br>(CI 95% 0.26 — 1.41)<br>Based on data from 52 participants in 1 studies. [5]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious risk of bias and very serious imprecision [6] | There were too few who experienced one or more adverse events to determine whether triazavirin made a difference (6 events). |
| **Virological clearance (Negative PCR)**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 1.14<br>(CI 95% 0.92 — 1.42)<br>Based on data from 52 participants in 1 studies. [7]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious risk of bias and very serious imprecision [8] | We are uncertain whether triazavirin increases virological clearance. |
| **Time to improvement**<br>Within 28 days of commencing treatment<br>6 Important | Lower better<br>[9] (Randomized controlled) | **12**<br>Days (Median) | **7**<br>Days (Median)<br>CI 95% | **Very low**<br>Due to very serious risk of bias and very serious imprecision [10] | We are uncertain whether triazavirin decreases time to improvement. |

1, 3, 5, 7. Systematic review [52] with included studies: Wu 2020.
2. **Risk of Bias: very serious.** Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, stopped without reaching pre-defined stopping criteria., Selective outcome reporting. , Selective outcome reporting, due to [reason], Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, Selective outcome reporting, Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, due to [reason]. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Only data from one study, Low number of patients, Wide confidence intervals, Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias: no serious.**
4. **Risk of Bias: very serious.** Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, stopped without reaching pre-defined stopping criteria., Selective outcome reporting. . **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Only data from one study, Low number of patients, Wide confidence intervals.. **Publication bias: no serious.**
6. **Risk of Bias: very serious.** Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, stopped without reaching pre-defined stopping criteria., Selective outcome reporting. , Selective outcome reporting, due to [reason], Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias: no serious.**
8, 10. **Risk of Bias: very serious.** Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, stopped without reaching pre-defined stopping criteria., Selective outcome reporting. , Selective outcome reporting, due to [reason], Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias: no serious.**
9. with included studies: [51].

### References

51. Wu X, Yu K, Wang Y, Xu W, Ma H, Hou Y, et al. Efficacy and safety of triazavirin therapy for coronavirus disease 2019: a pilot randomized controlled trial. Engineering (Beijing, China) 2020. Pubmed Journal

52. Triazavirin for COVID-19.

## 2.6.7 Umifenovir

Only in research settings

Do not use umifenovir for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Umifenovir should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use umifenovir for the treatment of COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### Evidence to decision

**Benefits and harms**

**General adult population**
As the safety profile for umifenovir is incompletely characterised in humans, there is uncertainty around the benefits and harms for patients with COVID-19.

**Certainty of the evidence**

Low

Certainty of the evidence is low for all outcomes. This judgement is based on very serious imprecision due to low patient numbers and reliance on a single study (clinical improvement and negative PCR) and few events (adverse events and clinical progression).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer

to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

**General adult population**
There is currently limited evidence about the impact of umifenovir on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that umifenovir should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of umifenovir for the treatment of COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Umifenovir
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether umifenovir is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from three randomised trials that compared umifenovir with standard care in 135 adults hospitalised with mild or moderate COVID-19 *[71][56][54]*.

**Publication status**
One study is only available as a preprint (Ghaderkhani et al. posted to Res Sq on 18 October 2020) and has therefore not been peer reviewed.

**Study characteristics**
In Li et al. mean age was 51 years in the umifenovir group (54% women) and 44 years in the standard care group (59% women). In Yethindra et al. mean age was 36 years (40% women)—patients over 60 years were excluded. In Ghaderkhani et al. median age was 47 years in the umifenovir group (68% women) and 42 years in the standard care group (52% women). In all three studies, pregnant and breastfeeding women were ineligible.

**What are the main results?**
No patients died or experienced a serious adverse event in any of the three studies. There were too few patients experiencing an adverse event or clinical deterioration to determine whether umifenovir makes a difference to these outcomes. It is unclear whether umifenovir increases the rate of negative polymerase chain reaction (PCR) at day 14, however umifenovir may be less effective than standard care alone in facilitating clinical improvement based on chest computed tomography scans at day 14.

**Our confidence in the results**
Certainty of the evidence is low for all outcomes. This judgement is based on very serious imprecision due to low patient numbers and reliance on a single study (clinical improvement and negative PCR) and few events (adverse events and clinical progression).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
As of 21 September 2020, umifenovir (Arbidol) is not listed in the Australian Register of Therapeutic Goods and is not approved for use in Australia. The safety profile for umifenovir is incompletely characterised in humans.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Umifenovir | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 21 days of commencing treatment<br>9 Critical | Based on data from 52 participants in 1 studies. [1] | | | | No patients died. |
| **Adverse events**<br>Within 21 days of commencing treatment<br>6 Important | Relative risk 4.18<br>(CI 95% 0.51 — 34.19)<br>Based on data from 135 participants in 3 studies. [2]<br>(Randomized controlled) | | | **Low**<br>Due to very serious imprecision [3] | There were too few who experienced one or more adverse events to determine whether umifenovir makes a difference (6 events). |
| **Serious adverse events**<br>Within 21 days of commencing treatment<br>6 Important | Based on data from 82 participants in 2 studies. [4] | | | | No patients experienced a serious adverse event. |
| **Clinical deterioration (mild/mod to sev/crit)** [5]<br>Within 21 days of commencing treatment<br>6 Important | Relative risk 0.73<br>(CI 95% 0.13 — 3.96)<br>Based on data from 82 participants in 2 studies. [6]<br>(Randomized controlled) | **63**<br>per 1000<br><br>Difference: | **46**<br>per 1000<br><br>**17 fewer per 1000**<br>( CI 95% 55 fewer — 186 more ) | **Low**<br>Due to very serious imprecision [7] | There were too few who experienced clinical deterioration to determine whether umifenovir makes a difference (5 events). |
| **Clinical improvement** [8]<br>Based on chest CT scan 14 days after commencing | Relative risk 0.75<br>(CI 95% 0.57 — 0.98)<br>Based on data from 47 participants in 1 studies. [9]<br>(Randomized controlled) | **929**<br>per 1000<br><br>Difference: | **697**<br>per 1000<br><br>**232 fewer per 1000** | **Low**<br>Due to very serious imprecision [10] | Umifenovir may decrease clinical improvement slightly at day 14 (36 events). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Umifenovir | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| treatment<br><br>6 Important | | | ( CI 95% 399 fewer — 19 fewer ) | | |
| **Negative PCR**<br>Within 14 days of commencing treatment<br><br>6 Important | Relative risk 1.2<br>(CI 95% 0.9 — 1.59)<br>Based on data from 52 participants in 1 studies. [11]<br>(Randomized controlled) | **765**<br>per 1000<br><br>Difference: | **918**<br>per 1000<br><br>**153 more per 1000**<br>( CI 95% 77 fewer — 451 more ) | **Low**<br>Due to very serious imprecision [12] | Umifenovir may have little impact on negative PCR (45 events). |
| **Discharge from hospital**<br>Within 21 days of commencing treatment<br><br>6 Important | Relative risk 1<br>(CI 95% 0.88 — 1.13)<br>Based on data from 30 participants in 1 studies. [13]<br>(Randomized controlled) | **1,000**<br>per 1000<br><br>Difference: | **1,000**<br>per 1000<br><br>**0 fewer per 1000**<br>( CI 95% 120 fewer — 130 more ) | **Low**<br>Due to very serious imprecision [14] | Umifenovir may have little impact on discharge from hospital (30 events). |

1, 9, 11. Systematic review [53] with included studies: Li 2020.
2. Systematic review [53] with included studies: Li 2020, Yethindra 2020, [54].
3, 7. **Imprecision: very serious.** Low number of patients, due to few events.
4. Systematic review [53] with included studies: Li 2020, Yethindra 2020.
5. The number of patients who deteriorated from a mild or moderate form of disease to a severe or critical form.
6. Systematic review [53] with included studies: Yethindra 2020, Li 2020.
8. Criteria of chest CT improvement included: 1) no new exudative lesions; 2) decreasing size of exudative lesions; 3) decreasing densities of lesions.
10, 12, 14. **Imprecision: very serious.** Only data from one study, Low number of patients.
13. Systematic review [53] with included studies: Yethindra 2020.

**References**

53. Arbidol for COVID-19.

54. Ghaderkhani S, Khaneshan A, Salami A. Efficacy and safety of Arbidol in treatment of patients with COVID-19 infection: a randomized clinical trial. Research Square 2020. Journal

56. Yethindra V, Tagaev T, Uulu M. Efficacy of umifenovir in the treatment of mild and moderate COVID-19 patients. International Journal of Research in Pharmaceutical Sciences 2020. Journal Website

71. Li Y, Xie Z, Lin W, Cai W, Wen C, Guan Y, et al. Efficacy and safety of lopinavir/ritonavir or arbidol in adult patients with mild/moderate COVID-19: an exploratory randomized controlled trial. Med (N Y) 2020;2020.03.19.20038984 Pubmed Journal Website

## 2.7 Human and blood derived products

### 2.7.1 Human umbilical cord mesenchymal stem cells

Only in research settings

Do not use human umbilical cord mesenchymal stem cells for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Human umbilical cord mesenchymal stem cells should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use human umbilical cord mesenchymal stem cells (hUC-MSCs) to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

## Evidence to decision

### Benefits and harms

Important harms

**General adult population**
There is uncertainty around benefits and harms associated with human umbilical cord mesenchymal stem cells (hUC-MSCs) in patients with COVID-19.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There are additional concerns regarding harms as hUC-MSCs have not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain. There is insufficient evidence pertaining to the safety of hUC-MSCs for pregnant or breastfeeding women (for any indication) *[242]*.

In Australia, stem cell therapy is only approved for haematopoietic stem cell (HPC) transplantation (using stem cells from umbilical cord blood or bone marrow), which is standard practice for the treatment of disorders of the blood and immune system, such as leukaemia *[242]*.

### Certainty of the evidence

Very low

**General adult population**
Certainty of the evidence is low for all-cause mortality and adverse events due to very serious imprecision (low patient numbers, few events and wide confidence intervals). Certainty is very low for all other outcomes due to very serious risk of bias (incomplete randomisation, lack of blinding, deviation from intended intervention and selective outcome reporting) and very serious imprecision (low patient numbers, few events, wide confidence intervals and reliance on a single study for four outcomes).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is downgraded for indirectness due to limited inclusion (or absence) of these populations in the study.

### Values and preferences

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel

believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of hUC-MSCs in pregnancy are unknown.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications. There is very limited capacity to produce stem cell-related products, which would limit implementation of this treatment if effective.

### Rationale

**General adult population**
There is currently limited evidence about the impact of human umbilical cord mesenchymal stem cells (hUC-MSCs) on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that human umbilical cord mesenchymal stem cells should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of hUC-MSCs to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Human umbilical cord mesenchymal stem cells (hUC-MSC)
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether therapy with human umbilical cord mesenchymal stem cells (hUC-MSCs) is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from four randomised trials that compared hUC-MSC therapy with standard care in 181 adults hospitalised with severe or critical COVID-19 *[61][59][60]* and 24 adults with mild-to-severe disease *[83]*.

**Study characteristics**
Median age of patients was ~60 years and 44% were women. Standard care across the studies included supplemental oxygen (non-invasive or invasive ventilation), antiviral agents (abidor/oseltamivir), antibiotic agents and glucocorticoid therapy. Pregnant and breastfeeding women were ineligible in three studies *[83][59][60]*; in one study their eligibility was unclear *[61]*.

Patients in the intervention groups received either: 2 x $10^6$ cells/kg on day 0 *[61]*, 100 x $10^6$ cells on days 0 and 3 *[83]*, 4 x $10^7$ cells on days 0, 3 and 6 *[59]*, or 1 x $10^6$ cells/kg on day 0 *[60]*.

**What are the main results?**
Preliminary results demonstrate that hUC-MSC therapy may reduce the incidence of death. There were too few events to determine whether hUC-MSC had an impact on mechanical ventilation or serious adverse events. hUC-MSC therapy may decrease adverse events slightly. We are uncertain whether hUC-MSC therapy decreases time to clinical improvement and duration of hospital stay, or increases clinical improvement and hospital discharge.

**Our confidence in the results**
Certainty of the evidence is low for all-cause mortality and adverse events due to very serious imprecision (low patient numbers, few events and wide confidence intervals). Certainty is very low for all other outcomes due to very serious risk of bias (incomplete randomisation, lack of blinding, deviation from intended intervention and selective outcome reporting) and very serious imprecision (low patient numbers, few events, wide confidence intervals and reliance on a single study for four outcomes).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
Stem cell therapies outside of specific settings and diseases are very experimental and highly regulated in Australia *[85]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>hU-MSC | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 28 days of commencing treatment<br>9 Critical | Relative risk 0.56<br>(CI 95% 0.36 — 0.89)<br>Based on data from 205 participants in 4 studies. [1]<br>(Randomized controlled) | **271**<br>per 1000<br>Difference: | **152**<br>per 1000<br>**119 fewer per 1000**<br>( CI 95% 173 fewer — 30 fewer ) | **Low**<br>Due to very serious imprecision [2] | hU-MSC may decrease death (38 events). |
| **Invasive mechanical ventilation**<br>End of follow-up<br>9 Critical | Relative risk 0.26<br>(CI 95% 0.01 — 4.43)<br>Based on data from 41 participants in 1 studies. [3]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious risk of bias and very serious imprecision [4] | There were too few who required invasive mechanical ventilation to determine whether hU-MSC makes a difference (4 patients). |
| **Serious adverse events**<br>End of follow-up<br>9 Critical | Relative risk 0.25<br>(CI 95% 0.07 — 0.94)<br>Based on data from 24 participants in 1 studies. [5]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision [6] | There were too few who experienced serious adverse events to determine whether hU-MSC makes a difference (10 events). |
| **Adverse events**<br>End of follow-up<br>6 Important | Relative risk 0.86<br>(CI 95% 0.65 — 1.12)<br>Based on data from 124 participants in 2 studies. [7]<br>(Randomized controlled) | **681**<br>per 1000<br>Difference: | **586**<br>per 1000<br>**95 fewer per 1000**<br>( CI 95% 238 fewer — 82 more ) | **Low**<br>Due to very serious imprecision [8] | hU-MSC may decrease adverse events slightly (77 events). |
| **Hospital discharge**<br>End of follow-up<br>6 Important | Relative risk 2.42<br>(CI 95% 0.85 — 6.85)<br>Based on data from 41 participants in 1 studies. [9]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious risk of bias and very serious imprecision [10] | We are uncertain whether hU-MSC increases hospital discharge. |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>hU-MSC | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Clinical improvement**<br>End of follow-up<br><br>6 Important | Relative risk 1.13<br>(CI 95% 0.94 — 1.36)<br>Based on data from 41 participants in 1 studies. [11]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious risk of bias and very serious imprecision [12] | We are uncertain whether hU-MSC increases clinical improvement. |
| **Duration of hospital stay**<br>Days<br><br>6 Important | Lower better<br>Based on data from 40 participants in 1 studies. [13]<br>(Randomized controlled) | **10.44**<br>(Mean)<br><br>Difference: | **12.23**<br>(Mean)<br><br>**MD 1.79 higher**<br>( CI 95% 3.26 lower — 6.84 higher ) | **Very low**<br>Due to very serious imprecision [14] | We are uncertain whether hu-msc increases or decreases duration of hospital stay |
| **Duration of hospital stay**<br>End of follow-up<br><br>6 Important | Based on data from 41 participants in 1 studies. [15]<br>(Randomized controlled) | Median duration of hospital stay was 20 days (IQR 16 to 24) with hU-MSC therapy vs 24 days (IQR 20 to 27) with standard care. | | **Very low**<br>Due to very serious risk of bias and very serious imprecision [16] | We are uncertain whether hU-MSC decreases duration of hospital stay. |
| **Time to clinical improvement** [17]<br>End of follow-up<br><br>6 Important | Based on data from 41 participants in 1 studies. [18]<br>(Randomized controlled) | Median time to clinical improvement was 9 days (IQR 6 to 13) with hU-MSC therapy vs 14 days (IQR 10 to 21) with standard care. | | **Very low**<br>Due to very serious risk of bias and very serious imprecision [19] | We are uncertain whether hU-MSC decreases time to clinical improvement. |

1. Systematic review [80] with included studies: Shi 2020, Dilogo 2021, Lanzoni 2020, Shu 2020.
2. **Imprecision: very serious.** Wide confidence intervals, Low number of patients.
3, 9, 11. Systematic review [57] with included studies: Shu 2020.
4. **Risk of Bias: very serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Low number of patients, Only data from one study, due to few events. **Publication bias: no serious.**
5. Systematic review [57] with included studies: Lanzoni 2020. **Comparator:** Systematic review [57] with included studies: Lanzoni 2020.
6. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study, Few events. **Publication bias: no serious.**
7. Systematic review [57] with included studies: Lanzoni 2020, Shi 2020.
8. **Imprecision: very serious.** Wide confidence intervals, due to few events, Low number of patients. **Publication bias: no serious.**
10. **Risk of Bias: very serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias,. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Low number of patients, Only data from one study, due to few events, Wide confidence intervals. **Publication bias: no serious.**
12. **Risk of Bias: very serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Selective outcome reporting. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study, due to few events. **Publication bias: no serious.**
13. Systematic review [80] with included studies: Dilogo 2021.
14. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study.
15, 18. **Supporting references:** [61],

16, 19. **Risk of Bias: very serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Selective outcome reporting. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals, Only data from one study, Low number of patients.
17. 2-point change on a 7-point ordinal scale

**References**

57. Mesenchymal stem cells (hU-MSC) for COVID-19.

59. Shi L, Huang H, Lu X, Yan X, Jiang X, Xu R, et al. Effect of human umbilical cord-derived mesenchymal stem cells on lung damage in severe COVID-19 patients: a randomized, double-blind, placebo-controlled phase 2 trial. Signal Transduction and Targeted Therapy 2021;6(1):58 Pubmed Journal

60. Dilogo IH, Aditianingsih D, Sugiarto A, Burhan E, Damayanti T, Sitompul PA, et al. Umbilical cord mesenchymal stromal cells as critical COVID-19 adjuvant therapy: a randomized controlled trial. Stem Cells Translational Medicine 2021. Pubmed Journal

61. Shu L, Niu C, Li R, Huang T, Wang Y, Huang M, et al. Treatment of severe COVID-19 with human umbilical cord mesenchymal stem cells. Stem Cell Research & Therapy 2020;11(1):361 Pubmed Journal

80. Mesenchymal stem cells (hU-MSC) for COVID-19.

83. Lanzoni G, Linetsky E, Correa D, Messinger Cayetano S, Alvarez RA, Kouroupis D, et al. Umbilical cord mesenchymal stem cells for COVID-19 acute respiratory distress syndrome: a double-blind, phase 1/2a, randomized controlled trial. Stem Cells Translational Medicine 2021. Pubmed Journal

85. Therapeutic Goods Administration. Regulation of stem cell treatments: information for practitioners. May 2020. Website

## 2.7.2 Intravenous immunoglobulin

Only in research settings

Do not use immunoglobulin for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Intravenous immunoglobulin should still be considered for other evidence-based indications in people who have COVID-19.*

*This recommendation does not apply to the use of immunoglobulin in children and adolescents when managing paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS), Kawasaki disease or toxic shock syndrome related to COVID-19 (see section for specific guidance). The Taskforce is currently developing recommendations for the management of these conditions in children and adolescents with COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use combination immunoglobulin plus methylprednisolone to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

## Evidence to decision

### Benefits and harms

Important harms

**General adult population**
In addition to uncertainty around benefits for patients with COVID-19, there are well-known side effects and harms associated with intravenous immunoglobulin including flu-like symptoms, dermatologic side effects, arrhythmia, hypotension and transfusion-related acute lung injury.

**Children and adolescents, pregnant and breastfeeding women**
Intravenous immunoglobulin is used in these populations for other medical conditions.

**People requiring palliative care and older people living with frailty or cognitive impairment**
There are additional concerns regarding harms, as intravenous immunoglobulin has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

### Certainty of the evidence

Very low

**General adult population**
Certainty of the evidence is very low for all outcomes due to very serious imprecision (reliance on a single study and few events) and serious risk of bias (missing data).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

### Values and preferences

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of intravenous immunoglobulin in pregnancy are unknown.

### Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Equity

Important issues, or potential issues not investigated

**General adult population**
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Children and adolescents, pregnant and breastfeeding women**
Because the benefit-to-harm ratio is uncertain, this recommendation may protect these more vulnerable

populations.

**People requiring palliative care and older people living with frailty or cognitive impairment**
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit-to-harm ratio, this recommendation protects these more vulnerable populations.

**Acceptability** Important issues, or potential issues not investigated

**General adult population, children and adolescents, pregnant and breastfeeding women**
Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

**People requiring palliative care and older people living with frailty or cognitive impairment**
Because the benefit-to-harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

**Feasibility** Important issues, or potential issues not investigated

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

### Rationale

**General adult population**
There is currently limited evidence about the impact of intravenous immunoglobulin on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that intravenous immunoglobulin should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of intravenous immunoglobulin to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Immunoglobulin
**Comparator:** Control

### Summary

There remains significant uncertainty whether intravenous immunoglobulin is more effective and safer than placebo in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from a single randomised trial that compared intravenous immunoglobulin (IVIg) with placebo in 64 hospitalised adults with severe COVID-19 *[219]*.

Additional data were provided for the patients excluded from the analysis (two in the IVIg arm and three in the placebo arm) who died in the 72 hours following randomisation.

**Study characteristics**
Mean age of participants was 56 years in both groups and 31% were women. Pregnant women were ineligible.

**What are the main results?**
Only two outcomes—mortality and duration of hospital stay—were reported. Significant uncertainty remains as to whether intravenous immunoglobulin affects either of these outcomes.

**Our confidence in the results**
Certainty of the evidence is very low for mortality and duration of hospital stay. This judgement is based on very serious imprecision due to low patient numbers and reliance on a single study, and serious risk of bias due to missing data.

For children and adolescents and pregnant and breastfeeding women, certainty is downgraded to very low due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
Adverse effects associated with intravenous immunoglobulin include flu-like symptoms, dermatologic side effects, arrhythmia, hypotension and transfusion-related acute lung injury *[88]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Control | **Intervention**<br>Immunoglobulin | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>End of treatment<br><br>9 Critical | Based on data from 64 participants in 1 studies. [1]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious risk of bias and very serious imprecision [2] | We are uncertain whether immunoglobulin increases or decreases risk of death (25 events). |
| **Duration of hospital stay**<br>During follow-up<br><br>6 Important | Lower better<br>Based on data from 59 participants in 1 studies.<br>(Randomized controlled) | **7**<br>(Median) | **9**<br>(Median)<br><br>CI 95% | **Very low**<br>Due to very serious risk of bias and very serious imprecision [3] | We are uncertain whether immunoglobulin increases or decreases duration of hospital stay. |

1. Systematic review [218] with included studies: Gharebaghi 2020.
2. **Risk of Bias: very serious.** Missing intention-to-treat analysis, Incomplete data and/or large loss to follow up, Selective outcome reporting. **Imprecision: very serious.** Low number of patients, Only data from one study, Wide confidence intervals.
3. **Risk of Bias: very serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting, Missing intention-to-treat analysis. **Imprecision: very serious.** Low number of patients, Only data from one study.

### References

218. [Immunoglobulin] for [COVID-19].

## 2.7.3 Intravenous immunoglobulin plus methylprednisolone

Only in research settings

Do not use immunoglobulin plus methylprednisolone for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Intravenous immunoglobulin plus methylprednisolone should still be considered for other evidence-based indications in people who have COVID-19.*

*This recommendation does not apply to the use of immunoglobulin plus methylprednisolone in children and adolescents when managing paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS), Kawasaki disease or toxic shock syndrome related to COVID-19 (see section for specific guidance). The Taskforce is currently developing recommendations for the management of these conditions in children and adolescents with COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use combination immunoglobulin plus methylprednisolone to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### Evidence to decision

**Benefits and harms**

Important harms

**General adult population**
In addition to uncertainty around benefits for patients with COVID-19, there are well-known side effects and harms associated with immunoglobulin including flu-like symptoms, dermatologic side effects, arrhythmia, hypotension and transfusion-related acute lung injury.

**Children and adolescents, pregnant and breastfeeding women**
Intravenous immunoglobulin and methylprednisolone are used in these populations for other medical conditions.

**People requiring palliative care and older people living with frailty or cognitive impairment**
There are additional concerns regarding harms as intravenous immunoglobulin and methylprednisolone has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

**Certainty of the evidence**

Very low

**General adult population**
Certainty of the evidence is very low for all outcomes based on very serious imprecision due to the low number of trial participants, low number of events and reliance on a single study.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of immunoglobulin in pregnancy are unknown.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

**General adult population**
There is currently limited evidence about the impact of immunoglobulin plus methylprednisolone on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that immunoglobulin plus methylprednisolone should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of immunoglobulin plus methylprednisolone to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Immunoglobulin plus methylprednisolone
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether intravenous immunoglobulin plus methylprednisolone is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from a single randomised trial that compared combination intravenous immunoglobulin plus methylprednisolone with standard care in 34 patients with moderate or severe COVID-19 *[62]*.

We have found one new study comparing intravenous immunoglobulin with standard care (Tabarsi et al. Int Immunopharmacol doi: 10.1016/j.intimp.2020.107205). This study is currently under review and an updated recommendation will be included in a future version of the guideline.

**Study characteristics**
Mean age of participants was 54 years in both groups and 39% were women. It is unclear if pregnant and breastfeeding women were eligible.

**What are the main results?**
For the critical outcomes of death and invasive mechanical ventilation, there were too few events (four deaths and eight requiring ventilation) to determine whether combination immunoglobulin plus methylprednisolone makes a difference. No patient experienced an adverse event.

**Our confidence in the results**

Certainty of the evidence is very low for all outcomes. This judgement is based on very serious imprecision due to low patient numbers, few events and reliance on a single study.

**Additional information**
Adverse effects associated with intravenous immunoglobulin include flu-like symptoms, dermatologic side effects, arrhythmia, hypotension and transfusion-related acute lung injury *[88]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Immunoglobulin plus methylprednisolone | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>30 days after commencing treatment<br>9 Critical | Relative risk 0.33<br>(CI 95% 0.04 — 2.89)<br>Based on data from 34 participants in 1 studies. [1]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision [2] | There were too few who died to determine whether combination immunoglobulin plus methylprednisolone makes a difference (4 events). |
| **Invasive mechanical ventilation**<br>30 days after commencing treatment<br>9 Critical | Relative risk 0.29<br>(CI 95% 0.07 — 1.18)<br>Based on data from 34 participants in 1 studies. [3]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision [4] | There were too few who experienced invasive mechanical ventilation to determine whether combination immunoglobulin plus methylprednisolone makes a difference (9 events). |
| **Adverse events**<br>Within 30 days of commencing treatment<br>6 Important | Based on data from 34 participants in 1 studies. [5] | | | | No patients experienced an adverse event. |
| **Serious adverse events**<br>Within 30 days of commencing treatment<br>6 Important | [6] | | | | No studies were found that looked at serious adverse events. |

1, 3, 5. Systematic review [63] with included studies: Sakoulas 2020.
2. **Imprecision: very serious.** Low number of patients, Only data from one study, low events.
4. **Imprecision: very serious.** Low number of patients, Only data from one study, few events.
6. Systematic review [63]

### References

62. Sakoulas G, Geriak M, Kullar R, Greenwood KL, Habib M, Vyas A, et al. Intravenous immunoglobulin plus methylprednisolone mitigate respiratory morbidity in coronavirus disease 2019. Critical Care Explorations 2020;2(11):e0280 Pubmed Journal

63. Immunoglobulin for COVID-19.

88. Guo YI, Tian X, Wang X, Xiao Z. Adverse effects of immunoglobulin therapy. Frontiers in Immunology 2018;9:1299 Pubmed Journal

### Clinical question/ PICO

**Population:** Special populations with COVID-19
**Intervention:** Immunoglobulin plus methylprednisolone
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether immunoglobulin is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from a single randomised trial that compared combination immunoglobulin plus methylprednisolone with standard care in 34 patients with moderate or severe COVID-19 *[62]*.

We have found one new study comparing intravenous immunoglobulin with standard care (Tabarsi et al. Int Immunopharmacol doi: 10.1016/j.intimp.2020.107205). This study is currently under review and an updated recommendation will be included in a future version of the guideline.

**Study characteristics**
Mean age of participants was 54 years in both groups and 39% were women. It is unclear if pregnant and breastfeeding women were eligible.

**What are the main results?**
For the critical outcomes of death and mechanical ventilation there were too few events (four deaths and eight requiring ventilation) to determine whether combination immunoglobulin plus methylprednisolone makes a difference. No patient experienced an adverse event.

**Our confidence in the results**
Certainty of the evidence is very low for all outcomes. This judgement is based on serious indirectness and very serious imprecision due to low patient numbers, few events and reliance on a single study.

**Additional information**
Adverse effects associated with intravenous immunoglobulin include flu-like symptoms, dermatologic side effects, arrhythmia, hypotension and transfusion-related acute lung injury *[88]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Immunoglobulin plus methylprednisolone | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>30 days after commencing treatment | Relative risk 0.33<br>(CI 95% 0.04 — 2.89)<br>Based on data from 34 participants in 1 studies. [1]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision and serious indirectness [2] | There were too few who died to determine whether combination immunoglobulin plus methylprednisolone makes a difference (4 events). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Immunoglobulin plus methylprednisolone | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| 9 Critical | | | | | |
| **Invasive mechanical ventilation**<br>30 days after commencing treatment<br>9 Critical | Relative risk 0.29<br>(CI 95% 0.07 — 1.18)<br>Based on data from 34 participants in 1 studies. [3]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision and serious indirectness [4] | There were too few who experienced invasive mechanical ventilation to determine whether combination immunoglobulin plus methylprednisolone makes a difference (9 events). |
| **Adverse events**<br>Within 30 days of commencing treatment<br>6 Important | Based on data from 34 participants in 1 studies. [5] | | | | No patients experienced an adverse event. |
| **Serious adverse events**<br>Within 30 days of commencing treatment<br>6 Important | 6 | | | | No studies were found that looked at serious adverse events. |

1, 3, 5. Systematic review [63] with included studies: Sakoulas 2020.
2. **Indirectness: serious. Imprecision: very serious.** Low number of patients, Only data from one study, low events.
4. **Indirectness: serious. Imprecision: very serious.** Low number of patients, Only data from one study, few events.
6. Systematic review [63]

**References**

62. Sakoulas G, Geriak M, Kullar R, Greenwood KL, Habib M, Vyas A, et al. Intravenous immunoglobulin plus methylprednisolone mitigate respiratory morbidity in coronavirus disease 2019. Critical Care Explorations 2020;2(11):e0280 Pubmed Journal

63. Immunoglobulin for COVID-19.

88. Guo YI, Tian X, Wang X, Xiao Z. Adverse effects of immunoglobulin therapy. Frontiers in Immunology 2018;9:1299 Pubmed Journal

## 2.8 Immunomodulating drugs

### 2.8.1 Anakinra

Only in research settings

Do not use anakinra for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Anakinra should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use anakinra to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

## Evidence to decision

### Benefits and harms

Important harms

**General adult population**
In addition to uncertainty around benefits for patients with COVID-19, common side effects include headache, injection site reactions, serious infections, neutropaenia and thrombocytopaenia *[184]*. It remains unclear if anakinra is safe for the treatment of COVID-19.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There are additional concerns regarding harms as anakinra has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain. There is insufficient evidence pertaining to the safety of anakinra for pregnant or breastfeeding women.

### Certainty of the evidence

Low

**General adult population**
Certainty of the evidence is moderate for serious adverse events due to serious imprecision (wide confidence intervals). Certainty is low for death due to serious imprecision and serious inconsistency (wide confidence intervals and inconsistent direction of effect), and the composite of death or mechanical ventilation, respiratory failure or acute respiratory distress syndrome and clinical recovery (wide confidence intervals and reliance on a single study). Certainty is very low for sepsis and hospital discharge due to serious risk of bias and very serious imprecision (trial stopped early, wide confidence intervals and reliance on a single study).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

### Values and preferences

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of anakinra in pregnancy are unknown.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

**General adult population**
There is currently limited evidence about the impact of anakinra on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that anakinra should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of anakinra to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Anakinra
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether anakinra is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from four randomised trials that compared anakinra with standard care in 1607 adults hospitalised with moderate to critical COVID-19 *[64][96][93][90]*.

**Study characteristics**
Mean/median age of participants ranged from 60 to 66 years. The proportion of women ranged from 14% (in the anakinra arm of Declercq et al.) to 43% (Kyriazopoulou et al.). Doses varied between trials: in Declercq and Kyriazpoulou patients received 100 mg anakinra once daily for 28 and 10 days, respectively; in REMAP-CAP patients received a single 300 mg loading dose followed by 100 mg four times daily for 14 days; in CORIMUNO-19 patients received 200 mg twice daily for 3 days, 100 mg twice on day 4 and a single 100 mg dose on day 5.

**What are the main results?**
Anakinra probably has little impact on incidence of serious adverse events. We are uncertain whether anakinra impacts all-cause mortality, the need for invasive mechanical ventilation/ECMO or NIV/HFNO, clinical recovery, sepsis, hospital discharge and adverse events.

**Our confidence in the results**
Certainty of the evidence is moderate for serious adverse events due to serious imprecision (wide confidence intervals). Certainty is low for mortality due to serious imprecision and serious inconsistency (wide confidence intervals and inconsistent direction of effect), and the composite of mortality or mechanical ventilation, respiratory failure or ARDS and clinical recovery (wide confidence intervals and reliance on a single study). Certainty is very low for sepsis and hospital discharge due to serious risk of bias and very serious imprecision (trial stopped early, wide confidence intervals and reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**

According to the Therapeutic Goods Administration, common side effects associated with anakinra include headache, injection site reactions, serious infections, neutropaenia and thrombocytopaenia *[69]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Anakinra | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 28 days of commencing treatment<br>9 Critical | Relative risk 0.98<br>(CI 95% 0.65 — 1.48)<br>Based on data from 1,597 participants in 4 studies. [1]<br>(Randomized controlled) | **256**<br>per 1000<br>Difference: | **251**<br>per 1000<br>**5 fewer per 1000**<br>( CI 95% 90 fewer — 123 more ) | **Low**<br>Due to serious imprecision and serious inconsistency [2] | Anakinra may have little impact on all-cause mortality (366 events) |
| **All-cause mortality or mechanical ventilation [composite]**<br>Within 14 days of commencing treatment<br>9 Critical | Relative risk 0.98<br>(CI 95% 0.59 — 1.63)<br>Based on data from 114 participants in 1 studies. [3]<br>(Randomized controlled) | **345**<br>per 1000<br>Difference: | **338**<br>per 1000<br>**7 fewer per 1000**<br>( CI 95% 141 fewer — 217 more ) | **Low**<br>Due to very serious imprecision [4] | We are uncertain whether anakinra impacts the composite outcome of death or mechanical ventilation (39 events). |
| **Respiratory failure or ARDS**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 0.79<br>(CI 95% 0.39 — 1.61)<br>Based on data from 114 participants in 1 studies. [5]<br>(Randomized controlled) | **236**<br>per 1000<br>Difference: | **186**<br>per 1000<br>**50 fewer per 1000**<br>( CI 95% 144 fewer — 144 more ) | **Low**<br>Due to very serious imprecision [6] | We are uncertain whether anakinra increases or decreases respiratory failure or ARDS (24 events). |
| **Sepsis**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 2.33<br>(CI 95% 0.78 — 7)<br>Based on data from 114 participants in 1 studies. [7]<br>(Randomized controlled) | **73**<br>per 1000<br>Difference: | **170**<br>per 1000<br>**97 more per 1000**<br>( CI 95% 16 fewer — 438 more ) | **Very low**<br>Due to serious risk of bias and very serious imprecision [8] | We are uncertain whether anakinra increases or decreases sepsis (14 events). |
| **Serious adverse events**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 0.93<br>(CI 95% 0.69 — 1.26)<br>Based on data from 1,486 participants in 3 studies. [9]<br>(Randomized controlled) | **112**<br>per 1000<br>Difference: | **104**<br>per 1000<br>**8 fewer per 1000**<br>( CI 95% 35 fewer — 29 more ) | **Moderate**<br>Due to serious imprecision [10] | Anakinra probably has little impact on serious adverse events (178 events). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Anakinra | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Adverse events**<br>Within 28 days of commencing treatment<br><br>6 Important | Relative risk 0.98<br>(CI 95% 0.87 — 1.1)<br>Based on data from 708 participants in 2 studies. [11]<br>(Randomized controlled) | **791**<br>per 1000<br><br>Difference: | **775**<br>per 1000<br><br>**16 fewer per 1000**<br>( CI 95% 103 fewer — 79 more ) | **Low**<br>Due to serious inconsistency and serious imprecision [12] | Anakinra may have little impact on adverse events (574 events). |
| **Hospital discharge**<br>Within 28 days of commencing treatment<br><br>6 Important | Relative risk 0.93<br>(CI 95% 0.69 — 1.26)<br>Based on data from 114 participants in 1 studies. [13]<br>(Randomized controlled) | **618**<br>per 1000<br><br>Difference: | **575**<br>per 1000<br><br>**43 fewer per 1000**<br>( CI 95% 192 fewer — 161 more ) | **Very low**<br>Due to serious risk of bias and very serious imprecision [14] | We are uncertain whether anakinra increases or decreases hospital discharge (68 events). |
| **Clinical recovery**<br>Within 28 days of commencing treatment<br><br>6 Important | Relative risk 1.9<br>(CI 95% 1.47 — 2.46)<br>Based on data from 594 participants in 1 studies. [15]<br>(Randomized controlled) | **265**<br>per 1000<br><br>Difference: | **503**<br>per 1000<br><br>**238 more per 1000**<br>( CI 95% 125 more — 387 more ) | **Low**<br>Due to very serious imprecision [16] | Anakinra may improve clinical recovery (254 events). |
| **Time to discharge from hospital**<br>Days<br>(Kyriazopoulou)<br><br>6 Important | Lower better<br>Based on data from 594 participants in 1 studies.<br>(Randomized controlled) | **12**<br>(Median) | **11**<br>(Median)<br><br>CI 95% | **Low**<br>Due to very serious imprecision [17] | Anakinra may have little impact on time to discharge from hospital. |

1. Systematic review [68] with included studies: Declercq 2021, Kyriazopoulou 2021, REMAP-CAP 2021, CORIMUNO-19 2020.
2, 12. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. **Imprecision: serious.** Wide confidence intervals.
3, 5, 7, 13. Systematic review [98] with included studies: CORIMUNO-19 2020.
4. **Risk of Bias: no serious.** Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Imprecision: very serious.** Low number of patients, Wide confidence intervals, Only data from one study.
6. **Risk of Bias: no serious.** Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study.
8. **Risk of Bias: serious.** Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study.
9. Systematic review [68] with included studies: CORIMUNO-19 2020, REMAP-CAP 2021, Kyriazopoulou 2021.
10. **Imprecision: serious.** Wide confidence intervals.
11. Systematic review [68] with included studies: Kyriazopoulou 2021, CORIMUNO-19 2020.
14. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/ lack of blinding of outcome assessors, resulting in potential for detection bias, Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study.
15. Systematic review [68] with included studies: Kyriazopoulou 2021.
16, 17. **Imprecision: very serious.** Wide confidence intervals, Only data from one study.

**References**

64. CORIMUNO-19 Collaborative Group. Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild to moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial. Lancet Respiratory Medicine 2020. Pubmed Journal Website

66. Kyriazopoulou E, Poulakou G, Milionis H. Early Anakinra Treatment for COVID-19 Guided by Urokinase Plasminogen Receptor. medRxiv 18 May 2021. Journal Website

68. Anakinra for COVID-19.

69. Therapeutic Goods Administration. Australian Product Information - Kineret (anakinra). 16 February 2021. Website

90. Kyriazopoulou E, Poulakou G, Milionis H, Metallidis S, Adamis G, Tsiakos K, et al. Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial. Nature Medicine 2021;27(10):1752-1760 Pubmed Journal

93. Derde L, The REMAP-CAP Investigators. Effectiveness of Tocilizumab, Sarilumab, and Anakinra for critically ill patients with COVID-19. medRxiv 22 June 2021. Journal Website

96. Declercq J, Van Damme KFA, De Leeuw E, Maes B, Bosteels C, Tavernier SJ, et al. Effect of anti-interleukin drugs in patients with COVID-19 and signs of cytokine release syndrome (COV-AID): a factorial, randomised, controlled trial. Lancet Respiratory Medicine 2021;9(12):1427-1438 Pubmed Journal

98. Anakinra for COVID-19.

## 2.8.2 CD24Fc

Only in research settings

Do not use CD24Fc for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use CD24Fc to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

**Evidence to decision**

**Benefits and harms**

Small net benefit, or little difference between alternatives

There were no differences with regards to all-cause mortality, adverse events or serious adverse events. CD24Fc may result in a greater incidence of clinical improvement and discharge from hospital, decreased incidence of clinical progression, and reduced time to improvement and hospital discharge, however we are uncertain whether this is close to the true effect.

**Certainty of the evidence**

Low

Certainty of the evidence is low for all outcomes due to very serious imprecision (reliance on a single small study, and wide confidence intervals).

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
Variability may be expected in preferences and values for these populations given the potentially different goals of care.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

There is currently limited evidence about the impact of CD24Fc on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that CD24Fc should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** CD24Fc
**Comparator:** Placebo

### Summary

There remains significant uncertainty whether the immunomodulator CD24Fc is more effective and safer than placebo in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial that compared CD24Fc with placebo in 234 hospitalised adults who required oxygen support (oxygen saturation of 94% or less) *[70]*.

**Study characteristics**
Mean age of participants was 58 years and 38% were women. Approximately two thirds of participants had two or more comorbidities, with the highest proportion being hypertension (55%) and diabetes (21%). A total of 84% of participants received concomitant corticosteroids, over two thirds (68%) received remdesivir, and almost all patients received treatment with antithrombotic agents (95%). Pregnant and breastfeeding women were ineligible.

**What are the main results?**
There were no differences with regards to all-cause mortality, adverse events or serious adverse events. CD24Fc may result in a greater incidence of clinical improvement and discharge from hospital, decreased incidence of clinical progression, and reduced time to improvement and hospital discharge, however we are uncertain whether this is close to the true effect.

**Our confidence in the results**
Certainty of the evidence is low for all outcomes due to very serious imprecision (reliance on a single small study, and wide confidence intervals).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Placebo | **Intervention** CD24Fc | **Certainty of the evidence** (Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality** Within 29 days of treatment 9 Critical | Relative risk 0.9 (CI 95% 0.49 — 1.69) Based on data from 234 participants in 1 studies. [1] (Randomized controlled) | **153** per 1000 Difference: | **138** per 1000 **15 fewer per 1000** ( CI 95% 78 fewer — 106 more ) | **Low** Due to very serious imprecision [2] | We are uncertain whether CD24Fc impacts death (34 events). |
| **All-cause mortality or respiratory failure** Within 29 days of treatment 9 Critical | Relative risk 0.8 (CI 95% 0.51 — 1.25) Based on data from 234 participants in 1 studies. [3] (Randomized controlled) | **280** per 1000 Difference: | **224** per 1000 **56 fewer per 1000** ( CI 95% 137 fewer — 70 more ) | **Low** Due to very serious imprecision [4] | CD24Fc may decrease death or respiratory failure (59 events). |
| **Clinical improvement** Within 28 days of treatment 6 Important | Relative risk 1.16 (CI 95% 0.99 — 1.37) Based on data from 234 participants in 1 studies. [5] (Randomized controlled) | **661** per 1000 Difference: | **767** per 1000 **106 more per 1000** ( CI 95% 7 fewer — 245 more ) | **Low** Due to very serious imprecision [6] | CD24Fc may increase clinical improvement (167 events). |
| **Discharge from hospital** Within 28 days of treatment 6 Important | Relative risk 1.18 (CI 95% 1 — 1.39) Based on data from 234 participants in 1 studies. [7] (Randomized controlled) | **653** per 1000 Difference: | **771** per 1000 **118 more per 1000** ( CI 95% 0 fewer — 255 more ) | **Low** Due to very serious imprecision [8] | CD24Fc may increase discharge from hospital (166 events). |
| **Clinical progression** Within 28 days of treatment 6 Important | Relative risk 0.62 (CI 95% 0.39 — 0.99) Based on data from 234 participants in 1 studies. [9] (Randomized controlled) | **305** per 1000 Difference: | **189** per 1000 **116 fewer per 1000** ( CI 95% 186 fewer — 3 fewer ) | **Low** Due to very serious imprecision [10] | CD24Fc may decrease clinical progression (48 events). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>CD24Fc | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Adverse events**<br>Within 29 days of treatment<br><br>6 Important | Relative risk 0.92<br>(CI 95% 0.62 — 1.38)<br>Based on data from 229 participants in 1 studies. [11]<br>(Randomized controlled) | **304**<br>per 1000<br><br>Difference: | **280**<br>per 1000<br><br>**24 fewer per 1000**<br>( CI 95% 116 fewer — 116 more ) | **Low**<br>Due to very serious imprecision [12] | CD24Fc may have little impact on adverse events (67 events). |
| **Serious adverse events**<br>Within 29 days of treatment<br><br>6 Important | Relative risk 0.97<br>(CI 95% 0.61 — 1.56)<br>Based on data from 229 participants in 1 studies. [13]<br>(Randomized controlled) | **235**<br>per 1000<br><br>Difference: | **228**<br>per 1000<br><br>**7 fewer per 1000**<br>( CI 95% 92 fewer — 132 more ) | **Low**<br>Due to very serious imprecision [14] | CD24Fc may have little impact on serious adverse events (53 events). |
| **Time to improvement**<br>Days<br><br>6 Important | Based on data from 234 participants in 1 studies. [15]<br>(Randomized controlled) | **6**<br>(Median)<br><br>Difference: | **10**<br>(Median)<br><br>**4 more**<br>CI 95% | **Low**<br>Due to very serious imprecision [16] | CD24Fc may decrease time to improvement. |
| **Time to discharge**<br>Days<br><br>6 Important | Based on data from 234 participants in 1 studies. [17]<br>(Randomized controlled) | **7**<br>(Median)<br><br>Difference: | **10.5**<br>(Median)<br><br>**3.5 more**<br>CI 95% | **Low**<br>Due to very serious imprecision [18] | CD24Fc may decrease time to discharge. |

1, 3, 5, 7, 9, 11, 13. Systematic review [104] with included studies: Welker et al 2022.
2. **Imprecision: very serious.** Only data from one study, Wide confidence intervals.
4, 6, 8, 10, 12, 14. **Imprecision: very serious.** Wide confidence intervals, Only data from one study.
15, 17. Systematic review [104]
16, 18. **Imprecision: very serious.** Wide confidence intervals, Only data from one study, due to [reason].

### References

70. Welker J, Pulido JD, Catanzaro AT, Malvestutto CD, Li Z, Cohen JB, et al. Efficacy and safety of CD24Fc in hospitalised patients with COVID-19: a randomised, double-blind, placebo-controlled, phase 3 study. Lancet Infectious Diseases 2022. Pubmed Journal

104. CD24Fc for COVID-19.

105. Dougan M, Azizad M, Chen P. Bebtelovimab, alone or together with bamlanivimab and etesevimab, as a broadly neutralizing monoclonal antibody treatment for mild to moderate, ambulatory COVID-19. medRxiv 12 March 2022. Journal Website

## 2.8.3 Lenzilumab

Only in research settings

Do not use lenzilumab for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use lenzilumab for the treatment of COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### Evidence to decision

**Benefits and harms**

There is insufficient information to determine whether lenzilumab is safe for the treatment of COVID-19. As lenzilumab is not listed in the Australian Register of Therapeutic Goods and is currently not approved for use in Australia, there are no reliable safety data to inform treatment with lenzilumab.

**Certainty of the evidence**

Very low

Certainty of the evidence is low for adverse and serious adverse events and time to recovery due to very serious imprecision (wide confidence intervals and reliance on a single study), and very low for septic shock (few events).

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the effects of lenzilumab during pregnancy and breastfeeding are unknown in the context of COVID-19.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

**General adult population**
There is currently limited evidence about the impact of lenzilumab on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that lenzilumab should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or**

**cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of lenzilumab to treat COVID-19 in these populations should be avoided until evidence becomes available.

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### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Lenzilumab
**Comparator:** Placebo

### Summary

We are uncertain if lenzilumab is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial that compared lenzilumab with placebo in 479 adults hospitalised with moderate to severe COVID-19 *[111]*.

**Publication status**
The study is only available as a preprint (posted to medRxiv on 5 May 2021) and has therefore not been peer reviewed.

**Study characteristics**
Median age of participants was 61 years and 35% were women. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
No critical outcomes (mortality, invasive mechanical ventilation or respiratory failure or ARDS) were reported. For the important outcomes, lenzilumab may decrease the incidence of adverse and serious adverse events slightly. It is unclear whether lenzilumab increases or decreases the incidence of septic shock and time to recovery.

**Our confidence in the results**
Certainty of the evidence is low for adverse and serious adverse events and time to recovery due to very serious imprecision (wide confidence intervals and reliance on a single study), and very low for septic shock (wide confidence intervals, reliance on a single study and few events).

**Additional information**
As of 14 May 2021, lenzilumab is not listed in the Australian Register of Therapeutic Goods and is not approved for use in Australia. There are no reliable safety data to inform treatment with lenzilumab.

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Placebo | **Intervention** Lenzilumab | **Certainty of the evidence** (Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Serious adverse events** End of follow-up<br>6 Important | Relative risk 0.84 (CI 95% 0.63 — 1.11) Based on data from 512 participants in 1 studies. [1] (Randomized controlled) | 296 per 1000<br>Difference: | 249 per 1000<br>**47 fewer per 1000** ( CI 95% 110 fewer — 33 more ) | **Low** Due to very serious imprecision [2] | Lenzilumab may decrease serious adverse events slightly (139 events). |
| **Adverse events** End of follow-up<br>6 Important | Relative risk 0.82 (CI 95% 0.62 — 1.07) Based on data from 512 participants in 1 studies. [3] (Randomized controlled) | 327 per 1000<br>Difference: | 268 per 1000<br>**59 fewer per 1000** ( CI 95% 124 fewer — 23 more ) | **Low** Due to very serious imprecision [4] | Lenzilumab may decrease adverse events slightly (152 events). |
| **Septic shock** End of follow-up | Relative risk 0.56 (CI 95% 0.19 — 1.63) | | | **Very low** Due to very serious | We are uncertain whether lenzilumab increases or |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Lenzilumab | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| 6 Important | Based on data from 512 participants in 1 studies. [5] (Randomized controlled) | | | imprecision [6] | decreases septic shock (14 events). |
| **Time to recovery**<br>Median (Days)<br>6 Important | Lower better<br>Based on data from 479 participants in 1 studies.<br>(Randomized controlled) | 8<br>(Median) | 8<br>(Median)<br>CI 95% | **Low**<br>Due to very serious imprecision [7] | Lenzilumab may make little or no difference to time to recovery. |

1. Systematic review [109] with included studies: Temesgen 2021.
2, 4. **Imprecision: very serious.** Wide confidence intervals, Only data from one study.
3, 5. Systematic review [72] with included studies: Temesgen 2021.
6. **Imprecision: very serious.** Only data from one study, Wide confidence intervals, due to few events.
7. **Imprecision: very serious.** Only data from one study, Wide confidence intervals.

### References

72. Lenzilumab for COVID-19.

109. Lenzilumab for COVID-19.

111. Temesgen Z, Burger C, Baker J. Lenzilumab efficacy and safety in newly hospitalized COVID-19 subjects: results from the live-air phase 3 randomized double-blind placebo-controlled trial. medRxiv 2021. Journal Website

## 2.8.4 Ruxolitinib

Only in research settings

Do not use ruxolitinib for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Ruxolitinib should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use ruxolitinib to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

## Evidence to decision

### Benefits and harms

Important harms

**General adult population**
In addition to uncertainty around the benefits for patients with COVID-19, there are well-known side effects and harms of ruxolitinib. Although most of the information on side effects and harms is derived from long-term use, potential harms include thrombocytopaenia and other haematological adverse reactions, and increased incidence of bacterial and other infections.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There are additional concerns regarding harms as ruxolitinib has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain. No studies pertained to the safety of ruxolitinib (for any indication) for pregnant or breastfeeding women.

### Certainty of the evidence

Very low

**General adult population**
Certainty of the evidence is low for death and very low for all other outcomes due to serious risk of bias (lack of blinding of outcome assessors) and very serious imprecision (low number of patients and observed events).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

### Values and preferences

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of ruxolitinib in pregnancy are unknown.

### Resources and other considerations

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

## Rationale

**General adult population**
There is currently limited evidence about the impact of ruxolitinib on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that ruxolitinib should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of ruxolitinib to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Special populations with COVID-19
**Intervention:** Ruxolitinib
**Comparator:** Placebo

### Summary

We are uncertain if ruxolitinib is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from a single randomised trial that compared ruxolitinib with placebo (vitamin C) in 41 adults hospitalised with severe COVID-19 *[73]*.

**Study characteristics**
Median age of participants was 63 years and 42% were women. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
For the critical outcomes, there were too few events (three deaths, nine who required invasive mechanical ventilation and two who experienced septic shock) to determine whether ruxolitinib makes a difference. We are uncertain whether ruxolitinib increases or decreases the likelihood of clinical improvement, time to discharge from hospital or adverse events. Four patients in the control group experienced serious adverse events.

**Our confidence in the results**
Certainty of the evidence is very low for all outcomes. This judgement is based on serious risk of bias (unblinded outcome assessors), serious indirectness (limited inclusion or absence of these populations) and very serious imprecision (low patient numbers, few observed events and reliance on a single study). Death was not downgraded for risk of bias as this outcome is unlikely to be affected by lack of blinding.

**Additional information**
The Therapeutic Goods Administration highlights several potential side effects associated with ruxolitinib, including thrombocytopaenia and other haematological adverse reactions, and increased incidence of bacterial and other infections. Cases of progressive multifocal leukoencephalopathy and non-melanoma skin cancer have also been reported in patients treated with ruxolitinib *[74]*.

There is insufficient safety data on the use of ruxolitinib in **children and adolescents** for other indications.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Ruxolitinib | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality (Day 28)**<br>Within 28 days of commencing treatment<br>9 Critical | Odds ratio 0.13<br>(CI 95% 0.01 — 2.67)<br>Based on data from 41 participants in 1 studies. [1]<br>(Randomized controlled) | | | **Very low**<br>Due to serious indirectness and very serious imprecision [2] | There were too few who died to determine whether ruxolitinib makes a difference (3 events). |
| **Invasive mechanical ventilation**<br>Within 28 days of commencing treatment<br>9 Critical | Odds ratio 0.22<br>(CI 95% 0.04 — 1.24)<br>Based on data from 41 participants in 1 studies. [3]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and indirectness, and very serious imprecision [4] | There were too few who required invasive mechanical ventilation to determine whether ruxolitinib makes a difference (9 events). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Ruxolitinib | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Septic shock**<br>Within 28 days of commencing treatment<br><br>9 Critical | Odds ratio 0.19<br>(CI 95% 0.01 — 4.22)<br>Based on data from 41 participants in 1 studies. [5]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and indirectness, and very serious imprecision [6] | There were too few who experienced septic shock to determine whether ruxolitinib makes a difference (2 events). |
| **Clinical improvement**<br>At day 14 of treatment<br><br>6 Important | Odds ratio 2<br>(CI 95% 0.58 — 6.94)<br>Based on data from 41 participants in 1 studies. [7]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and indirectness, and very serious imprecision [8] | We are uncertain whether ruxolitinib improves or worsens clinical improvement (21 events). |
| **Adverse events**<br>Within 28 days of commencing treatment<br><br>6 Important | Odds ratio 1.35<br>(CI 95% 0.36 — 5.04)<br>Based on data from 41 participants in 1 studies. [9]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and indirectness, and very serious imprecision [10] | We are uncertain whether ruxolitinib increases or decreases adverse events (13 events). |
| **Serious adverse events**<br>Within 28 days of commencing treatment<br><br>6 Important | Odds ratio 0.09<br>(CI 95% 0 — 1.89)<br>Based on data from 41 participants in 1 studies. [11]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and indirectness, and very serious imprecision [12] | There were too few who experienced serious adverse events to determine whether ruxolitinib makes a difference (4 events). |
| **Clinical deterioration**<br>At day 14 of treatment<br><br>6 Important | Odds ratio 0.09<br>(CI 95% 0 — 1.89)<br>Based on data from 41 participants in 1 studies. [13]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and indirectness, and very serious imprecision [14] | We are uncertain whether ruxolitinib improves or worsens clinical deterioration (4 events). |
| **Time to improvement**<br>Median days to improvement<br><br>6 Important | Lower better [15]<br>(Randomized controlled) | **15**<br>(Median) | **12**<br>(Median)<br><br>CI 95% | **Very low**<br>Due to serious risk of bias and indirectness, and very serious imprecision [16] | We are uncertain whether ruxolitinib decreases time to improvement. |
| **Time to discharge**<br>Median days to discharge | Lower better [17]<br>(Randomized controlled) | **16**<br>(Median) | **17**<br>(Median) | **Very low**<br>Due to serious risk of bias and indirectness, and | We are uncertain whether ruxolitinib increases or decreases time to discharge. |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Placebo | **Intervention** Ruxolitinib | **Certainty of the evidence** (Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| 6 Important | | | CI 95% | very serious imprecision [18] | |

1, 3, 5, 7, 9, 11, 13. Systematic review [75] with included studies: Cao Y 2020.
2. **Indirectness: serious. Imprecision: very serious.** Low number of patients, Only data from one study.
4, 6, 8, 10, 12, 14, 16, 18. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Indirectness: serious. Imprecision: very serious.** Low number of patients, Only data from one study.
15, 17. with included studies: [73].

### References

73. Cao Y, Wei J, Zou L. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-2019): a multicenter, single-blind, randomized controlled trial. Journal of Allergy and Clinical Immunology 2020. Pubmed Journal Website

74. Therapeutic Goods Administration. Australian Product Information: Jakavi (ruxolitinib). 2018. Website

75. Ruxolitinib for COVID-19.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Ruxolitinib
**Comparator:** Placebo

### Summary

We are uncertain if ruxolitinib is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from a single randomised trial that compared ruxolitinib with placebo (vitamin C) in 41 adults hospitalised with severe COVID-19 *[73]*.

**Study characteristics**
Median age of participants was 63 years and 42% were women. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
For the critical outcomes, there were too few events (three deaths, nine who required invasive mechanical ventilation and two who experienced septic shock) to determine whether ruxolitinib makes a difference. We are uncertain whether ruxolitinib increases or decreases the likelihood of clinical improvement, time to discharge from hospital or adverse events. Four patients in the control group experienced serious adverse events.

**Our confidence in the results**
Certainty of the evidence is low for death and very low for all other outcomes. This judgement is based on serious risk of bias (unblinded outcome assessors) and very serious imprecision (low patient numbers, few observed events and reliance on a single study). Death was not downgraded for risk of bias as this outcome is unlikely to be affected by lack of blinding.

**Additional information**
The Therapeutic Goods Administration highlights several potential side effects associated with ruxolitinib, including thrombocytopaenia and other haematological adverse reactions, and increased incidence of bacterial and other infections. Cases of progressive multifocal leukoencephalopathy and non-melanoma skin cancer have also been reported in patients treated with ruxolitinib *[74]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Ruxolitinib | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality (Day 28)**<br>Within 28 days of commencing treatment<br>9 Critical | Odds ratio 0.13<br>(CI 95% 0.01 — 2.67)<br>Based on data from 41 participants in 1 studies. [1]<br>(Randomized controlled) | **143**<br>per 1000<br>Difference: | **21**<br>per 1000<br>**122 fewer per 1000**<br>( CI 95% 141 fewer — 165 more ) | **Very low**<br>Due to extremely serious imprecision [2] | There were too few who died to determine whether ruxolitinib makes a difference (3 events). |
| **Invasive mechanical ventilation**<br>Within 28 days of commencing treatment<br>9 Critical | Odds ratio 0.22<br>(CI 95% 0.04 — 1.24)<br>Based on data from 41 participants in 1 studies. [3]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [4] | There were too few who required invasive mechanical ventilation to determine whether ruxolitinib makes a difference (9 events). |
| **Septic shock**<br>Within 28 days of commencing treatment<br>9 Critical | Odds ratio 0.19<br>(CI 95% 0.01 — 4.22)<br>Based on data from 41 participants in 1 studies. [5]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [6] | There were too few who experienced septic shock to determine whether ruxolitinib makes a difference (2 events). |
| **Clinical improvement**<br>At day 14 of treatment<br>6 Important | Odds ratio 2<br>(CI 95% 0.58 — 6.94)<br>Based on data from 41 participants in 1 studies. [7]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [8] | We are uncertain whether ruxolitinib improves or worsens clinical improvement (21 events). |
| **Adverse events**<br>Within 28 days of commencing treatment<br>6 Important | Odds ratio 1.35<br>(CI 95% 0.36 — 5.04)<br>Based on data from 41 participants in 1 studies. [9]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [10] | We are uncertain whether ruxolitinib increases or decreases adverse events (13 events). |
| **Serious adverse events**<br>Within 28 days of commencing treatment<br>6 Important | Odds ratio 0.09<br>(CI 95% 0 — 1.89)<br>Based on data from 41 participants in 1 studies. [11]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [12] | There were too few who experienced serious adverse events to determine whether ruxolitinib makes a difference (4 events). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Ruxolitinib | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Clinical deterioration**<br>At day 14 of treatment<br><br>6 Important | Odds ratio 0.09<br>(CI 95% 0 — 1.89)<br>Based on data from 41 participants in 1 studies. [13]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [14] | We are uncertain whether ruxolitinib improves or worsens clinical deterioration (4 events). |
| **Time to improvement**<br>Median days to improvement<br><br>6 Important | Lower better<br>[15] (Randomized controlled) | **15**<br>(Median) | **12**<br>(Median)<br><br>CI 95% | **Very low**<br>Due to serious risk of bias and very serious imprecision [16] | We are uncertain whether ruxolitinib decreases time to improvement. |
| **Time to discharge**<br>Median days to discharge<br><br>6 Important | Lower better<br>[17] (Randomized controlled) | **16**<br>(Median) | **17**<br>(Median)<br><br>CI 95% | **Very low**<br>Due to serious risk of bias and very serious imprecision [18] | We are uncertain whether ruxolitinib increases or decreases time to discharge. |

1, 3, 5, 7, 9, 11, 13. Systematic review [75] with included studies: Cao Y 2020.
2. **Imprecision: extremely serious.** Low number of patients, Only data from one study, Wide confidence intervals, due to few events.
4, 6, 8, 10, 12, 14, 16, 18. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: very serious.** Low number of patients, Only data from one study.
15, 17. with included studies: [73].

### References

73. Cao Y, Wei J, Zou L. Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-2019): a multicenter, single-blind, randomized controlled trial. Journal of Allergy and Clinical Immunology 2020. Pubmed Journal Website

74. Therapeutic Goods Administration. Australian Product Information: Jakavi (ruxolitinib). 2018. Website

75. Ruxolitinib for COVID-19.

## 2.8.5 Tofacitinib

Only in research settings

Do not use tofacitinib for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Tofacitinib should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use tofacitinib for the treatment of COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### Evidence to decision

**Benefits and harms**

Small net benefit, or little difference between alternatives

**General adult population**
In addition to uncertainty around benefits for patients with COVID-19, there are well-known side effects and harms associated with tofacitinib, including thrombosis and increased risk of serious infection.

**Certainty of the evidence**

Low

**General adult population**
Certainty of the evidence for all outcomes is low due to very serious imprecision (reliance on a single study and wide confidence intervals and/or few events).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of tofacitinib in pregnancy are unknown.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

**General adult population**
There is currently limited evidence about the impact of tofacitinib on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that tofacitinib should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of tofacitinib to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Tofacitinib
**Comparator:** Placebo

### Summary

There remains significant uncertainty whether tofacitinib is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial that compared tofacitinib with placebo in 289 adults hospitalised with moderate-to-critical COVID-19 *[77]*.

**Study characteristics**
Mean age of participants was 56 years and 35% were women. Most patients received concomitant corticosteroids (90%) and prophylactic anticoagulation (78%). Pregnant women were ineligible.

**What are the main results?**
We are uncertain whether tofacitinib makes a difference to death, adverse or serious adverse events, discontinuation due to adverse events or discharge from hospital.

**Our confidence in the results**
Certainty of the evidence for all outcomes is low due to very serious imprecision (reliance on a single study, wide confidence intervals and/or few events).

For children and adolescents and pregnant and breastfeeding women, certainty is very low due to serious indirectness (absence of inclusion of these populations in the included study).

**Additional information**
According to the Therapeutic Goods Administration, potential side effects of tofacitinib include an increased risk of serious infections and thrombosis. It is noted that tofacitinib must not be used in combination with biological agents or other potent immunosuppressive agents.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Tofacitinib | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 28 days of commencing treatment | Relative risk 0.49<br>(CI 95% 0.14 — 1.66)<br>Based on data from 289 participants in 1 studies. [1] | **55**<br>per 1000<br><br>Difference: | **27**<br>per 1000<br><br>**28 fewer per 1000**<br>( CI 95% 47 fewer | **Low**<br>Due to very serious imprecision | We are uncertain whether tofacitinib impacts risk of death (12 events). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Tofacitinib | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| 9 Critical | | | — 36 more ) | | |
| **Serious adverse events**<br>End of follow-up<br>6 Important | Relative risk 1.21<br>(CI 95% 0.6 — 2.41)<br>Based on data from 284 participants in 1 studies. [2] | **120**<br>per 1000<br>Difference: | **145**<br>per 1000<br>**25 more per 1000**<br>( CI 95% 48 fewer — 169 more ) | **Low**<br>Due to very serious imprecision | We are uncertain whether tofacitinib increases or decreases serious adverse events (37 events). |
| **Adverse events**<br>End of follow-up<br>6 Important | Relative risk 1.21<br>(CI 95% 0.7 — 2.09)<br>Based on data from 284 participants in 1 studies. [3] | **225**<br>per 1000<br>Difference: | **272**<br>per 1000<br>**47 more per 1000**<br>( CI 95% 67 fewer — 245 more ) | **Low**<br>Due to very serious imprecision | Tofacitinib may increase adverse events slightly (69 events). |
| **Discontinuation due to adverse events**<br>During treatment<br>6 Important | Relative risk 3.2<br>(CI 95% 1.2 — 8.5)<br>Based on data from 284 participants in 1 studies. [4] | **35**<br>per 1000<br>Difference: | **112**<br>per 1000<br>**77 more per 1000**<br>( CI 95% 7 more — 263 more ) | **Low**<br>Due to very serious imprecision | Tofacitinib may increase discontinuation due to adverse events slightly (21 events). |
| **Discharge from hospital**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 1.05<br>(CI 95% 0.97 — 1.12)<br>Based on data from 289 participants in 1 studies. [5] | **890**<br>per 1000<br>Difference: | **934**<br>per 1000<br>**44 more per 1000**<br>( CI 95% 27 fewer — 107 more ) | **Low**<br>Due to very serious imprecision | Tofacitinib may increase discharge from hospital slightly (134 events). |

1, 2, 3, 4, 5. Systematic review [76] with included studies: GuimarÃ£es 2021.

### References

76. Tofacitinib for COVID-19.

77. Guimarães PO, Quirk D, Furtado RH, Maia LN, Saraiva JF, Antunes MO, et al. Tofacitinib in patients hospitalized with Covid-19 pneumonia. New England Journal of Medicine 2021. Pubmed Journal

## 2.9 Interferons

### 2.9.1 Interferon beta-1a (inhaled)

Only in research settings

Do not use inhaled interferon beta-1a for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Inhaled interferon β-1a should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use inhaled interferon β-1a to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

**Evidence to decision**

**Benefits and harms**

Important harms

**General adult population**
Although there remains uncertainty about the effects of inhaled interferon β-1a on adverse or serious adverse events in patients with COVID-19, there are well-known side effects and harms associated with interferon β-1a including thrombotic microangiopathy, hepatic injury, nephrotic syndrome and depression with suicidal ideation.

**Children and adolescents, people requiring palliative care and older people living with frailty or cognitive impairment**
There are additional concerns regarding harms as interferon β-1a has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

**Pregnant and breastfeeding women**
Evidence suggests that interferon β-1a in pregnant women is not associated with an increase in early pregnancy loss, stillbirths or congenital anomalies.

**Certainty of the evidence**

Very low

Certainty of the evidence is low for adverse and serious adverse events, discharge from hospital and the composite outcome of invasive mechanical ventilation or death. This judgement is based on very serious imprecision due to low patient numbers and reliance on a single study.

Certainty is very low for death based on very serious imprecision (due to the aforementioned issues, with the addition of low event numbers). Certainty was also very low for clinical recovery and clinical improvement, as many of these values were derived using the last observation carried forward method.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

**General adult population**
There is currently limited evidence about the impact of inhaled interferon β-1a on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that inhaled interferon β-1a should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of inhaled interferon β-1a to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Inhaled interferon β-1a
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether inhaled interferon β-1a is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial that compared inhaled interferon β-1a with placebo in 98 adults hospitalised with moderate or severe COVID-19 *[79]*.

**Study characteristics**
Mean age of patients was 58 years and 41% were women. Patients in the intervention group received 6 mIU of nebulised interferon β-1a a day for 14 days. Pregnant women were ineligible.

**What are the main results?**
We are uncertain whether inhaled interferon β-1a has an impact on death, the composite outcome of invasive mechanical ventilation or death, discharge from hospital, adverse or serious adverse events, or the number of patients who experience clinical recovery or clinical improvement.

**Our confidence in the results**
Certainty of the evidence is low for adverse or serious adverse events, discharge from hospital and the composite outcome of invasive mechanical ventilation or death. This judgement is based on very serious imprecision due to low patient numbers and reliance on a single

study. Certainty is very low for death based on very serious imprecision (due to the aforementioned issues, with the addition of low event numbers). Certainty was also very low for clinical recovery and clinical improvement, as many of these values were derived using the last observation carried forward method.

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
The Therapeutic Goods Administration highlights several potential side effects associated with the use of interferon β-1a, including thrombotic microangiopathy, hepatic injury, nephrotic syndrome and depression with suicidal ideation. Interferon β-1a is also associated with immune reactions that can produce flu-like symptoms *[84][81]*.

Paediatricians have limited experience with interferon β-1a in **children and adolescents** for other indications. To date, no specific information on its benefits or harms has been collected for treating COVID-19 in this population.

Interferon β-1a is used in **pregnancy** for the treatment of multiple sclerosis. Evidence has shown no correlation between the use of interferon β-1a and increases in early pregnancy loss, stillbirths or congenital anomalies *[78]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Inhaled interferon β-1a | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 28 days of commencing treatment<br><br>9 Critical | Relative risk 0.15<br>(CI 95% 0.01 — 2.8)<br>Based on data from 98 participants in 1 studies. [1]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision [2] | There were too few who died to determine whether inhaled interferon β-1a makes a difference (3 deaths). |
| **Invasive mechanical ventilation or death [composite]**<br>Within 28 days of commencing treatment<br><br>9 Critical | Relative risk 0.63<br>(CI 95% 0.16 — 2.47)<br>Based on data from 98 participants in 1 studies. [3]<br>(Randomized controlled) | **100**<br>per 1000<br><br>Difference: | **63**<br>per 1000<br><br>**37 fewer per 1000**<br>( CI 95% 84 fewer — 147 more ) | **Low**<br>Due to very serious imprecision [4] | We are uncertain whether inhaled interferon β-1a decreases invasive mechanical ventilation or death [composite] (8 events) |
| **Discharge from hospital**<br>Within 28 days of commencing treatment<br><br>6 Important | Relative risk 1.1<br>(CI 95% 0.85 — 1.44)<br>Based on data from 98 participants in 1 studies. [5]<br>(Randomized controlled) | **660**<br>per 1000<br><br>Difference: | **726**<br>per 1000<br><br>**66 more per 1000**<br>( CI 95% 99 fewer — 290 more ) | **Low**<br>Due to very serious imprecision [6] | We are uncertain whether inhaled interferon β-1a increases discharge from hospital at day 28 (68 events). |
| **Serious adverse events**<br>Within 28 days of | Relative risk 0.49<br>(CI 95% 0.22 — 1.09)<br>Based on data from 98 | **300**<br>per 1000 | **147**<br>per 1000 | **Low**<br>Due to very serious imprecision [8] | We are uncertain whether inhaled interferon β-1a increases or decreases serious adverse events (22 |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Inhaled interferon β-1a | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| commencing treatment<br><br>6 Important | participants in 1 studies. [7]<br>(Randomized controlled) | Difference: | **153 fewer per 1000**<br>( CI 95% 234 fewer — 27 more ) | | events). |
| **Adverse events**<br>Within 28 days of commencing treatment<br><br>6 Important | Relative risk 0.9<br>(CI 95% 0.64 — 1.27)<br>Based on data from 98 participants in 1 studies. [9]<br>(Randomized controlled) | **600**<br>per 1000<br><br>Difference: | **540**<br>per 1000<br><br>**60 fewer per 1000**<br>( CI 95% 216 fewer — 162 more ) | **Low**<br>Due to very serious imprecision [10] | We are uncertain whether inhaled interferon β-1a increases or decreases adverse events (56 events). |
| **Clinical recovery**<br>Within 28 days of commencing treatment<br><br>6 Important | Relative risk 1.99<br>(CI 95% 1.08 — 3.67)<br>Based on data from 98 participants in 1 studies. [11]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [12] | We are uncertain whether inhaled interferon β-1a increases or decreases clinical recovery. |
| **Clinical improvement**<br>Within 28 days of commencing treatment<br><br>6 Important | Relative risk 1.43<br>(CI 95% 1.01 — 2.02)<br>Based on data from 98 participants in 1 studies. [13]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [14] | We are uncertain whether inhaled interferon β-1a increases or decreases clinical improvement. |

1, 3, 5, 7, 9, 11, 13. Systematic review [82] with included studies: Monk 2020.
2. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study, due to few events.
4. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study.
6. **Imprecision: very serious.** Wide confidence intervals, Low number of patients.
8. **Imprecision: very serious.** Low number of patients, Only data from one study, Wide confidence intervals.
10. **Imprecision: very serious.** Low number of patients, Wide confidence intervals, Only data from one study.
12. **Risk of Bias: serious.** due to LOCF used for 28 days for clinical recovery. **Imprecision: very serious.** Low number of patients, Only data from one study, Wide confidence intervals.
14. **Risk of Bias: serious.** due to LOCF being used at day 28 of improvement. **Imprecision: very serious.** Low number of patients, Wide confidence intervals, Only data from one study.

### References

78. Hellwig K, Geissbuehler Y, Sabidó M, Popescu C, Adamo A, Klinger J, et al. Pregnancy outcomes in interferon-beta-exposed patients with multiple sclerosis: results from the European Interferon-beta Pregnancy Registry. Journal of Neurology 2020;267(6):1715-23 Pubmed Journal

79. Monk PD, Marsden RJ, Tear VJ, Brookes J, Batten TN, Mankowski M, et al. Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Respiratory Medicine 2020. Pubmed Journal

81. Therapeutic Goods Administration. Australian Product Information: Avonex (interferon beta-1a). 2019. Website

82. Interferon beta-1a for COVID-19.

84. Therapeutic Goods Administration. Australian Product Information: Rebif (interferon beta-1a). 2020. Website

## 2.9.2 Interferon beta-1b

Only in research settings

Do not use interferon beta-1b for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Interferon β-1b should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use interferon β-1b to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### Evidence to decision

**Benefits and harms**

Important harms

**General adult population**
In addition to uncertainty around benefits for patients with COVID-19, there are well-known side effects and harms associated with interferon beta-1b, including thrombotic microangiopathy, hepatic injury, nephrotic syndrome and depression with suicidal ideation.

**Children and adolescents, people requiring palliative care and older people living with frailty or cognitive impairment**
There are additional concerns regarding harms as interferon beta-1b has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

**Pregnant and breastfeeding women**
Evidence suggests that interferon beta-1b in pregnant women is not associated with an increase in early pregnancy loss, stillbirths or congenital anomalies.

**Certainty of the evidence**

Very low

Certainty of the evidence is low for discharge from hospital (days 14 and 28) and clinical deterioration (admission to intensive care unit) due to very serious imprecision (low patient numbers and reliance on a single study). Certainty for the remaining outcomes is additionally downgraded due to few observed events.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**

In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

**General adult population**
There is currently limited evidence about the impact of interferon β-1b on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that interferon β-1b should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of interferon β-1b to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Special populations with COVID-19
**Intervention:** Interferon β-1b
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether interferon beta-1b is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from a single randomised trial that compared interferon beta-1b with standard care in 66 adults hospitalised with severe COVID-19 *[129]*.

We have found one new study comparing interferon beta-1b with standard care (Darazam et al. Res Sq doi: 10.21203/rs.3.rs-136499/v1). This study is currently under review and an updated recommendation will be included in a future version of the guideline.

**Study characteristics**
Median age of patients was ~60 years in both groups and ~40% were women. Pregnant and breastfeeding women were ineligible.

**What are the main results?**

For the critical outcomes, there were too few events (eight deaths and eight who experienced respiratory failure) to determine whether interferon beta-1b makes a difference. We are uncertain whether interferon beta-1b reduces septic shock, clinical deterioration, discharge from hospital or time to discharge from hospital. Data for adverse and serious events were not reported.

**Our confidence in the results**
Certainty of the evidence is very low for all outcomes. This judgement is based on serious risk of bias (lack of blinding), very serious imprecision (low patient numbers, few observed events and reliance on a single study) and serious indirectness (limited inclusion of these populations). Death, respiratory failure or acute respiratory distress syndrome and septic shock were not downgraded for risk of bias as these outcomes are unlikely to be affected by lack of blinding.

**Additional information**
According to the Therapeutic Goods Administration, there are well-known side effects and harms associated with interferon beta-1b, including thrombotic microangiopathy, hepatic injury, nephrotic syndrome and depression with suicidal ideation *[125]*.

Efficacy and safety of interferon beta-1b has not been investigated in **children and adolescents** for other indications. To date, no specific information on its benefits or harms has been collected for treating COVID-19 in this population.

Interferon beta-1b is used in **pregnancy** for the treatment of multiple sclerosis. Evidence has shown no correlation between the use of Interferon beta-1b and increases in early pregnancy loss, stillbirths or congenital anomalies *[86]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Interferon β-1b | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 14 days of commencing treatment<br>9 Critical | Relative risk 0.33<br>(CI 95% 0.04 — 3.04)<br>Based on data from 66 participants in 1 studies. [1]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision and serious indirectness [2] | We are uncertain whether interferon β-1b increases or decreases death at 14 days (4 events). |
| **All-cause mortality**<br>Within 28 days of commencing treatment<br>9 Critical | Relative risk 0.33<br>(CI 95% 0.07 — 1.53)<br>Based on data from 66 participants in 1 studies. [3]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision and serious indirectness [4] | We are uncertain whether interferon β-1b increases or decreases death at 28 days (8 events). |
| **Respiratory failure or ARDS**<br>Within 28 days after commencing treatment<br>9 Critical | Relative risk 0.33<br>(CI 95% 0.07 — 1.53)<br>Based on data from 66 participants in 1 studies. [5]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision and serious indirectness [6] | We are uncertain whether interferon β-1b increases or decreases respiratory failure or ARDS (8 events). |
| **Septic shock**<br>Within 28 days of commencing treatment | Relative risk 0.25<br>(CI 95% 0.03 — 2.12)<br>Based on data from 66 participants in 1 studies. [7] | | | **Very low**<br>Due to very serious imprecision and serious | We are uncertain whether interferon β-1b increases or decreases septic shock (5 events). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Interferon β-1b | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| 6 Important | (Randomized controlled) | | | indirectness [8] | |
| **Adverse events**<br>6 Important | [9] | | | | Data for adverse events were not reported. |
| **Serious adverse events**<br>6 Important | [10] | | | | Data for serious adverse events were not reported. |
| **Discharge from hospital**<br>Within 14 days of commencing treatment<br>6 Important | Relative risk 1.44<br>(CI 95% 1.01 — 2.07)<br>Based on data from 66 participants in 1 studies. [11]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision, serious risk of bias and serious indirectness [12] | We are uncertain whether interferon β-1b may increases discharge from hospital within 14 days (44 events). |
| **Discharge from hospital**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 1.15<br>(CI 95% 0.96 — 1.38)<br>Based on data from 66 participants in 1 studies. [13]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision, serious risk of bias and serious indirectness [14] | We are uncertain whether interferon β-1b has any impact on discharge from hospital within 28 days (58 events). |
| **Clinical deterioration (admission to ICU)**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 0.64<br>(CI 95% 0.4 — 1.01)<br>Based on data from 66 participants in 1 studies. [15]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision, serious risk of bias and serious indirectness [16] | We are uncertain whether interferon β-1b has any impact on on clinical deterioration (based on admission to ICU; 36 events). |
| **Time to discharge from hospital**<br>Days<br>6 Important | Based on data from 66 participants in 1 studies. [17]<br>(Randomized controlled) | **13**<br>(Median) | **11**<br>(Median)<br>CI 95% | **Very low**<br>Due to very serious imprecision, serious risk of bias and serious indirectness [18] | We are uncertain whether interferon β-1b increases or decreases time to discharge from hospital. |

1, 3, 5, 7, 11, 13. Systematic review [126] with included studies: Rahmani 2020.
2, 4, 8. **Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: very serious.** Low number of patients, Only data from one study, due to few events.
6. **Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: very serious.** Low number of patients, due to few events, Only data from one study.
9, 10. Systematic review [126]
12, 14, 16, 18. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: very serious.** Low number of patients, Only data from one study.
15. Systematic review [122] with included studies: Rahmani 2020.
17. [129].

### References

86. Hellwig K, Geissbuehler Y, Sabidó M, Popescu C, Adamo A, Klinger J, et al. Pregnancy outcomes in interferon-beta-exposed patients with multiple sclerosis: results from the European Interferon-beta Pregnancy Registry. Journal of Neurology 2020;267(6):1715-23 Pubmed Journal

122. Interferon beta-1b for COVID-19.

125. Therapeutic Goods Administration. Australian Product Information: Betaferon (interferon beta-1b). July 2019. Website

126. Interferon beta-1b for COVID-19.

129. Rahmani H, Davoudi-Monfared E, Nourian A, Khalili H, Hajizadeh N, Jalalabadi NZ, et al. Interferon β-1b in treatment of severe COVID-19: a randomized clinical trial. International Immunopharmacology 2020;88:106903 Pubmed Journal

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Interferon β-1b
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether interferon beta-1b is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from a single randomised trial that compared interferon beta-1b with standard care in 66 adults hospitalised with severe COVID-19 *[129]*.

We have found one new study comparing interferon beta-1b with standard care (Darazam et al. Sci Rep doi: 10.1038/s41598-021-86859-y. This study is currently under review and an updated recommendation will be included in a future version of the guideline.

**Study characteristics**
Median age of patients was ~60 years in both groups and ~40% were women.

**What are the main results?**
For the critical outcomes, there were too few events (eight deaths and eight who experienced respiratory failure) to determine whether interferon beta-1b makes a difference. We are uncertain whether interferon beta-1b reduces septic shock, clinical deterioration, discharge from hospital or time to discharge from hospital. Data for adverse and serious events were not reported.

**Our confidence in the results**
Certainty of the evidence is low for discharge from hospital (days 14 and 28) and clinical deterioration (admission to intensive care unit) due to very serious imprecision (low patient numbers and reliance on a single study). Certainty for the remaining outcomes is additionally downgraded due to few observed events.

**Additional information**
According to the Therapeutic Goods Administration, there are well-known side effects and harms associated with interferon beta-1b, including thrombotic microangiopathy, hepatic injury, nephrotic syndrome and depression with suicidal ideation *[125]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Interferon β-1b | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 14 days of commencing treatment<br>9 Critical | Relative risk 0.33<br>(CI 95% 0.04 — 3.04)<br>Based on data from 66 participants in 1 studies. [1]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision [2] | There were too few events to determine whether interferon β-1b increases or decreases death at 14 days (4 events). |
| **All-cause mortality**<br>Within 28 days of commencing treatment<br>9 Critical | Relative risk 0.33<br>(CI 95% 0.07 — 1.53)<br>Based on data from 66 participants in 1 studies. [3]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision [4] | There were too few events to determine whether interferon β-1b increases or decreases death at 28 days (8 events). |
| **Respiratory failure or ARDS**<br>Within 28 days after commencing treatment<br>9 Critical | Relative risk 0.33<br>(CI 95% 0.07 — 1.53)<br>Based on data from 66 participants in 1 studies. [5]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision [6] | There were too few events to determine whether interferon β-1b increases or decreases respiratory failure or ARDS (8 events). |
| **Septic shock**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 0.25<br>(CI 95% 0.03 — 2.12)<br>Based on data from 66 participants in 1 studies. [7]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision [8] | There were too few events to determine whether interferon β-1b increases or decreases septic shock (5 events). |
| **Adverse events**<br>6 Important | [9] | | | | Data for adverse events were not reported. |
| **Serious adverse events** | [10] | | | | Data for serious adverse events were not reported. |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Interferon β-1b | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| 6 Important | | | | | |
| **Discharge from hospital**<br>Within 14 days of commencing treatment<br>6 Important | Relative risk 1.44<br>(CI 95% 1.01 — 2.07)<br>Based on data from 66 participants in 1 studies. [11]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision and serious risk of bias [12] | We are uncertain if interferon β-1b increases discharge from hospital within 14 days (44 events). |
| **Discharge from hospital**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 1.15<br>(CI 95% 0.96 — 1.38)<br>Based on data from 66 participants in 1 studies. [13]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision and serious risk of bias [14] | We are uncertain if interferon β-1b makes any difference to discharge from hospital within 28 days (58 events). |
| **Clinical deterioration (admission to ICU)**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 0.64<br>(CI 95% 0.4 — 1.01)<br>Based on data from 66 participants in 1 studies. [15]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision and serious risk of bias [16] | We are uncertain if interferon β-1b decreases clinical deterioration (based on admission to ICU; 36 events). |
| **Time to discharge from hospital**<br>Days<br>6 Important | Based on data from 66 participants in 1 studies. [17]<br>(Randomized controlled) | **13**<br>(Median) | **11**<br>(Median)<br>CI 95% | **Very low**<br>Due to very serious imprecision and serious risk of bias [18] | We are uncertain whether interferon β-1b increases or decreases time to discharge from hospital. |

1, 3, 5, 7, 11, 13. Systematic review [126] with included studies: Rahmani 2020.
2, 4, 8. **Imprecision: very serious.** Low number of patients, Only data from one study, due to few events.
6. **Imprecision: very serious.** Low number of patients, due to few events, Only data from one study.
9, 10. Systematic review [126]
12, 14, 16, 18. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: very serious.** Low number of patients, Only data from one study.
15. Systematic review [122] with included studies: Rahmani 2020.
17. [129].

**References**

86. Hellwig K, Geissbuehler Y, Sabidó M, Popescu C, Adamo A, Klinger J, et al. Pregnancy outcomes in interferon-beta-exposed patients with multiple sclerosis: results from the European Interferon-beta Pregnancy Registry. Journal of Neurology 2020;267(6):1715-23 Pubmed Journal

122. Interferon beta-1b for COVID-19.

125. Therapeutic Goods Administration. Australian Product Information: Betaferon (interferon beta-1b). July 2019. Website

126. Interferon beta-1b for COVID-19.

129. Rahmani H, Davoudi-Monfared E, Nourian A, Khalili H, Hajizadeh N, Jalalabadi NZ, et al. Interferon β-1b in treatment of severe COVID-19: a randomized clinical trial. International Immunopharmacology 2020;88:106903 Pubmed Journal

## 2.9.3 Interferon gamma

Only in research settings

Do not use interferon gamma for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Interferon gamma should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use interferon gamma to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

**Evidence to decision**

**Benefits and harms**

Important harms

**General adult population**
In addition to uncertainty around benefits for patients with COVID-19, there are well-known side effects and harms associated with interferon gamma including gastrointestinal disorders (such as diarrhoea, vomiting, nausea and abdominal pain), rash, fever and headache, and depression.

**Certainty of the evidence**

Very low

**General adult population**
Certainty of the evidence is very low for all outcomes due to serious imprecision (low patient numbers and the reliance on a single study) and risk of bias (missing outcome data for negative polymerase chain reaction and adverse events, and lack of blinding for discharge from hospital).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older**

**people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the effects of interferon gamma during pregnancy and breastfeeding are unknown in the context of COVID-19.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

**General adult population**
There is currently limited evidence about the impact of interferon gamma on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that interferon gamma should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of interferon gamma to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Special populations with COVID-19
**Intervention:** Interferon gamma
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether interferon gamma is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from a single randomised trial that compared interferon gamma with standard care in 63 adults hospitalised with mild or moderate COVID-19 *[87]*.

We have found one new study comparing interferon gamma with control (Myasnikov et al. Vopr Virusol doi: 10.36233/0507-4088-24). This study is currently under review and an updated recommendation will be included in a future version of the guideline.

**Publication status**
The study is only available as a preprint (posted to medRxiv on 4 August 2020) and has therefore not been peer reviewed.

**Study characteristics**
Median age was 42 years in the interferon gamma group and 31 years in the control group; the proportion of women was 53% and 39% respectively. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
No patients died or experienced serious adverse events. We are uncertain whether interferon gamma increases or decreases the likelihood of negative polymerase chain reaction (PCR) at days 3 and 5, discharge from hospital or adverse events.

**Our confidence in the results**
Certainty of the evidence is very low for all outcomes due to serious imprecision (low patient numbers and reliance on a single study), serious risk of bias (missing outcome data for negative PCR and adverse events, and lack of blinding for discharge from hospital) and serious indirectness (absence of these populations from the included studies).

**Additional information**
According to the Therapeutic Goods Administration, common adverse effects related to interferon gamma include gastrointestinal disorders (such as diarrhoea, vomiting, nausea and abdominal pain), rash, depression, fever and headache *[89]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Interferon gamma | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>21 days after commencing treatment<br>9 Critical | Based on data from 63 participants in 1 studies. [1] | | | | No patients died in the study. |
| **Adverse events**<br>21 days after commencing treatment<br>6 Important | Relative risk 1.21<br>(CI 95% 0.56 — 2.61)<br>Based on data from 57 participants in 1 studies. [2]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias, very serious imprecision and serious indirectness [3] | We are uncertain whether interferon gamma increases or decreases adverse events (18 events). |
| **Serious adverse events**<br>21 days after commencing treatment | Based on data from 63 participants in 1 studies. [4] | | | | No patients had serious adverse events. |
| **Negative PCR (Day 3)**<br>3 days after commencing treatment<br>6 Important | Relative risk 1.84<br>(CI 95% 1.04 — 3.25)<br>Based on data from 59 participants in 1 studies. [5]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias, very serious imprecision and serious indirectness [6] | We are uncertain whether interferon gamma increases the number of patients with negative PCR at day 3 (29 events). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Interferon gamma | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Negative PCR (Day 5)**<br>5 days after commencing treatment<br><br>6 Important | Relative risk 1.3<br>(CI 95% 1 — 1.68)<br>Based on data from 47 participants in 1 studies. [7]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias, very serious imprecision and serious indirectness [8] | We are uncertain whether interferon gamma increases the number of patients with negative PCR at day 5 (40 events). |
| **Discharge from hospital**<br>14 days after commencing treatment<br><br>6 Important | Relative risk 1.1<br>(CI 95% 0.97 — 1.24)<br>Based on data from 63 participants in 1 studies. [9]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias, very serious imprecision and serious indirectness [10] | We are uncertain whether interferon gamma increases discharge from hospital (60 events). |

1, 2, 4, 5, 7, 9. Systematic review [91] with included studies: Moynelo 2020.
3, 6, 8. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up. **Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: very serious.** Low number of patients, Only data from one study.
10. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/ lack of blinding of outcome assessors, resulting in potential for detection bias. **Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: very serious.** Low number of patients, Only data from one study.

### References

87. Moynelo E, Escribano P, Roberts D. Effect and safety of combination of interferon alpha-2b and gamma or interferon alpha-2b for negativization of SARS-CoV-2 viral RNA. Preliminary results of a randomized controlled clinical trial. medRxiv 2020. Journal Website

89. Therapeutic Goods Administration. Australian Product Information: Imukin. 13 September 2019. Website

91. Interferon gamma for COVID-19.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Interferon gamma
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether interferon gamma is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from a single randomised trial that compared interferon gamma with standard care in 63 adults hospitalised with mild or moderate COVID-19 *[87]*.

We have found one new study comparing interferon gamma with control (Myasnikov et al. Vopr Virusol doi: 10.36233/0507-4088-24). This study is currently under review and an updated recommendation will be included in a future version of the guideline.

**Publication status**
The study is only available as a preprint (posted to medRxiv on 4 August 2020) and has therefore not been peer reviewed.

**Study characteristics**
Median age was 42 years in the interferon gamma group and 31 years in the control group; the proportion of women was 53% and 39% respectively. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
No patients died or experienced serious adverse events. We are uncertain whether interferon gamma increases or decreases the likelihood of negative polymerase chain reaction (PCR) at days 3 and 5, discharge from hospital or adverse events.

**Our confidence in the results**
Certainty of the evidence is very low for all outcomes due to serious imprecision (low patient numbers and reliance on a single study) and serious risk of bias (missing outcome data for negative PCR and adverse events, and lack of blinding for discharge from hospital).

**Additional information**
According to the Therapeutic Goods Administration, common adverse effects related to interferon gamma include gastrointestinal disorders (such as diarrhoea, vomiting, nausea and abdominal pain), rash, depression, fever and headache *[89]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Interferon gamma | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>21 days after commencing treatment<br>9 Critical | Based on data from 63 participants in 1 studies. [1] | | | | No patients died in the study. |
| **Adverse events**<br>21 days after commencing treatment<br>6 Important | Relative risk 1.21<br>(CI 95% 0.56 — 2.61)<br>Based on data from 57 participants in 1 studies. [2]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [3] | We are uncertain whether interferon gamma increases or decreases adverse events (18 events). |
| **Serious adverse events**<br>21 days after commencing treatment | Based on data from 63 participants in 1 studies. [4] | | | | No patients had serious adverse events. |
| **Negative PCR (Day 3)**<br>3 days after commencing treatment | Relative risk 1.84<br>(CI 95% 1.04 — 3.25)<br>Based on data from 59 participants in 1 studies. [5]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [6] | We are uncertain whether interferon gamma increases the number of patients with negative PCR at day 3 (29 events). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Interferon gamma | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| 6 Important | | | | | |
| **Negative PCR (Day 5)**<br>5 days after commencing treatment<br>6 Important | Relative risk 1.3<br>(CI 95% 1 — 1.68)<br>Based on data from 47 participants in 1 studies. [7]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [8] | We are uncertain whether interferon gamma increases the number of patients with negative PCR at day 5 (40 events). |
| **Discharge from hospital**<br>14 days after commencing treatment<br>6 Important | Relative risk 1.1<br>(CI 95% 0.97 — 1.24)<br>Based on data from 63 participants in 1 studies. [9]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [10] | We are uncertain whether interferon gamma increases discharge from hospital (60 events). |

1, 2, 4, 5, 7, 9. Systematic review [91] with included studies: Moynelo 2020.
3, 6, 8. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up. **Imprecision: very serious.** Low number of patients, Only data from one study.
10. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/ lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: very serious.** Low number of patients, Only data from one study.

### References

87. Moynelo E, Escribano P, Roberts D. Effect and safety of combination of interferon alpha-2b and gamma or interferon alpha-2b for negativization of SARS-CoV-2 viral RNA. Preliminary results of a randomized controlled clinical trial. medRxiv 2020. Journal Website

89. Therapeutic Goods Administration. Australian Product Information: Imukin. 13 September 2019. Website

91. Interferon gamma for COVID-19.

## 2.9.4 Interferon kappa plus trefoil factor 2 (IFN-κ plus TFF2)

Only in research settings

Do not use interferon kappa plus trefoil factor 2 for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Interferon kappa plus trefoil factor 2 (IFN-κ plus TFF2) should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use IFN-κ plus TFF2 to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### Evidence to decision

**Benefits and harms**

**General adult population**
Data for deaths, adverse events or serious adverse events were not reported in the study. There remains uncertainty regarding the benefits of interferon kappa plus trefoil factor 2 (IFN-κ plus TFF2) in patients with COVID-19, as well as uncertainty regarding the safety profile of this combination therapy.

**Certainty of the evidence**

Very low

Certainty of the evidence is very low for all reported outcomes due to serious risk of bias (lack of blinding of patients and personnel) and very serious imprecision (reliance on a single study with low patient numbers and wide confidence intervals).

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the effects of IFN-κ plus TFF2 during pregnancy and breastfeeding are unknown in the context of COVID-19.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

**General adult population**

There is currently limited evidence about the impact of IFN-κ plus TFF2 on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that IFN-κ plus TFF2 should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of IFN-κ plus TFF2 for the treatment of COVID-19 in these populations should be avoided until evidence becomes available.

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### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** IFN-κ plus TFF2
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether therapy with interferon kappa plus trefoil factor 2 (IFN-κ plus TFF2) is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial that compared IFN-κ plus TFF2 with standard care in 80 adults hospitalised with COVID-19 *[135]*.

**Study characteristics**
Mean age of patients was 35 years in both groups and 36% were women. IFN-κ (2 mg) and TFF2 (5 mg) were dissolved in 5 ml of water and administered via aerosol inhalation once every 24 hours for six days. Standard care included hydroxychloroquine, antibiotics, vasopressors, antifever medicine, vitamin C, immune enhancers and/or traditional Chinese medicine. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
There were no deaths or serious adverse events in either group. Compared with standard care, we are uncertain if IFN-κ plus TFF2 leads to clinical improvement based on chest CT scans, or increases or decreases time to discharge from hospital or time to negative PCR.

**Our confidence in the results**
Certainty of the evidence is very low for all reported outcomes due to serious risk of bias (lack of blinding of patients and personnel) and very serious imprecision (reliance on a single study with low patient numbers and wide confidence intervals).

**Additional information**
As of 5 October 2020, IFN-κ plus TFF2 is not listed on the Australian Register of Therapeutic Goods and is not available for use in Australia.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>IFN-κ plus TFF2 | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 12 days of commencing treatment<br><br>9 Critical | Based on data from 80 participants in 1 studies. [1] | | | | No patients died. |
| **Serious adverse events**<br>Within 12 days of commencing treatment | Based on data from 80 participants in 1 studies. [2] | | | | No patients experienced a serious adverse event. |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>IFN-κ plus TFF2 | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| 6 Important | | | | | |
| **Clinical improvement** [3]<br>Within 12 days of commencing treatment<br>6 Important | Relative risk 1.21<br>(CI 95% 0.96 — 1.51)<br>Based on data from 80 participants in 1 studies. [4]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [5] | We are uncertain whether IFN-κ plus TFF2 increases or decreases clinical improvement based on chest CT scan (64 events). |
| **Time to discharge from hospital**<br>Days<br>6 Important | Lower better<br>Based on data from 80 participants in 1 studies.<br>(Randomized controlled) | **20.1**<br>(Mean)<br>Difference: | **15.5**<br>(Mean)<br>**MD 4.55 lower**<br>CI 95% | **Very low**<br>Due to serious risk of bias and very serious imprecision [6] | We are uncertain whether IFN-κ plus TFF2 increases or decreases time to discharge from hospital. |
| **Time to negative PCR**<br>Days<br>6 Important | Lower better<br>Based on data from 80 participants in 1 studies. | **7.4**<br>(Mean)<br>Difference: | **3.8**<br>(Mean)<br>**MD 3.6 lower**<br>CI 95% | **Very low**<br>Due to very serious imprecision [7] | We are uncertain whether IFN-κ plus TFF2 increases or decreases time to negative PCR |

1, 2, 4. Systematic review [92] with included studies: Fu 2020.
3. Based on chest CT imaging; reduction in the size and density of lesions.
5, 6. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: very serious.** Low number of patients, Only data from one study.
7. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study.

### References

92. IFN kappa + TFF-2 for COVID-19.

135. Fu W, Liu Y, Liu LI, Hu H, Cheng X, Liu P, et al. An open-label, randomized trial of the combination of IFN-κ plus TFF2 with standard care in the treatment of patients with moderate COVID-19. EClinicalMedicine 2020;100547 Pubmed Journal

## 2.9.5 Peginterferon lambda

Only in research settings

Do not use peginterferon lambda for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Peginterferon lambda should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use peginterferon lambda to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### Evidence to decision

**Benefits and harms**

**General adult population**
As the safety profile for peginterferon lambda is incompletely characterised in humans, there is uncertainty around the benefits and harms for patients with COVID-19.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There are additional concerns regarding harms as peginterferon lambda has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

**Certainty of the evidence**

Low

Certainty of the evidence is low for all outcomes due to very serious imprecision (wide confidence intervals, low patient numbers and/or low number of events).

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the effects of peginterferon lambda during pregnancy and breastfeeding are unknown in the context of COVID-19.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered, but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

**General adult population**
There is currently limited evidence about the impact of peginterferon lambda on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that peginterferon lambda should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of peginterferon lambda to treat COVID-19 in these populations should be avoided until evidence becomes available.

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### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Peginterferon lambda
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether therapy with peginterferon lambda is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from two randomised trials that compared a single 180 microgram dose of subcutaneously delivered peginterferon lambda with placebo in 180 adult outpatients with mild or moderate COVID-19 *[141][94]*.

**Study characteristics**
Median age of participants was 36 years in Jagannathan et al. and 46 years in Feld et al. In both studies, 42% were women. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
Reporting of critical outcomes was minimal across both studies due to the inclusion of outpatients with mild or moderate illness. There were no deaths in either study. We are uncertain whether peginterferon lambda increases or decreases the incidence of serious adverse events (six events) or adverse events, or whether it improves or worsens hospitalisation or time to clinical progression.

**Our confidence in the results**
Certainty of the evidence is low for all outcomes due to very serious imprecision (wide confidence intervals, low patient numbers and/or low number of events).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
Whereas peginterferon alpha and beta are listed on the Australian Register of Therapeutic Goods, as of 11 December 2020, peginterferon lambda is not listed. The safety profile of peginterferon lambda is incompletely characterised in humans.

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Standard care | **Intervention** Peginterferon lambda | **Certainty of the evidence** (Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality** Within 28 days of commencing treatment<br><br>9 Critical | Based on data from 60 participants in 1 studies. [1] | | | | There were no deaths in the study that reported this outcome. |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Peginterferon lambda | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Serious adverse events**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 1<br>(CI 95% 0.21 — 4.82)<br>Based on data from 180 participants in 2 studies. [2]<br>(Randomized controlled) | 33<br>per 1000<br>Difference: | 33<br>per 1000<br>**0 fewer per 1000**<br>( CI 95% 26 fewer — 126 more ) | **Low**<br>Due to very serious imprecision [3] | We are uncertain whether peginterferon lambda increases or decreases serious adverse events (6 events). |
| **Adverse events**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 1.21<br>(CI 95% 0.77 — 1.9)<br>Based on data from 180 participants in 2 studies. [4]<br>(Randomized controlled) | 244<br>per 1000<br>Difference: | 295<br>per 1000<br>**51 more per 1000**<br>( CI 95% 56 fewer — 220 more ) | **Low**<br>Due to very serious imprecision [5] | We are uncertain whether peginterferon lambda increases or decreases adverse events (49 events). |
| **Hospitalisation**<br>End of follow-up<br>6 Important | Relative risk 1<br>(CI 95% 0.21 — 4.82)<br>Based on data from 180 participants in 2 studies. [6]<br>(Randomized controlled) | 33<br>per 1000<br>Difference: | 33<br>per 1000<br>**0 fewer per 1000**<br>( CI 95% 26 fewer — 126 more ) | **Low**<br>Due to very serious imprecision [7] | We are uncertain whether peginterferon lambda increases or decreases incidence of hospitalisation (6 events). |
| **Time to clinical progression**<br>Days<br>6 Important | Based on data from 120 participants in 1 studies.<br>(Randomized controlled) | Jagannathan 2020 provided data for time to clinical progression (HR 1.38, 95% CI 0.52 to 3.63). | | **Low**<br>Due to very serious imprecision [8] | We are uncertain whether peginterferon lambda increases or decreases time to clinical progression. |

1. Systematic review [139] with included studies: Feld 2020.
2, 4. Systematic review [139] with included studies: Feld 2020, Jagannathan 2020.
3, 7. **Imprecision: very serious.** Low number of patients, Wide confidence intervals, due to few events.
5. **Imprecision: very serious.** Low number of patients, Wide confidence intervals.
6. Systematic review [139] with included studies: Jagannathan 2020, Feld 2020.
8. **Imprecision: very serious.** Low number of patients, Wide confidence intervals, Only data from one study.

### References

94. Jagannathan P, Andrews JR, Bonilla H, Hedlin H, Jacobson KB, Balasubramanian V, et al. Peginterferon Lambda-1a for treatment of outpatients with uncomplicated COVID-19: a randomized placebo-controlled trial. Nature Communications 2021;12(1):1967 Pubmed Journal

139. Peginterferon alpha for COVID-19.

141. Feld JJ, Kandel C, Biondi MJ, Kozak RA, Zahoor MA, Lemieux C, et al. Peginterferon lambda for the treatment of outpatients with COVID-19: a phase 2, placebo-controlled randomised trial. Lancet Respiratory Medicine 2021. Pubmed Journal

# 2.10 Other antibody related therapies

## 2.10.1 Bamlanivimab

Only in research settings

Do not use bamlanivimab for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use bamlanivimab to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### Evidence to decision

**Benefits and harms**

**General adult population**
Although preliminary evidence suggests that compared with standard care bamlanivimab does not result in more adverse or serious adverse events, it remains unclear if bamlanivimab is safe for the treatment of COVID-19.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There are additional concerns regarding harms as bamlanivimab has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain. There is insufficient evidence pertaining to the safety of bamlanivimab for pregnant or breastfeeding women.

**Certainty of the evidence**

Very low

**General adult population**
Certainty of the evidence for all outcomes is low due to very serious imprecision (either reliance on a single study and wide confidence intervals, or few events). Certainty for serious adverse events is very low.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of bamlanivimab in pregnancy are unknown.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

**General adult population**
There is currently limited evidence about the impact of bamlanivimab on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that bamlanivimab should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of bamlanivimab to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Bamlanivimab
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether the neutralising antibody bamlanivimab is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from two randomised trials. BLAZE-1 compared bamlanivimab with standard care in 465 adult outpatients with mild COVID-19 *[97]*, and ACTIV-3/TICO compared bamlanivimab with placebo in 314 patients with moderate-to-severe illness *[142]*.

**Study characteristics**
In BLAZE-1 mean age of participants was 45 years and 55% were women. Patients allocated bamlanivimab were assigned to three different dosage groups (700 mg, 2800 mg and 7000 mg); however, results were similar and were pooled for analysis. In ACTIV-3/TICO median age was ~60 years and 44% were women. Pregnant women were ineligible in both studies.

**What are the main results?**
We are uncertain whether bamlanivimab makes a difference with regards to death, adverse events, hospitalisation, discharge from hospital, virological clearance (defined as negative PCR) or rate of clinical recovery/clinical improvement. No patients experienced a serious adverse event.

**Our confidence in the results**
Certainty of the evidence for all outcomes is low due to very serious imprecision (either reliance on a single study and wide confidence intervals, or few events). Certainty for serious adverse events is very low.

For children and adolescents and pregnant and breastfeeding women, certainty is downgraded to very low due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
Bamlanivimab was developed as a highly specific treatment for COVID-19. The treatment is not approved for use in Australia and, as of 16 November 2020, there are no reliable safety data to inform treatment.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Bamlanivimab | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 28 days of commencing treatment<br>9 Critical | Relative risk 1.67<br>(CI 95% 0.57 — 4.86)<br>Based on data from 779 participants in 2 studies. [1]<br>(Randomized controlled) | **16**<br>per 1000<br>Difference: | **27**<br>per 1000<br>**11 more per 1000**<br>( CI 95% 7 fewer — 62 more ) | **Low**<br>Due to very serious imprecision [2] | We are uncertain whether bamlanivimab impacts death (19 events). |
| **Serious adverse events**<br>Within 30 days of commencing treatment<br>6 Important | Based on data from 465 participants in 1 studies. [3]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision [4] | No patients experienced a serious adverse event. |
| **Adverse events**<br>Within 30 days of commencing treatment<br>6 Important | Relative risk 0.9<br>(CI 95% 0.65 — 1.25)<br>Based on data from 465 participants in 1 studies. [5]<br>(Randomized controlled) | **269**<br>per 1000<br>Difference: | **242**<br>per 1000<br>**27 fewer per 1000**<br>( CI 95% 94 fewer — 67 more ) | **Low**<br>Due to very serious imprecision [6] | We are uncertain whether bamlanivimab increases or decreases adverse events (117 events). |
| **Hospitalisation**<br>Within 30 days of commencing treatment<br>6 Important | Relative risk 0.28<br>(CI 95% 0.1 — 0.82)<br>Based on data from 465 participants in 1 studies. [7]<br>(Randomized controlled) | **58**<br>per 1000<br>Difference: | **16**<br>per 1000<br>**42 fewer per 1000**<br>( CI 95% 52 fewer — 10 fewer ) | **Low**<br>Due to very serious imprecision [8] | We are uncertain whether bamlanivimab increases or decreases hospitalisation (14 events). |
| **Discharge from hospital**<br>Within 30 days of commencing treatment<br>6 Important | Relative risk 0.97<br>(CI 95% 0.9 — 1.05)<br>Based on data from 314 participants in 1 studies. [9]<br>(Randomized controlled) | **901**<br>per 1000<br>Difference: | **874**<br>per 1000<br>**27 fewer per 1000**<br>( CI 95% 90 fewer — 45 more ) | **Low**<br>Due to very serious imprecision [10] | We are uncertain whether bamlanivimab increases or decreases discharge from hospital (279 events). |
| **Virological clearance (negative PCR)**<br>End of follow-up<br>6 Important | Relative risk 0.85<br>(CI 95% 0.67 — 1.08)<br>Based on data from 431 participants in 1 studies. [11]<br>(Randomized controlled) | **459**<br>per 1000<br>Difference: | **390**<br>per 1000<br>**69 fewer per 1000**<br>( CI 95% 151 fewer — 37 more ) | **Low**<br>Due to very serious imprecision [12] | We are uncertain whether bamlanivimab increases or decreases negative PCR (177 events). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Bamlanivimab | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Clinical recovery**<br>Within 30 days of commencing treatment<br><br>6 Important | Relative risk 1.03<br>(CI 95% 0.89 — 1.2)<br>Based on data from 168 participants in 1 studies. [13]<br>(Randomized controlled) | **790**<br>per 1000<br><br>Difference: | **814**<br>per 1000<br><br>**24 more per 1000**<br>( CI 95% 87 fewer — 158 more ) | **Low**<br>Due to very serious imprecision [14] | We are uncertain whether bamlanivimab improves or worsens clinical recovery (135 events). |
| **Clinical improvement**<br>Within 30 days of commencing treatment<br><br>6 Important | Relative risk 1.11<br>(CI 95% 0.93 — 1.33)<br>Based on data from 253 participants in 1 studies. [15]<br>(Randomized controlled) | **632**<br>per 1000<br><br>Difference: | **702**<br>per 1000<br><br>**70 more per 1000**<br>( CI 95% 44 fewer — 209 more ) | **Low**<br>Due to very serious imprecision [16] | We are uncertain whether bamlanivimab improves or worsens clinical improvement (167 events). |

1. Systematic review [95] with included studies: Lundgren 2020, Gottlieb 2021.
2. **Imprecision: very serious.** Wide confidence intervals, due to few events.
3, 5, 7, 11, 15. Systematic review [95] with included studies: Gottlieb 2021.
4. **Imprecision: very serious.** Low number of patients, Only data from one study, due to few events.
6, 8, 10, 14. **Imprecision: very serious.** Wide confidence intervals, Only data from one study.
9, 13. Systematic review [95] with included studies: Lundgren 2020.
12. **Imprecision: very serious.** Wide confidence intervals.
16. **Imprecision: very serious.** Low number of patients, Only data from one study, Wide confidence intervals.

### References

95. Bamlanivimab for COVID-19.

97. Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, Morris J, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. JAMA 2021. Pubmed Journal

142. Lundgren JD, Grund B, Barkauskas CE, Holland TL, Gottlieb RL, Sandkovsky U, et al. A neutralizing monoclonal antibody for hospitalized patients with Covid-19. New England Journal of Medicine 2020. Pubmed Journal

## 2.10.2 Bamlanivimab plus etesevimab

Only in research settings

Do not use bamlanivimab plus etesevimab for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Bamlanivimab plus etesevimab should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use bamlanivimab plus etesevimab to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### Evidence to decision

**Benefits and harms**

**General adult population**
As the safety profile for bamlanivimab plus etesevimab is incompletely characterised in humans, there is uncertainty around the benefits and harms for patients with COVID-19.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There are additional concerns regarding harms as bamlanivimab plus etesevimab has not been sufficiently tested in these populations. For people requiring palliative care, the benefits for symptom management are uncertain.

**Certainty of the evidence**

Low

**General adult population**
Certainty is low for all outcomes due to very serious imprecision (reliance on a single study, wide confidence intervals and few events).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the potential effects of bamlanivimab plus etesevimab in pregnancy are unknown.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

**General adult population**
There is currently limited evidence about the impact of bamlanivimab plus etesevimab on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that bamlanivimab plus etesevimab should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of bamlanivimab plus etesevimab to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Bamlanivimab plus etesevimab
**Comparator:** Placebo

### Summary

There remains significant uncertainty whether bamlanivimab plus etesevimab is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from two randomised trials (phase II and III of the BLAZE-1 trial) that compared bamlanivimab plus etesevimab with placebo in 248 adults with mild COVID-19 *[100]* and 1033 adults with mild or moderate COVID-19 who were at high risk for progression to severe disease *[147]*.

**Study characteristics**
Median age of participants in phase II (Gottlieb et al.) and phase III (Dougan et al.) of BLAZE-1 was 45 and 54 years, respectively. Across both phases 52% were women. Patients received either a single one-hour infusion of 2,800 mg bamlanivimab plus 2,800 mg etesevimab or placebo solution. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
There were too few who died or experienced a serious adverse event or required hospitalisation to determine whether bamlanivimab plus etesevimab makes a difference. We are uncertain if bamlanivimab plus etesevimab increases or decreases adverse events, clinical improvement, clinical recovery or negative PCR.

**Our confidence in the results**
Certainty of the evidence is low for all outcomes due to very serious imprecision (reliance on a single study, low patient numbers and few events) or serious imprecision and serious inconsistency (point estimates do not overlap or inconsistency in direction of effect).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
Bamlanivimab and etesevimab were developed as highly specific treatments for COVID-19. These treatments are not approved for use in Australia and, as of 1 August 2021, there are no reliable safety data to inform treatment.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Bam+etesevimab | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>End of treatment<br>9 Critical | Relative risk 0.05<br>(CI 95% 0 — 0.81)<br>Based on data from 1,303 participants in 2 studies. [1]<br>(Randomized controlled) | **15**<br>per 1000<br>Difference: | **1**<br>per 1000<br>**14 fewer per 1000**<br>( CI 95% 15 fewer — 3 fewer ) | **Low**<br>Due to serious inconsistency and serious imprecision [2] | We are uncertain whether bamlanivimab plus etesevimab impacts death (10 events). |
| **Serious adverse events**<br>End of follow-up<br>6 Important | Relative risk 1.4<br>(CI 95% 0.49 — 4.01)<br>Based on data from 1,303 participants in 2 studies. [3]<br>(Randomized controlled) | **9**<br>per 1000<br>Difference: | **13**<br>per 1000<br>**4 more per 1000**<br>( CI 95% 5 fewer — 27 more ) | **Low**<br>Due to very serious imprecision [4] | We are uncertain whether bamlanivimab plus etesevimab increases or decreases serious adverse events (14 events). |
| **Adverse events**<br>End of follow-up<br>4 Important | Relative risk 0.87<br>(CI 95% 0.49 — 1.57)<br>Based on data from 1,303 participants in 2 studies. [5]<br>(Randomized controlled) | **152**<br>per 1000<br>Difference: | **132**<br>per 1000<br>**20 fewer per 1000**<br>( CI 95% 78 fewer — 87 more ) | **Low**<br>Due to serious inconsistency, Due to serious imprecision [6] | Bamlanivimab plus etesevimab may have little impact on adverse events (190 events). |
| **Hospitalisation**<br>Within 29 days of commencing treatment<br>6 Important | Relative risk 0.15<br>(CI 95% 0.02 — 1.21)<br>Based on data from 261 participants in 1 studies. [7]<br>(Randomized controlled) | **59**<br>per 1000<br>Difference: | **9**<br>per 1000<br>**50 fewer per 1000**<br>( CI 95% 58 fewer — 12 more ) | **Low**<br>Due to very serious imprecision [8] | We are uncertain whether bamlanivimab plus etesevimab increases or decreases hospitalisation (10 events). |
| **Clinical improvement**<br>Within 22 days of commencing treatment<br>6 Important | Relative risk 1.13<br>(CI 95% 0.96 — 1.34)<br>Based on data from 261 participants in 1 studies. [9]<br>(Randomized controlled) | **632**<br>per 1000<br>Difference: | **714**<br>per 1000<br>**82 more per 1000**<br>( CI 95% 25 fewer — 215 more ) | **Low**<br>Due to very serious imprecision [10] | We are uncertain whether bamlanivimab plus etesevimab improves or worsens clinical improvement (174 events). |
| **Clinical recovery**<br>Within 22 days of commencing treatment<br>6 Important | Relative risk 1.19<br>(CI 95% 0.99 — 1.43)<br>Based on data from 261 participants in 1 studies. [11]<br>(Randomized controlled) | **579**<br>per 1000<br>Difference: | **689**<br>per 1000<br>**110 more per 1000**<br>( CI 95% 6 fewer — 249 more ) | **Low**<br>Due to very serious imprecision [12] | We are uncertain whether bamlanivimab plus etesevimab improves or worsens clinical recovery (163 events). |
| **Negative PCR**<br>Day 22 | Relative risk 1<br>(CI 95% 0.72 — 1.38)<br>Based on data from 261 | **368**<br>per 1000 | **368**<br>per 1000 | **Low**<br>Due to very serious imprecision [14] | We are uncertain whether bamlanivimab plus etesevimab increases or |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Placebo | **Intervention** Bam+etesevimab | **Certainty of the evidence** (Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| 6 Important | participants in 1 studies. [13] (Randomized controlled) | Difference: | **0 fewer per 1000** ( CI 95% 103 fewer — 140 more ) | | decreases negative PCR (96 events). |

1. Systematic review [99] with included studies: Gottlieb 2021, BLAZE-1 pIII.
2. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. **Imprecision: serious.** due to few events.
3, 5. Systematic review [99] with included studies: BLAZE-1 pIII, Gottlieb 2021.
4. **Imprecision: very serious.** due to few events.
6. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. **Imprecision: serious.** Wide confidence intervals.
7, 9, 11, 13. Systematic review [150] with included studies: Gottlieb 2021.
8. **Imprecision: very serious.** Low number of patients, Only data from one study, Wide confidence intervals, due to few events.
10, 12, 14. **Imprecision: very serious.** Wide confidence intervals, Only data from one study.

### References

99. Bamlanivimab plus etesevimab for COVID-19.

100. Gottlieb RL, Nirula A, Chen P, Boscia J, Heller B, Morris J, et al. Effect of bamlanivimab as monotherapy or in combination with etesevimab on viral load in patients with mild to moderate COVID-19: a randomized clinical trial. JAMA 2021. Pubmed Journal

147. Dougan M, Nirula A, Azizad M, Mocherla B, Gottlieb RL, Chen P, et al. Bamlanivimab plus etesevimab in mild or moderate Covid-19. New England Journal of Medicine 2021. Pubmed Journal

150. Bamlanivimab plus etesevimab for COVID-19.

## 2.10.3 Bebtelovimab

Only in research settings

Do not use bebtelovimab for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use bebtelovimab to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a high priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### Evidence to decision

**Benefits and harms**

Small net benefit, or little difference between alternatives

No participants died or experienced a serious adverse event. There were too few who required hospitalisation to determine whether bebtelovimab makes a difference (four events; two per arm). Time to clinical recovery was slightly lower in placebo (6 days versus 8 days).

**Certainty of the evidence**

Low

Certainty of the evidence is low for hospitalisation due to very serious imprecision (only one study, wide confidence intervals and few events) and very low for all-cause mortality, serious adverse events due to extremely serious imprecision (one study, no events) and time to clinical recovery due to very serious imprecision and serious risk of bias (due to the study being unblinded).

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
Variability may be expected in preferences and values for these populations given the potentially different goals of care.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

There is currently limited evidence about the impact of bebtelovimab on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that bebtelovimab should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Bebtelovimab
**Comparator:** Placebo

### Summary

There remains significant uncertainty whether bebtelovimab is more effective and safer than placebo in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial that compared bebtelovimab with placebo in 253 unvaccinated adult outpatients with mild or moderate COVID-19 within 3 days of laboratory diagnosis of SARS-CoV-2 infection *[103]*.

**Study characteristics**

Mean age of participants was 34 years and 53% were women. The trial included a total of 706 participants, however almost half of these were in an open-label high risk analysis with no control arm (n=326). Of the remaining 380 participants, 125 received bebtelovimab (175 mg IV dose), 128 received placebo and the remaining 127 received a combination treatment consisting of bebtelovimab and bamlanivimab plus etesevimab (not included within the analysis). Pregnant and breastfeeding women were ineligible.

**What are the main results?**
No participants died or experienced a serious adverse event. There were too few who required hospitalisation to determine whether bebtelovimab makes a difference (four events; two per arm). Time to clinical recovery was slightly lower in placebo (6 days versus 8 days).

**Our confidence in the results**
Certainty of the evidence is low for hospitalisation due to very serious imprecision (only one study, wide confidence intervals and few events) and very low for all-cause mortality, serious adverse events due to extremely serious imprecision (one study, no events) and time to clinical recovery due to very serious imprecision and serious risk of bias (due to the study being unblinded).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Bebtelovimab | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 29 days of treatment<br>9 Critical | Based on data from 253 participants in 1 studies. [1] | | | | No participants died. |
| **Hospitalisation**<br>Within 29 days of treatment<br>6 Important | Relative risk 1.02<br>(CI 95% 0.15 — 7.16)<br>Based on data from 253 participants in 1 studies. [2]<br>(Randomized controlled) | **16**<br>per 1000<br>Difference: | **16**<br>per 1000<br>**0 fewer per 1000**<br>( CI 95% 14 fewer — 99 more ) | **Low**<br>Due to very serious imprecision [3] | We are uncertain whether bebtelovimab impacts hospitalisation (4 events). |
| **Serious adverse events**<br>Within 29 days of treatment<br>6 Important | Based on data from 253 participants in 1 studies. [4] | | | | No participants experienced a serious adverse event. |
| **Time to clinical recovery**<br>Days<br>6 Important | Based on data from 253 participants in 1 studies. [5]<br>(Randomized controlled) | **6**<br>(Median) | **8**<br>(Median)<br>CI 95% | **Very low**<br>Due to serious risk of bias and very serious imprecision [6] | We are uncertain whether bebtelovimab increases or decreases time to clinical recovery. |

1, 2, 4. Systematic review [102] with included studies: Dougan et al 2022.
3. **Imprecision: very serious.** Only data from one study, due to few events, Wide confidence intervals.

5. Systematic review [102]
6. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: very serious.** Only data from one study, Wide confidence intervals.

### References

101. Altay O, Arif M, Li X, Yang H, Aydın M, Alkurt G, et al. Combined metabolic activators accelerates recovery in mild-to-moderate COVID-19. Advanced Science (Weinheim) 2021;e2101222 Pubmed Journal

102. Bebtelovimab for COVID-19.

103. Dougan M, Azizad M, Chen P. Bebtelovimab, alone or together with bamlanivimab and etesevimab, as a broadly neutralizing monoclonal antibody treatment for mild to moderate, ambulatory COVID-19. medRxiv 12 March 2022. Journal Website

106. Australian Medicines Handbook 2020 (online). 2020. Website

156. Therapeutic Goods Administration. Australian Product Information: DBL Acetylcysteine Injection Concentrate. May 2019. Website

## 2.11 Other therapies

Only in research settings

New

Do not use aprepitant for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Sabizabulin should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use sabizabulin to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

## 2.11.1 Almitrine

Only in research settings

New

Do not use almitrine for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Almitrine should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use almitrine to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### Evidence to decision

**Benefits and harms**

Small net benefit, or little difference between alternatives

**General adult population**
Evidence suggests that almitrine may reduce all-cause mortality and increase hospital discharge, and may reduce the incidence of serious adverse events slightly, however uncertainty remains and further data is needed.

**Certainty of the evidence**

Low

**General adult population**
Certainty of the evidence is low for death, hospital discharge and serious adverse events due to very serious imprecision (reliance on a single study and wide confidence intervals).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Values and preferences**

Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as this treatment has shown no clear benefits, most informed patients would prefer not to use it, while some patients may choose to participate in clinical trials of this treatment.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Clinical question/ PICO

**Population:** Patients with COVID-19

**Intervention:** Almitrine
**Comparator:** Placebo

### Summary

There remains significant uncertainty whether almitrine is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from a single randomised trial that compared almitrine with standard care in 181 adults hospitalised with severe-critical laboratory-confirmed COVID-19 *[228]*.

**Study characteristics**
Mean age of participants was 60 years; the proportion of women was 34% across both arms. Over half of included participants had hypertension at baseline, with 20% and 37% experiencing other cardiovascular disease and type 2 diabetes at baseline, respectively.

**What are the main results?**
Results suggest that almitrine may reduce all-cause mortality and serious adverse events, and increase hospital discharge at 28 days, however there remains uncertainty.

**Our confidence in the results**
Certainty of the evidence is very low for all three outcomes. This judgement is based on very serious imprecision (results based on only one study with relatively low patient numbers and wide confidence intervals).

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Placebo | **Intervention** Almitrine | **Certainty of the evidence** (Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality** Within 28 days of commencing treatment 9 Critical | Relative risk 0.48 (CI 95% 0.21 — 1.13) Based on data from 179 participants in 1 studies. [1] (Randomized controlled) | **165** per 1000 Difference: | **79** per 1000 **86 fewer per 1000** ( CI 95% 130 fewer — 21 more ) | **Low** Due to very serious imprecision [2] | Almitrine may decrease all-cause mortality (22 events) |
| **Hospital discharge** Within 28 days of commencing treatment 6 Important | Relative risk 1.11 (CI 95% 0.87 — 1.42) Based on data from 178 participants in 1 studies. [3] (Randomized controlled) | **560** per 1000 Difference: | **622** per 1000 **62 more per 1000** ( CI 95% 73 fewer — 235 more ) | **Low** Due to very serious imprecision [4] | Almitrine may increase hospital discharge (103 events) |
| **Serious adverse events** Within 28 days of commencing treatment 6 Important | Relative risk 1.1 (CI 95% 0.74 — 1.65) Based on data from 179 participants in 1 studies. [5] (Randomized controlled) | **330** per 1000 Difference: | **363** per 1000 **33 more per 1000** ( CI 95% 86 fewer — 214 more ) | **Low** Due to very serious imprecision [6] | Almitrine may decrease serious adverse events slightly (62 events) |

1, 3, 5. Systematic review [227] with included studies: Kalfon 2022.
2, 4, 6. **Imprecision: very serious.** Only data from one study, Wide confidence intervals.

### References

227. Almitrine for COVID-19.

## 2.11.2 Aprepitant

Only in research settings

Do not use aprepitant for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Aprepitant should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use aprepitant to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### Evidence to decision

**Benefits and harms**

Important harms

**General adult population**
In addition to uncertainty around benefits for patients with COVID-19, there are well-known side effects and harms associated with aprepitant, including fatigue, muscle weakness, headache or dizziness, gastrointestinal symptoms and rash.

**Certainty of the evidence**

Very low

**General adult population**
Certainty of the evidence is very low for both outcomes. This judgement is based on very serious risk of bias (patients and personnel not blinded, deviation from intended intervention [20 mg dexamethasone provided to both groups compared to 6 mg as stated in the ClinicalTrials.gov entry] and selective outcome reporting), serious indirectness (due to insufficient timeframe), and very serious imprecision (results based on only one study with low patient numbers and few events).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trial.

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

**General adult population**
There is currently limited evidence about the impact of aprepitant on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that aprepitant should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of aprepitant to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Aprepitant
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether aprepitant is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from a single randomised trial that compared aprepitant with standard care in 18 adults hospitalised with laboratory-confirmed COVID-19 *[162]*.

**Publication status**
The study is only available as a preprint paper (posted to medRxiv on 4 August 2020) and has therefore not been peer reviewed. In addition to our daily evidence surveillance processes, we follow up with the corresponding author every two months to request an update on the study's publication status.

**Study characteristics**
Median age was 61 years in the aprepitant group and 48 years in the control group; the proportion of women was 20% and 63% respectively. Both groups received 20 mg of dexamethasone daily, and standard care included treatment with azithromycin, remdesivir and tocilizumab. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
Preliminary results were presented for death and discharge from hospital within 5 days of starting treatment. For both outcomes, there were too few events (two deaths and two discharged from hospital) to determine whether aprepitant makes a difference. No data were reported on

adverse or serious adverse events.

**Our confidence in the results**
Certainty of the evidence is very low for both outcomes. This judgement is based on very serious risk of bias (patients and personnel not blinded, deviation from intended intervention and selective outcome reporting), serious indirectness (insufficient timeframe), and very serious imprecision (results based on only one study with low patient numbers and few events).

**Additional information**
According to the Therapeutic Goods Administration, known acute harms for aprepitant include fatigue, muscle weakness, headache or dizziness, gastrointestinal symptoms, chills, hot flushes, hiccups and rash *[107]*. There are several known and potential interactions with other drugs, including hormonal contraceptives *[107]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Aprepitant | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 5 days of commencing treatment<br>9 Critical | Relative risk 0.8<br>(CI 95% 0.06 — 10.89)<br>Based on data from 18 participants in 1 studies. [1]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious risk of bias, very serious imprecision and serious indirectness [2] | There were too few who died to determine whether aprepitant makes a difference (2 events). |
| **Invasive mechanical ventilation**<br>Within 5 days of commencing treatment<br>9 Critical | | | | | No studies were found that looked at patients requiring invasive mechanical ventilation. |
| **Adverse events**<br>Within 5 days of commencing treatment<br>6 Important | | | | | No studies were found that looked at adverse events. |
| **Serious adverse events**<br>Within 5 days of commencing treatment<br>6 Important | | | | | No studies were found that looked at serious adverse events. |
| **Discharge from hospital** | Relative risk 0.8<br>(CI 95% 0.06 — 10.89)<br>Based on data from 18 | | | **Very low**<br>Due to very serious | There were too few who were discharged from hospital (2 events) to |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Aprepitant | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| Within 5 days of commencing treatment<br><br>6 Important | participants in 1 studies. [3]<br>(Randomized controlled) | | | risk of bias, very serious imprecision and serious indirectness [4] | determine whether aprepitant makes a difference. |

1, 3. Systematic review [159] with included studies: Mehboob 2020.
2. **Risk of Bias: very serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Indirectness: serious.** The outcome time frame in studies were insufficient. **Imprecision: very serious.** Low number of patients, Only data from one study, due to few events.
4. **Risk of Bias: very serious.** Selective outcome reporting, Incomplete data and/or large loss to follow up, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Indirectness: serious.** The outcome time frame in studies were insufficient. **Imprecision: very serious.** Only data from one study, Low number of patients, due to few events.

### References

107. Therapeutic Goods Administration. Product Information Emend capsule (aprepitant). 2014. Website

159. Aprepitant for COVID-19.

162. Mehboob R, Ahmad F, Qayyum A. Aprepitant as a combinant with dexamethasone reduces the inflammation via neurokinin 1 receptor antagonism in severe to critical Covid-19 patients and potentiates respiratory recovery: a novel therapeutic approach. medRxiv 2020. Journal Website

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### Clinical question/ PICO

**Population:** Special populations with COVID-19
**Intervention:** Aprepitant
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether aprepitant is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from a single randomised trial that compared aprepitant with standard care alone in 18 adults hospitalised with laboratory confirmed COVID-19 *[162]*.

**Publication status**
The study is only available as a preprint paper (posted to medRxiv on 4 August 2020) and has therefore not been peer-reviewed. In addition to our daily evidence surveillance processes, we also follow up with the corresponding author every two months to request an update on the study's publication status.

**Study characteristics**
Median age was 61 in the aprepitant group and 48 in the control group; the proportion of women was 20% and 63% respectively. Both groups received 20 mg dexamethasone daily, and standard care included treatment with azithromycin, remdesivir and tocilizumab. Pregnant and breastfeeding women were ineligible.

**What are the main results?**

Preliminary results were presented for death and discharge from hospital within 5 days of starting treatment. For both outcomes, there were too few events (two deaths and two discharged from hospital) to determine whether aprepitant makes a difference. No data were reported on adverse or serious adverse events.

**Our confidence in the results**
Certainty of the evidence is very low for both outcomes. This judgement is based on very serious risk of bias (patients and personnel not blinded, deviation from intended intervention and selective outcome reporting), serious indirectness (insufficient timeframe and limited inclusion of these populations), and very serious imprecision (results based on only one study with low patient numbers and few events).

**Additional information**
According to the Therapeutic Goods Administration, known acute harms for aprepitant include fatigue, muscle weakness, headache or dizziness, gastrointestinal symptoms, chills, hot flushes, hiccups, rash *[107]*. There are several known and potential interactions with other drugs including hormonal contraceptives *[107]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Aprepitant | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 5 days of commencing treatment<br>9 Critical | Relative risk 0.8<br>(CI 95% 0.06 — 10.89)<br>Based on data from 18 participants in 1 studies. [1]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious risk of bias, very serious imprecision and serious indirectness [2] | There were too few who died to determine whether aprepitant makes a difference 2 events). |
| **Invasive mechanical ventilation**<br>Within 5 days of commencing treatment<br>9 Critical | | | | | No studies were found that looked at patients requiring invasive mechanical ventilation. |
| **Adverse events**<br>Within 5 days of commencing treatment<br>6 Important | | | | | No studies were found that looked at adverse events. |
| **Serious adverse events**<br>Within 5 days of commencing treatment<br>6 Important | | | | | No studies were found that looked at serious adverse events. |

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Standard care | **Intervention** Aprepitant | **Certainty of the evidence** (Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Discharge from hospital** Within 5 days of commencing treatment<br><br>6 Important | Relative risk 0.8 (CI 95% 0.06 — 10.89) Based on data from 18 participants in 1 studies. [3] (Randomized controlled) | | | **Very low** Due to very serious risk of bias, very serious imprecision and serious indirectness [4] | There were too few who were discharged from hospital to determine whether aprepitant makes a difference (2 events). |

1, 3. Systematic review [159] with included studies: Mehboob 2020.
2. **Risk of Bias: very serious.** Incomplete data and/or large loss to follow up, Selective outcome reporting, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Indirectness: serious.** The outcome timeframe in studies was insufficient, and there were differences between the population of interest and those studied. **Imprecision: very serious.** Low number of patients, Only data from one study, due to few events.
4. **Risk of Bias: very serious.** Selective outcome reporting, Incomplete data and/or large loss to follow up, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Indirectness: serious.** The outcome timeframe in studies was insufficient, and there were differences between the population of interest and those studied. **Imprecision: very serious.** Only data from one study, Low number of patients, due to few events.

### References

107. Therapeutic Goods Administration. Product Information Emend capsule (aprepitant). 2014. Website

159. Aprepitant for COVID-19.

162. Mehboob R, Ahmad F, Qayyum A. Aprepitant as a combinant with dexamethasone reduces the inflammation via neurokinin 1 receptor antagonism in severe to critical Covid-19 patients and potentiates respiratory recovery: a novel therapeutic approach. medRxiv 2020. Journal Website

## 2.11.3 Bromhexine hydrochloride

Only in research settings

Do not use bromhexine hydrochloride for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Bromhexine hydrochloride should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use bromhexine hydrochloride for the treatment of COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

## Evidence to decision

### Benefits and harms

**General adult population**
In addition to uncertainty around benefits for patients with COVID-19, there are common side effects associated with bromhexine hydrochloride including nausea, vomiting, diarrhoea, allergy and severe, low-risk skin reactions—erythema multiforme, Stevens-Johnson syndrome, acute generalised exanthematous pustulosis.

**Pregnant and breastfeeding women**
Benefits can be assumed to outweigh possible risks for pregnant women—limited clinical experience has not resulted in adverse effects to the fetus. Bromhexine hydrochloride is safe to use in women who are breastfeeding.

### Certainty of the evidence

Very low

**General adult population**
Certainty of the evidence is low for invasive mechanical ventilation due to serious risk of bias (lack of blinding of patients and outcome assessors) and serious imprecision (wide confidence intervals). Certainty is very low for all other outcomes due to very serious risk of bias (lack of blinding of patients and outcome assessors) and very serious imprecision (low patient numbers, few events and wide confidence intervals).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is further considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

### Values and preferences

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the effects of bromhexine hydrochloride during pregnancy and breastfeeding are unknown in the context of COVID-19.

### Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Equity

Important issues, or potential issues not investigated

**General adult population**
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**Children and adolescents, pregnant and breastfeeding women**
Because the benefit-to-harm ratio is uncertain, this recommendation protects these more vulnerable populations.

**People requiring palliative care and older people living with frailty or cognitive impairment**
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage

trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit-to-harm ratio, this recommendation protects these more vulnerable populations.

**Acceptability**

**General adult population, children and adolescents, pregnant and breastfeeding women**
We have no systematically collected evidence regarding acceptability. Substantial variability is expected as some patients would accept the treatment and others not.

**People requiring palliative care and older people living with frailty or cognitive impairment**
Because the benefit-to-harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

**Feasibility**

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

### Rationale

**General adult population**
There is currently limited evidence about the impact of bromhexine hydrochloride on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that bromhexine hydrochloride should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of bromhexine hydrochloride for the treatment of COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Bromhexine
**Comparator:** SOC

### Summary

There remains significant uncertainty whether bromhexine hydrochloride is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from three randomised trials that compared bromhexine hydrochloride with placebo in 196 adults hospitalised with mild or moderate COVID-19 *[189][190][220]*.

**Study characteristics**
Mean age of participants ranged from 50 to 60 years and the proportion of women ranged from 22 to 54%. Patients received bromhexine hydrochloride for 14 days at varying doses (8 mg three times a day *[189]*; 32 mg three times a day *[190]*; 8 mg four times a day *[220]*). Pregnant and breastfeeding women were ineligible.

**What are the main results?**
There were too few who died (nine deaths) or suffered adverse events to determine whether bromhexine hydrochloride makes a difference. No patients experienced a serious adverse event. It is unclear whether bromhexine hydrochloride increases or decreases time to clinical improvement, need for invasive mechanical ventilation, discontinuation due to adverse events, admission to ICU, discharge from hospital or viral clearance.

**Our confidence in the results**
Certainty of the evidence is low for invasive mechanical ventilation due to serious risk of bias (lack of blinding of patients and outcome assessors) and serious imprecision (wide confidence intervals). Certainty is very low for all other outcomes due to very serious risk of bias (lack of blinding of patients and outcome assessors) and very serious imprecision (low patient numbers, few events and wide confidence intervals).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
The safety profile for bromhexine hydrochloride indicates the following adverse effects: nausea, vomiting, diarrhoea and allergy (e.g. rash, urticaria, angioedema). Bromhexine hydrochloride has been associated with a low risk of severe skin reactions including erythema multiforme, Stevens-Johnson syndrome and acute generalised exanthematous pustulosis *[117]*.

Bromhexine hydrochloride is considered safe in **pregnancy** *[117]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>SOC | **Intervention**<br>Bromhexine | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All cause mortality**<br>End of follow-up<br>9 Critical | Relative risk 0.5<br>(CI 95% 0.1 — 2.47)<br>Based on data from 196 participants in 3 studies. [1]<br>(Randomized controlled) | **154**<br>per 1000<br>Difference: | **94**<br>per 1000<br>**60 fewer per 1000**<br>( CI 95% 120 fewer — 105 more ) | **Very low**<br>Due to serious risk of bias and very serious imprecision [2] | There were too few who died to determine whether bromhexine hydrochloride makes a difference (9 deaths). |
| **Serious adverse events**<br>End of follow-up<br>6 Important | Based on data from 178 participants in 2 studies. [3]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [4] | No patients experienced a serious adverse event. |
| **Invasive mechanical ventilation**<br>Within 28 days of commencing treatment<br>9 Critical | Relative risk 0.61<br>(CI 95% 0.22 — 1.68)<br>Based on data from 178 participants in 2 studies. [5]<br>(Randomized controlled) | | | **Low**<br>Due to serious risk of bias and serious imprecision [6] | There were too few who required invasive mechanical ventilation to determine whether bromhexine hydrochloride makes a difference (20 events). |
| **Adverse events**<br>End of follow-up<br>6 Important | Relative risk 0.38<br>(CI 95% 0.12 — 1.16)<br>Based on data from 118 participants in 2 studies. [7]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [8] | There were too few adverse events to determine whether bromhexine hydrochloride makes a difference (7 events). |
| **Discontinuation due to adverse events**<br>End of follow-up<br>6 Important | Based on data from 18 participants in 1 studies. [9]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [10] | No patients discontinued treatment due to adverse events. |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>SOC | **Intervention**<br>Bromhexine | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **ICU admission**<br>End of follow-up<br><br>6 Important | Relative risk 0.18<br>(CI 95% 0.04 — 0.77)<br>Based on data from 96 participants in 2 studies. [11]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [12] | There were too few who required ICU admission to determine whether bromhexine hydrochloride makes a difference (13 events). |
| **Discharge from hospital**<br>End of follow-up<br><br>6 Important | Relative risk 2.5<br>(CI 95% 0.78 — 7.97)<br>Based on data from 18 participants in 1 studies. [13]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [14] | We are uncertain whether bromhexine hydrochloride increases discharge from hospital. |

1. Systematic review [188] with included studies: Li 2020, Ansarin 2020, Tolouian 2021.
2. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: very serious.** Wide confidence intervals, few events.
3, 5. Systematic review [188] with included studies: Ansarin 2020, Tolouian 2021.
4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: very serious.** Wide confidence intervals, due to no events.
6. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: serious.** Wide confidence intervals.
7. Systematic review [188] with included studies: Li 2020, Tolouian 2021.
8. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: very serious.** Wide confidence intervals, due to few events.
9, 13. Systematic review [188] with included studies: Li 2020.
10. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: very serious.** Wide confidence intervals, due to no events, Low number of patients.
11. Systematic review [188] with included studies: Li 2020, Ansarin 2020.
12. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: very serious.** Wide confidence intervals, due to few events.
14. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: very serious.** Wide confidence intervals.

### References

188. [Intervention] for [COVID-19].

## 2.11.4 Fluvoxamine

Only in research settings

Do not use fluvoxamine for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Fluvoxamine should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use fluvoxamine to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### Evidence to decision

**Benefits and harms**

Important harms

**General adult population**
In addition to uncertainty around benefits for patients with COVID-19, there are well-known short-term harms associated with fluvoxamine use, including headache, dizziness, nausea and vomiting. Caution should be taken when prescribing fluvoxamine to patients with a history of depression due to the potential development of symptoms such as anxiety, panic attacks and mania *[241]*.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
The benefits and harms associated with fluvoxamine in pregnant women and young children with COVID-19 are not well established. Fluvoxamine is not recommended for the treatment of depression in pregnant women because of known harms to the fetus *[241]*. Caution should be taken when prescribing fluvoxamine to children, adolescents or elderly patients.

**Certainty of the evidence**

Low

**General adult population**
Certainty of the evidence is moderate for all-cause mortality due to serious imprecision (deaths only occurred in one study) and low for all other outcomes (due to reliance on a single study, few events and/or wide confidence intervals).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
For children and adolescents and pregnant and breastfeeding women, certainty is downgraded to very low due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older**

**people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. As there are known harms associated with fluvoxamine use in pregnant and breastfeeding women, these patients would likely not opt for treatment.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

**General adult population**
There is currently limited evidence about the impact of fluvoxamine on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that fluvoxamine should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of fluvoxamine to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Fluvoxamine
**Comparator:** Placebo

### Summary

There remains significant uncertainty whether fluvoxamine is more effective and safer than placebo in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from two randomised trials comparing fluvoxamine with placebo in over 1600 adult outpatients with mild COVID-19 *[164][168]*. The vast majority of data comes from the TOGETHER trial.

**Study characteristics**
Within the TOGETHER trial, median age of participants was 50 years and 58% were women. Pregnant women were ineligible.

**What are the main results?**
We are uncertain whether fluvoxamine increases or decreases all-cause mortality, adverse or serious adverse events, patients requiring hospitalisation or clinical deterioration. There were too few who required mechanical ventilation (one event) to determine whether fluvoxamine makes a difference.

**Our confidence in the results**
Certainty of the evidence is moderate for all-cause mortality due to serious imprecision (deaths only occurred in one study) and low for all other outcomes (due to reliance on a single study, few events and/or wide confidence intervals).

For children and adolescents and pregnant and breastfeeding women, certainty is downgraded to very low due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
According to the Therapeutic Goods Administration, known acute harms for fluvoxamine include headache, dizziness, palpitations, diarrhoea, nausea and vomiting *[112]*. Use of fluvoxamine to treat COVID-19 in patients with a history of depression should be carefully considered due to the possible development of symptoms such as anxiety, agitation, panic attacks and mania.

According to the Therapeutic Goods Administration, the use of fluvoxamine in **pregnant women**, particularly in late pregnancy, has been shown to increase the risk of persistent pulmonary hypertension in the newborn *[112]*. Neonates exposed to fluvoxamine during pregnancy are at risk of experiencing withdrawal symptoms that may lead to complications such as respiratory distress, cyanosis, seizures and vomiting,

potentially leading to prolonged hospitalisation, requirement of respiratory support and/or tube feeding. Fluvoxamine should not be used during pregnancy unless the clinical condition of the woman requires such treatment *[112]*.

Although fluvoxamine (and other selective serotonin reuptake inhibitors) show no detrimental effect on growth, development and maturation, it is currently not indicated in **children and adolescents** for other uses (as the efficacy and safety of fluvoxamine has not been satisfactorily investigated in this population) *[112]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Fluvoxamine | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>End of follow-up<br>9 Critical | Relative risk 0.7<br>(CI 95% 0.38 — 1.3)<br>Based on data from 1,624 participants in 2 studies. [1]<br>(Randomized controlled) | **30**<br>per 1000<br>Difference: | **21**<br>per 1000<br>**9 fewer per 1000**<br>( CI 95% 19 fewer — 9 more ) | **Moderate**<br>Due to serious imprecision [2] | Fluvoxamine probably has little impact on death (41 events). |
| **Mechanical ventilation**<br>Within 45 days of commencing treatment<br>6 Important | Based on data from 152 participants in 1 studies. [3]<br>(Randomized controlled) | | | **Low**<br>Due to very serious imprecision [4] | There were too few who required mechanical ventilation to determine whether fluvoxamine makes a difference (1 event). |
| **Serious adverse events**<br>Within 15 days of commencing treatment<br>6 Important | Relative risk 0.18<br>(CI 95% 0.02 — 1.5)<br>Based on data from 152 participants in 1 studies. [5]<br>(Randomized controlled) | **69**<br>per 1000<br>Difference: | **12**<br>per 1000<br>**57 fewer per 1000**<br>( CI 95% 68 fewer — 35 more ) | **Low**<br>Due to very serious imprecision [6] | We are uncertain whether fluvoxamine increases or decreases number of patients who experience one or more serious adverse events (6 events). |
| **Adverse events**<br>Within 15 days of commencing treatment<br>6 Important | Relative risk 1.65<br>(CI 95% 0.64 — 4.23)<br>Based on data from 152 participants in 1 studies. [7]<br>(Randomized controlled) | **83**<br>per 1000<br>Difference: | **137**<br>per 1000<br>**54 more per 1000**<br>( CI 95% 30 fewer — 268 more ) | **Low**<br>Due to very serious imprecision [8] | We are uncertain whether fluvoxamine increases or decreases number of patients who experience one or more adverse events (17 events). |
| **Clinical deterioration**<br>Within 15 days of commencing treatment<br>6 Important | Relative risk 0.07<br>(CI 95% 0 — 1.21)<br>Based on data from 152 participants in 1 studies. [9]<br>(Randomized controlled) | **83**<br>per 1000<br>Difference: | **6**<br>per 1000<br>**77 fewer per 1000**<br>( CI 95% 83 fewer — 17 more ) | **Low**<br>Due to very serious imprecision [10] | We are uncertain whether fluvoxamine improves or worsens clinical deterioration (6 events). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Fluvoxamine | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Hospitalisation**<br>End of follow-up<br><br>6 Important | Relative risk 0.47<br>(CI 95% 0.08 — 2.8)<br>Based on data from 1,624 participants in 2 studies. [11]<br>(Randomized controlled) | **119**<br>per 1000<br><br>Difference: | **56**<br>per 1000<br><br>**63 fewer per 1000**<br>( CI 95% 109 fewer — 214 more ) | **Low**<br>Due to very serious imprecision [12] | We are uncertain whether fluvoxamine increases or decreases hospitalisation (170 events). |

1, 11. Systematic review [108] with included studies: TOGETHER 2021, Lenze 2020.
2. **Imprecision: serious.** Deaths only occured in one included study.
3, 5, 7, 9. Systematic review [110] with included studies: Lenze 2020.
4. **Imprecision: very serious.** due to few events, Only data from one study.
6, 8. **Imprecision: very serious.** Wide confidence intervals, Only data from one study, due to few events.
10. **Imprecision: very serious.** Low number of patients, Wide confidence intervals, due to few events, Only data from one study.
12. **Imprecision: very serious.** Very wide confidence intervals, majority of events occured in one study.

### References

108. Fluvoxamine for COVID-19.

110. Fluvoxamine for COVID-19.

112. Therapeutic Goods Administration. Australian Product Information - APO-Fluvoxamine (Fluvoxamine Maleate) Film Coated Tablets. 22 May 2020. Website

164. Lenze EJ, Mattar C, Zorumski CF, Stevens A, Schweiger J, Nicol GE, et al. Fluvoxamine vs placebo and clinical deterioration in outpatients with symptomatic COVID-19: a randomized clinical trial. JAMA 2020. Pubmed Journal

168. Reis G, Dos Santos Moreira-Silva EA, Silva DCM, Thabane L, Milagres AC, Ferreira TS, et al. Effect of early treatment with fluvoxamine on risk of emergency care and hospitalisation among patients with COVID-19: the TOGETHER randomised, platform clinical trial. Lancet Global Health 2021. Pubmed Journal

## 2.11.5 Metformin

Only in research settings

Do not use metformin for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use metformin to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

## Evidence to decision

### Benefits and harms

Small net benefit, or little difference between alternatives

**General adult population**
Evidence indicates no difference between metformin and standard care for death, admission to hospital, adverse or serious adverse events.

### Certainty of the evidence

Low

**General adult population**
Certainty of the evidence is low for death, admission to hospital, and adverse or serious adverse events due to very serious imprecision (reliance on a single study, wide confidence intervals, few patients and few events).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

### Values and preferences

Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as this treatment has shown no clear benefits, most informed patients would prefer not to use it, while some patients may choose to participate in clinical trials of this treatment.

### Resources

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Equity

Important issues, or potential issues not investigated

**General adult population**
There is a risk of creating inequity as some populations are currently not eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

**People requiring palliative care and older people living with frailty or cognitive impairment**
As older people living with frailty or cognitive impairment are particularly at risk from COVID-19, we encourage trials that include this population (with appropriate baseline measurement of frailty and cognitive impairment). In people requiring palliative care, trials should consider symptom management and quality of life outcomes. Given the absence of trials and uncertain benefit-to-harm ratio, this recommendation protects these more vulnerable populations.

### Acceptability

Important issues, or potential issues not investigated

**General adult population**
Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

**People requiring palliative care and older people living with frailty or cognitive impairment**
Because the benefit-to-harm ratio is uncertain, acceptability may vary due to individual decision-making around goals of care.

**Feasibility** Important issues, or potential issues not investigated

Implementability is limited by the fact that not all populations are eligible to be enrolled in trials and some will live in geographic areas where opportunities for enrolment are limited or non-existent.

## Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Metformin
**Comparator:** Placebo

## Summary

There remains significant uncertainty whether metformin is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from the TOGETHER trial that compared metformin with placebo in 418 adults hospitalised with mild COVID-19 *[170]*.

**Study characteristics**
Median age of participants was 52 years and 57% were women. Patients with COVID-19 (confirmed by rapid antigen test) started treatment within 7 days of onset of symptoms and had at least one risk factor for disease progression (diabetes, hypertension, cardiovascular disease, chronic lung disease, asthma, BMI > 30, chronic kidney disease, immunocompromised, or aged 50 or over). Vaccinated patients were excluded.

**What are the main results?**
Metformin may have little impact on all-cause mortality, hospitalisation, and adverse or serious adverse events.

**Our confidence in the results**
Certainty of the evidence is low for all-cause mortality, hospitalisation, and adverse or serious adverse events due to very serious imprecision.

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included study).

**Additional information**
According to the Therapeutic Goods Administration, common side effects associated with metformin include nausea, vomiting, anorexia, diarrhoea, and malabsorption of vitamin B12.

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Placebo | **Intervention** Metformin | **Certainty of the evidence** (Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality** Within 28 days of commencing treatment 9 Critical | Relative risk 0.73 (CI 95% 0.28 — 1.94) Based on data from 418 participants in 1 studies. [1] (Randomized controlled) | 44 per 1000 Difference: | 32 per 1000 **12 fewer per 1000** ( CI 95% 32 fewer — 41 more ) | **Low** Due to very serious imprecision [2] | Metformin may have little or no difference on all-cause mortality (16 deaths). |
| **Serious adverse events** End of follow-up 6 Important | Relative risk 1.11 (CI 95% 0.7 — 1.75) Based on data from 418 participants in 1 studies. [3] (Randomized controlled) | 143 per 1000 Difference: | 159 per 1000 **16 more per 1000** ( CI 95% 43 fewer — 107 more ) | **Low** Due to very serious imprecision [4] | Metformin may have little or no difference on serious adverse events (63 events). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Metformin | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Adverse events**<br>End of follow-up<br><br>6 Important | Relative risk 0.89<br>(CI 95% 0.47 — 1.68)<br>Based on data from 418 participants in 1 studies. [5]<br>(Randomized controlled) | **89**<br>per 1000<br><br>Difference: | **79**<br>per 1000<br><br>**10 fewer per 1000**<br>( CI 95% 47 fewer — 61 more ) | **Low**<br>Due to very serious imprecision [6] | Metformin may have little or no difference on adverse events (35 events). |
| **Discontinuation due to an adverse event**<br>End of follow-up<br><br>6 Important | Relative risk 2.83<br>(CI 95% 0.12 — 69.15)<br>Based on data from 418 participants in 1 studies. [7]<br>(Randomized controlled) | **0**<br>per 1000<br><br>Difference: | **0**<br>per 1000<br><br>**0 fewer per 1000**<br>( CI 95% 0 fewer — 0 fewer ) | **Low**<br>Due to very serious imprecision [8] | Metformin may have little or no difference on discontinuation due to an adverse event (1 event). |
| **Hospitalisation**<br>Within 28 days of commencing treatment<br><br>6 Important | Relative risk 1.15<br>(CI 95% 0.72 — 1.82)<br>Based on data from 418 participants in 1 studies. [9]<br>(Randomized controlled) | **138**<br>per 1000<br><br>Difference: | **159**<br>per 1000<br><br>**21 more per 1000**<br>( CI 95% 39 fewer — 113 more ) | **Low**<br>Due to very serious imprecision [10] | Metformin may have little or no difference on hospitalisation (62 events). |

1, 3, 5, 7, 9. Systematic review [113] with included studies: Reis 2022.
2. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study, due to low event rate..
4, 6. **Imprecision: very serious.** Wide confidence intervals, Only data from one study, Wide confidence intervals, Only data from one study, due to [reason], Low number of patients, Low number of patients.
8. **Imprecision: very serious.** Wide confidence intervals, Only data from one study, due to only one event..
10. **Imprecision: very serious.** Wide confidence intervals, Only data from one study, Low number of patients.

### References

113. [Intervention] for [COVID-19].

170. Reis G, Dos Santos Moreira Silva EA, Medeiros Silva DC, Thabane L, Cruz Milagres A, Ferreira TS, et al. Effect of early treatment with metformin on risk of emergency care and hospitalization among patients with COVID-19: The TOGETHER randomized platform clinical trial. Lancet Regional Health – Americas 2022;6:100142 Pubmed Journal

172. Therapeutic Goods Administration. Australian Product Information - Kineret (anakinra). 16 February 2021. Website

## 2.11.6 Recombinant human granulocyte colony-stimulating factor (rhG-CSF)

Only in research settings

Do not use rhG-CSF for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Recombinant human granulocyte colony-stimulating factor should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use rhG-CSF to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### Evidence to decision

**Benefits and harms**

Important harms

**General adult population**
In addition to uncertainty around benefits for patients with COVID-19, there are well-known side effects and harms associated with rhG-CSF, including thrombocytopaenia (common), pulmonary haemorrhage, haemoptysis, aortitis and glomerulonephritis. There have also been occasional reports of adult respiratory distress syndrome in patients receiving rhG-CSF.

**Children and adolescents**
Paediatricians have considerable experience with the use of rhG-CSF in children and adolescents for other indications.

**Pregnant and breastfeeding women**
Transplacental passage of rhG-CSF has been demonstrated, and it is not known if rhG-CSF is excreted in human milk. rhG-CSF is therefore not recommended for pregnant and breastfeeding women unless the potential benefit outweighs the potential risk to the fetus or newborn/infant.

**People requiring palliative care and older people living with frailty or cognitive impairment**
The benefits of rhG-CSF for this population are uncertain.

**Certainty of the evidence**

Very low

**General adult population**
Certainty of the evidence is low for death and mechanical ventilation due to very serious imprecision (low patient numbers, few events and reliance on a single study); low for duration of hospital stay due serious risk of bias (lack of blinding) and serious imprecision (low patient numbers and reliance on a single study); and very low for adverse and serious adverse events due to serious risk of bias and very serious imprecision (low patient numbers and reliance on a single study).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the effects of rhG-CSF during pregnancy and breastfeeding are unknown in the context of COVID-19.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered, but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

**General adult population**
There is currently limited evidence about the impact of rhG-CSF on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that rhG-CSF should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of rhG-CSF to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** rhG-CSF
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether therapy with recombinant human granulocyte colony-stimulating factor (rhG-CSF) is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial that compared 3 days of subcutaneous rhG-CSF therapy (5 µg/kg) with standard care in 200 hospitalised lymphopaenic adults with no comorbidities and moderate-to-severe COVID-19 *[175]*.

**Study characteristics**
Median age of participants was 45 years and 44% were women. Standard care comprised supplemental oxygen, non-invasive ventilation, or intravenous antibiotics when indicated. Participants were required to have a peripheral blood leukocyte count ≤ 1500 per µL and peripheral blood lymphocyte ≤ 800 per µL for inclusion. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
For the critical outcomes of death and mechanical ventilation within 21 days of starting treatment, there were too few events (12 deaths and 16 who required ventilation) to determine whether rhG-CSF therapy makes a difference. It is unclear whether rhG-CSF therapy increases or decreases adverse or serious adverse events. rhG-CSF therapy may have little or no impact on the duration of hospital stay.

**Our confidence in the results**

Certainty of the evidence is low for death and mechanical ventilation due to very serious imprecision (low patient numbers, few events and reliance on a single study); low for duration of hospital stay due serious risk of bias (lack of blinding) and serious imprecision (low patient numbers and reliance on a single study); and very low for adverse and serious adverse events due to serious risk of bias and very serious imprecision (low patient numbers and reliance on a single study).

**Additional information**
There are well-known side effects and harms associated with rhG-CSF therapy, including thrombocytopaenia (common), pulmonary haemorrhage, haemoptysis, aortitis and glomerulonephritis. There have also been occasional reports of adult respiratory distress syndrome in patients receiving rhG-CSF therapy *[114]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>rhG-CSF | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 21 days of commencing treatment<br>9 Critical | Relative risk 0.2<br>(CI 95% 0.04 — 0.89)<br>Based on data from 200 participants in 1 studies. [1]<br>(Randomized controlled) | **100**<br>per 1000<br>Difference: | **20**<br>per 1000<br>**80 fewer per 1000**<br>( CI 95% 96 fewer — 11 fewer ) | **Very low**<br>Due to extremely serious imprecision [2] | There were too few who died to determine whether rhG-CSF makes a difference (12 events). |
| **Invasive mechanical ventilation**<br>Within 21 days of commencing treatment<br>9 Critical | Relative risk 0.14<br>(CI 95% 0.03 — 0.61)<br>Based on data from 200 participants in 1 studies. [3]<br>(Randomized controlled) | **140**<br>per 1000<br>Difference: | **20**<br>per 1000<br>**120 fewer per 1000**<br>( CI 95% 136 fewer — 55 fewer ) | **Very low**<br>Due to extremely serious imprecision [4] | There were too few who required invasive mechanical ventilation to determine whether rhG-CSF makes a difference (16 events). |
| **Serious adverse events**<br>End of treatment<br>6 Important | Relative risk 0.72<br>(CI 95% 0.49 — 1.05)<br>Based on data from 200 participants in 1 studies. [5]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [6] | We are uncertain whether rhG-CSF increases or decreases serious adverse events (71 events). |
| **Adverse events**<br>End of treatment<br>6 Important | Relative risk 2.02<br>(CI 95% 1.62 — 2.5)<br>Based on data from 200 participants in 1 studies. [7]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [8] | We are uncertain whether rhG-CSF increases adverse events (138 events). |
| **Duration of hospital stay**<br>Days<br>6 Important | Based on data from 200 participants in 1 studies. [9]<br>(Randomized controlled) | **14**<br>(Median)<br>Difference: | **13**<br>(Median)<br>**1 fewer** | **Low**<br>Due to serious risk of bias and serious imprecision [10] | RhG-CSF may have little impact on duration of hospital stay. |

1, 3, 5, 7, 9. Systematic review [115] with included studies: Cheng 2020.

2. **Risk of Bias: no serious.** Inadequate/lack of blinding of participants, personnel, and outcome assessors. **Inconsistency: no serious. Indirectness: no serious. Imprecision: extremely serious.** Only data from one study, Low number of patients, Few events, Wide confidence intervals. **Publication bias: no serious.**
4. **Risk of Bias: no serious.** Inadequate/lack of blinding of participants, personnel and outcome assessors. **Inconsistency: no serious. Indirectness: no serious. Imprecision: extremely serious.** Low number of patients, only data from one study, few events, Wide confidence intervals. **Publication bias: no serious.**
6. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Low number of patients, Wide confidence intervals, Only data from one study. **Publication bias: no serious.**
8. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias: no serious.**
10. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study, Low number of patients. **Publication bias: no serious.**

### References

114. Therapeutic Goods Administration. Product Information: Zarzio (Filgrastim; Recombinant Human Granulocyte Colony Stimulating Factor). May 2013. Website

115. rhG-CSF for COVID-19.

175. Cheng L-L, Guan W-J, Duan C-Y, Zhang N-F, Lei C-L, Hu YU, et al. Effect of recombinant human granulocyte colony-stimulating factor for patients with coronavirus disease 2019 (COVID-19) and lymphopenia: a randomized clinical trial. JAMA Internal Medicine 2020. Pubmed Journal

### Clinical question/ PICO

**Population:** Special populations with COVID-19
**Intervention:** rhG-CSF
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether therapy with recombinant human granulocyte colony-stimulating factor (rhG-CSF) is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial that compared 3 days of subcutaneous rhG-CSF therapy (5 µg/kg) with standard care in 200 hospitalised lymphopaenic adults with no comorbidities and moderate-to-severe COVID-19 *[175]*.

**Study characteristics**
Median age of participants was 45 years and 44% were women. Standard care comprised supplemental oxygen, non-invasive ventilation, or intravenous antibiotics when indicated. Participants were required to have a peripheral blood leukocyte count ≤ 1500 per µL and peripheral blood lymphocyte ≤ 800 per µL for inclusion. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
For the critical outcomes of death and invasive mechanical ventilation within 21 days of starting treatment, there were too few events (12 deaths and 16 who required ventilation) to determine whether rhG-CSF therapy makes a difference. It is unclear whether rhG-CSF therapy increases or decreases adverse or serious adverse events. rhG-CSF therapy may have little or no impact on the duration of hospital stay.

**Our confidence in the results**
Certainty of the evidence is very low for all outcomes. This judgement is based on serious risk of bias (lack of blinding), very serious imprecision (low patient numbers, few observed events and reliance on a single study) and serious indirectness (limited inclusion of these populations).

**Additional information**
There are well-known side effects and harms associated with rhG-CSF therapy, including thrombocytopaenia (common), pulmonary

haemorrhage, haemoptysis, aortitis and glomerulonephritis. There have also been occasional reports of adult respiratory distress syndrome in patients receiving rhG-CSF therapy *[114]*.

Paediatricians have considerable experience with the use of rhG-CSF in **children and adolescents** for other indications.

Transplacental passage of rhG-CSF has been demonstrated, and it is not known if rhG-CSF is excreted in human milk. rhG-CSF is therefore not recommended for **pregnant and breastfeeding women** unless the potential benefit outweighs the potential risk to the fetus or newborn/infant *[114]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>rhG-CSF | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 21 days of commencing treatment<br><br>9 Critical | Relative risk 0.2<br>(CI 95% 0.04 — 0.89)<br>Based on data from 200 participants in 1 studies. [1]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision and serious indirectness [2] | There were too few who died to determine whether rhG-CSF makes a difference (12 events). |
| **Invasive mechanical ventilation**<br>Within 21 days of commencing treatment<br><br>9 Critical | Relative risk 0.14<br>(CI 95% 0.03 — 0.61)<br>Based on data from 200 participants in 1 studies. [3]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision and serious indirectness [4] | There were too few who required invasive mechanical ventilation to determine whether rhG-CSF makes a difference (16 events). |
| **Serious adverse events**<br>End of treatment<br><br>6 Important | Relative risk 0.72<br>(CI 95% 0.49 — 1.05)<br>Based on data from 200 participants in 1 studies. [5]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision, serious risk of bias and serious indirectness [6] | We are uncertain whether rhG-CSF increases or decreases serious adverse events |
| **Adverse events**<br>End of treatment<br><br>6 Important | Relative risk 2.02<br>(CI 95% 1.62 — 2.5)<br>Based on data from 200 participants in 1 studies. [7]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision, serious risk of bias and serious indirectness [8] | We are uncertain whether rhG-CSF increases adverse events. |
| **Duration of hospital stay**<br>Days<br><br>6 Important | Based on data from 200 participants in 1 studies. [9]<br>(Randomized controlled) | **14**<br>(Median)<br><br>Difference: | **13**<br>(Median)<br><br>**1 fewer** | **Very low**<br>Due to serious risk of bias, serious imprecision and serious indirectness [10] | We are uncertain whether rhG-CSF increases or decreases duration of hospital stay. |

1, 3, 5, 7, 9. Systematic review [115] with included studies: Cheng 2020.

2. **Risk of Bias: no serious.** Inadequate/lack of blinding of participants, personnel, and outcome assessors. **Inconsistency: no serious. Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: very serious.** Only data from one study, Low number of patients, Few events. **Publication bias: no serious.**

4. **Risk of Bias: no serious.** Inadequate/lack of blinding of participants, personnel and outcome assessors. **Inconsistency: no serious. Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: very serious.** Low number of patients, only data from one study, few events. **Publication bias: no serious.**

6. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: very serious.** Low number of patients, Wide confidence intervals, Only data from one study. **Publication bias: no serious.**

8. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** Differences

between the population of interest and those studied. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias: no serious.**
10. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/ lack of blinding of outcome assessors, resulting in potential for detection bias. **Inconsistency: no serious. Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: serious.** Only data from one study, Low number of patients. **Publication bias: no serious.**

### References

114. Therapeutic Goods Administration. Product Information: Zarzio (Filgrastim; Recombinant Human Granulocyte Colony Stimulating Factor). May 2013. Website

115. rhG-CSF for COVID-19.

175. Cheng L-L, Guan W-J, Duan C-Y, Zhang N-F, Lei C-L, Hu YU, et al. Effect of recombinant human granulocyte colony-stimulating factor for patients with coronavirus disease 2019 (COVID-19) and lymphopenia: a randomized clinical trial. JAMA Internal Medicine 2020. Pubmed Journal

## 2.11.7 Sabizabulin

Only in research settings

New

Do not use sabizabulin for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Sabizabulin should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use sabizabulin to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a moderate priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### Evidence to decision

**Benefits and harms**

**General adult population**
In addition to uncertainty around benefits for patients with COVID-19, sabizabulin is an investigational treatment and the safety profile is not clearly defined.

**Certainty of the evidence**

Low

Certainty of the evidence is low for all outcomes due to very serious imprecision (reliance on a single study with low patient numbers and wide confidence intervals).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
Variability may be expected in preferences and values for these populations given the potentially different goals of care.

**Resources**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

**General adult population**
There is currently limited evidence about the impact of sabizabulin on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that sabizabulin should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of sabizabulin to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Sabizabulin for COVID-19
**Intervention:** Sabizabulin
**Comparator:** Placebo

### Summary

There remains significant uncertainty whether Sabizabulin is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial that compared Sabizabulin with placebo in 204 adults, hospitalised with moderate to severe COVID-19 *[196]*.

**Study characteristics**
Median age was 64 years in both the Sabizabulin group and in the control group; the proportion of women was 30% and 37% respectively. Sabizabulin was administered (in the form of 9-mg capsule) daily for up to 21 days or until the patient was discharged from the hospital, whichever came first. Pregnant or breastfeeding women were ineligible.

**What are the main results?**
There where 42 deaths (19 in the Sabizabulin group and 23 in the placebo). A total of 134 participants experienced adverse events and 70 participants experienced serious adverse events. A total of 82 treatment related serious adverse events occurred in the Sabizabulin group and 84 in the placebo group.

**Our confidence in the results**
Certainty of the evidence is low for all outcomes due to very serious imprecision (reliance on a single study with low patient numbers and wide confidence intervals).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**

Sabizabulin is an experimental treatment and is not listed on the Australian Register of Therapeutic Goods (ARTG).

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Sabizabulin | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 60 days of commencing treatment<br>9 Critical | Relative risk 0.44<br>(CI 95% 0.26 — 0.73)<br>Based on data from 150 participants in 1 studies. [1] | **442**<br>per 1000<br>Difference: | **194**<br>per 1000<br>**248 fewer per 1000**<br>( CI 95% 327 fewer — 119 fewer ) | **Low**<br>Due to very serious imprecision | Sabizabulin may decrease risk of death (42 deaths). |
| **Adverse events** [2]<br>End of follow-up<br>6 Important | Relative risk 0.79<br>(CI 95% 0.65 — 0.95)<br>Based on data from 199 participants in 1 studies. [3] | **783**<br>per 1000<br>Difference: | **619**<br>per 1000<br>**164 fewer per 1000**<br>( CI 95% 274 fewer — 39 fewer ) | **Low**<br>Due to very serious imprecision | Sabizabulin may decrease adverse events (134 events). |
| **Serious adverse events** [4]<br>End of follow-up<br>6 Important | Relative risk 0.63<br>(CI 95% 0.44 — 0.91)<br>Based on data from 199 participants in 1 studies. [5] | **464**<br>per 1000<br>Difference: | **292**<br>per 1000<br>**172 fewer per 1000**<br>( CI 95% 260 fewer — 42 fewer ) | **Low**<br>Due to very serious imprecision | Sabizabulin may decrease serious adverse events (70 events). |
| **Duration of hospitalisation (days)**<br>6 Important | Lower better<br>Based on data from 204 participants in 1 studies. | **34.6**<br>(Mean)<br>Difference: | **25.6**<br>(Mean)<br>**MD 9 lower**<br>CI 95% | **Low**<br>Due to very serious imprecision | Sabizabulin may decrease duration of hospitalisation. |

1, 3, 5. Systematic review [194] with included studies: Barnette 2022.
2, 4. Within 60 days of commencing treatment

**References**

194. Sabizabulin for COVID-19.

# 2.12 Vitamins, supplements and cofactors

## 2.12.1 Combined metabolic activators (CMA)

Only in research settings

Do not use combined metabolic activators (CMA) for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Combined metabolic activators (CMA) should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use CMA to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

**Evidence to decision**

| | |
|---|---|
| **Benefits and harms** | **General adult population**<br>As the safety profile for combined metabolic activators is incompletely characterised in humans, there is uncertainty around the benefits and harms for patients with COVID-19. |
| **Certainty of the evidence** | Very low<br><br>Certainty of the evidence is very low for all outcomes. This judgement is based on serious risk of bias and very serious imprecision due to low patient numbers, reliance on a single study and few events (adverse events).<br><br>**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**<br>In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials. |
| **Values and preferences** | Substantial variability is expected or uncertain<br><br>**General adult population**<br>We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.<br><br>**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**<br>Variability may be expected in preferences and values for these populations given the potentially different goals of care. |
| **Resources and other considerations** | Important issues, or potential issues not investigated |

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

**General adult population**
There is currently limited evidence about the impact of combined metabolic activators (CMA) on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that CMA should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of CMA to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Combined metabolic activators
**Comparator:** Control

### Summary

There remains significant uncertainty whether combined metabolic activators (CMA) are more effective and safer than placebo in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial that compared CMA with placebo in 93 non-hospitalised adults with mild or moderate COVID-19 *[116]*.

We have found one new study comparing CMA with placebo—the phase III component of the same study by Altay et al. (Advanced Science doi: 10.1002/advs.202101222). This study is currently under review and an updated recommendation will be included in a future version of the guideline.

**Study characteristics**
Mean age of participants was 36 years and 40% were women. Patients in the intervention group received CMAs (L-carnitine tartrate, 7.46 g/day; N-acetylcysteine, 5.1 g/day; nicotinamide riboside 2 g/day; serine 24.7 g/day) twice a day for 14 days as water-soluble powders containing the entire CMA dose. Standard care for symptomatic treatment included hydroxychloroquine. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
Data were not reported for the number of patients who died or experienced serious adverse events. There were too few who experienced adverse events to determine whether CMA makes a difference (2 events). It is unclear whether CMA increases or decreases clinical recovery at day 14 or time to clinical recovery.

**Our confidence in the results**
Certainty of the evidence is very low for all outcomes due to serious risk of bias and very serious imprecision.

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
Common side effects associated with N-acetylcysteine are nausea, vomiting and other gastrointestinal symptoms *[118]*.

For N-acetylcysteine, benefits can be assumed to outweigh possible risks for **pregnant women**; limited clinical experience has not resulted in adverse effects to the fetus. N-acetylcysteine is safe to use in women who are **breastfeeding** *[117]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Control | **Intervention**<br>CMA | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Mortality**<br>Within 14 days of commencing treatment<br>9 Critical | | | | | Data for number of patients who died were not reported. |
| **Serious adverse events**<br>End of follow-up<br>9 Critical | | | | | Data for number of patients experiencing one or more serious adverse events were not reported. |
| **Adverse events**<br>End of follow-up<br>6 Important | Relative risk 1.6<br>(CI 95% 0.08 — 32.08)<br>Based on data from 93 participants in 1 studies. [1]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [2] | Too few experienced adverse events to determine whether CMAs make a difference (2 events). |
| **Clinical recovery**<br>End of follow-up<br>6 Important | Relative risk 1.13<br>(CI 95% 0.95 — 1.33)<br>Based on data from 93 participants in 1 studies. [3]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [4] | We are uncertain whether CMAs increase or decrease clinical recovery (88 events). |
| **Time to recovery**<br>End of follow-up<br>6 Important | Hazard ratio 2.68<br>(CI 95% 1.57 — 4.59)<br>Based on data from 93 participants in 1 studies.<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [5] | We are uncertain whether CMAs decrease time to recovery. |

1, 3. Systematic review [182] with included studies: Altay 2020.
2. **Risk of Bias: serious.** Cointerventions and compliance with intervention not reported, selective outcome reporting, Use of unvalidated and/or subjective outcome measures, Selective outcome reporting. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals, Only data from one study, Low number of patients, Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias: no serious.**
4, 5. **Risk of Bias: serious.** Use of unvalidated and/or subjective outcome measures, Selective outcome reporting. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias: no serious.**

## References

116. Altay O, Arif M, Li X, Yang H, Aydın M, Alkurt G, et al. Combined metabolic activators accelerates recovery in mild-to-moderate COVID-19. Advanced Science (Weinheim) 2021;e2101222 Pubmed Journal

117. Australian Medicines Handbook 2020 (online). 2020. Website

118. Therapeutic Goods Administration. Australian Product Information: DBL Acetylcysteine Injection Concentrate. May 2019. Website

182. Combined metabolic cofactor supplementation (CMCS) for COVID-19.

## 2.12.2 N-acetylcysteine

Only in research settings

Do not use N-acetylcysteine for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*N-acetylcysteine should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use N-acetylcysteine to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### Evidence to decision

**Benefits and harms**

**General adult population**
In addition to uncertainty around benefits for patients with COVID-19, there are common side effects and harms associated with N-acetylcysteine, including nausea, vomiting and other gastrointestinal symptoms *[290]*.

**Pregnant and breastfeeding women**
Benefits can be assumed to outweigh possible risks for pregnant women; limited clinical experience has not resulted in adverse effects to the fetus. N-acetylcysteine is safe to use in women who are breastfeeding *[267]*.

**Certainty of the evidence**

Very low

**General adult population**
Certainty of the evidence is low for mechanical ventilation, intensive care unit (ICU) admission and hospital length of stay. This judgement is based on very serious imprecision due to reliance on a single study, low patient numbers and few events. Certainty of the evidence is additionally very low for death due to serious risk of bias (incomplete data).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is further considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care. Further, for pregnant and breastfeeding women, the effects of N-acetylcysteine during pregnancy and breastfeeding are unknown in the context of COVID-19.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

## Rationale

**General adult population**
There is currently limited evidence about the impact of N-acetylcysteine on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that N-acetylcysteine should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of N-acetylcysteine for the treatment of COVID-19 in these populations should be avoided until evidence becomes available.

## Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** N-acetylcysteine
**Comparator:** Placebo

## Summary

There remains significant uncertainty whether N-acetylcysteine is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial that compared N-acetylcysteine with placebo in 135 adults with suspected (5%) or confirmed (95%) severe COVID-19 *[119]*.

We have found two new studies comparing N-acetylcysteine with standard care (Gaynitdinova et al. Pulmonology doi: 10.18093/0869-0189-2021-31-1-21-29 and Taher et al. Pharmacol Rep doi: 10.1007/s43440-021-00296-2). These studies are currently under review and an updated recommendation will be included in a future version of the guideline.

**Study characteristics**
Median age was 59 years in the N-acetylcysteine group and 58 years in the control group; the proportion of women was 33% and 46% respectively. N-acetylcysteine was administered intravenously for each patient in two doses (totalling 1000 ml over 20 hours). Standard care included oxygen supplementation, non-invasive and invasive ventilation, and antibiotics (ceftriaxone 2 g/day and azithromycin 500 mg/day). Pregnant women were ineligible.

**What are the main results?**
There were too few events to determine whether N-acetylcysteine makes a difference to death. N-acetylcysteine may decrease the need for admission to the intensive care unit (ICU) but increase the need for invasive mechanical ventilation. N-acetylcysteine may have little or no

impact on ICU admission or hospital length of stay.

**Our confidence in the results**
Certainty of the evidence is low for mechanical ventilation and ICU admission, hospital length of stay and ICU length of stay. This judgement is based on very serious imprecision due to reliance on a single study, low patient numbers and few events. Certainty of the evidence is additionally very low for mortality due to serious risk of bias (incomplete data).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
Common side effects associated with N-acetylcysteine are nausea, vomiting and other gastrointestinal symptoms *[187]*.

Benefits can be assumed to outweigh possible risks for **pregnant women**; limited clinical experience has not resulted in adverse effects to the fetus. N-acetylcysteine is safe to use in women who are **breastfeeding** *[185]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>N-acetylcysteine | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>End of follow-up<br><br>9 Critical | Relative risk 1.01<br>(CI 95% 0.43 — 2.4)<br>Based on data from 135 participants in 1 studies. [1]<br>(Randomized controlled) | | | **Very low**<br>Due to serious risk of bias and very serious imprecision [2] | There were too few events to determine whether N-acetylcysteine made a difference regarding death (18 events). |
| **Invasive mechanical ventilation** [3]<br>End of follow-up<br><br>9 Critical | Relative risk 1.16<br>(CI 95% 0.62 — 2.18)<br>Based on data from 135 participants in 1 studies. [4]<br>(Randomized controlled) | **206**<br>per 1000<br><br>Difference: | **239**<br>per 1000<br><br>**33 more per 1000**<br>( CI 95% 78 fewer — 243 more ) | **Low**<br>Due to very serious imprecision [5] | N-acetylcysteine may make little or no difference to the need for invasive mechanical ventiliation (30 events). |
| **ICU admission**<br>End of follow-up<br><br>6 Important | Relative risk 0.92<br>(CI 95% 0.63 — 1.33)<br>Based on data from 135 participants in 1 studies. [6]<br>(Randomized controlled) | **471**<br>per 1000<br><br>Difference: | **433**<br>per 1000<br><br>**38 fewer per 1000**<br>( CI 95% 174 fewer — 155 more ) | **Low**<br>Due to very serious imprecision [7] | N-acetylcysteine may make little or no difference to ICU admission (61 events). |
| **Hospital length of stay**<br>Days<br><br>6 Important | Lower better<br>Based on data from 135 participants in 1 studies. [8]<br>(Randomized controlled) | **10**<br>(Median) | **11**<br>(Median)<br><br>CI 95% | **Low**<br>Due to very serious imprecision [9] | N-acetylcysteine may have little or no impact on hospital length of stay. |
| **ICU length of stay**<br>Days | Lower better<br>Based on data from 135 participants in 1 studies. [10]<br>(Randomized controlled) | **8**<br>(Median) | **9**<br>(Median)<br><br>CI 95% | **Low**<br>Due to very serious imprecision [11] | N-acetylcysteine may have little or no impact on ICU length of stay |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>N-acetylcysteine | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| 6 Important | | | | | |

1, 4, 6, 8, 10. Systematic review [120] with included studies: de Alencar 2020.
2. **Risk of Bias: serious.** Incomplete data (6 patients still in ICU at end of follow-up excluded from mortality analysis) and/or reporting error (denominator different between narrative and table result). Pre-print only. Wait for peer-reviewed publication.. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Low number of patients, Only data from one study, few events, Wide confidence intervals. **Publication bias: no serious.**
3. Need for endotracheal intubation/invasive mechanical ventilation
5, 7. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias: no serious.**
9. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Only data from one study, Low number of patients, Wide confidence intervals. **Publication bias: no serious.**
11. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Low number of patients, Only data from one study, Wide confidence intervals. **Publication bias: no serious.**

### References

119. de Alencar JCG, Moreira CDL, Müller AD, Chaves CE, Fukuhara MA, da Silva EA, et al. Double-blind, randomized, placebo-controlled trial with N-acetylcysteine for treatment of severe acute respiratory syndrome caused by COVID-19. Clinical Infectious Diseases 2020. Pubmed Journal

120. N-acetylcysteine for COVID-19.

185. Australian Medicines Handbook 2020 (online). 2020. Website

187. Therapeutic Goods Administration. Australian Product Information: DBL Acetylcysteine Injection Concentrate. May 2019. Website

## 2.12.3 Vitamin C

Only in research settings

Do not use vitamin C for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Vitamin C should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use vitamin C to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

## Evidence to decision

**Benefits and harms**

Small net benefit, or little difference between alternatives

**General adult population**
There are limited harms associated with vitamin C at the doses specified in the included studies. However, there remains significant uncertainty around benefits for patients with COVID-19.

**Certainty of the evidence**

Very low

**General adult population**
Certainty of the evidence for all outcomes is very low due to very serious risk of bias, serious inconsistency and serious imprecision (studies stopped early, direction not consistent, wide confidence intervals, low patient numbers and/or observed events).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the study.

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected information regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

## Rationale

**General adult population**
There is currently limited evidence about the impact of vitamin C on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that vitamin C should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of vitamin C to treat COVID-19 in these populations should be avoided until evidence becomes available.

## Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Vitamin C
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether vitamin C is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from four randomised trials that compared vitamin C with standard care in 364 adults with COVID-19 *[123][191][197][195]*.

**Study characteristics**
Mean age of participants across the studies ranged from 42 to 66 years and the proportion of women ranged from 43 to 62%. Pregnant and breastfeeding women were ineligible in all trials.

**What are the main results?**
We are uncertain whether vitamin C increases or decreases risk of death, patients requiring invasive mechanical ventilation or clinical deterioration.

**Our confidence in the results**
Certainty of the evidence is very low for death within 28 days due to very serious risk of bias, serious inconsistency and serious imprecision (based on studies stopping early, direction not consistent, wide confidence intervals and few patients). Certainty is very low for death and mechanical ventilation at end of follow-up due to serious inconsistency and serious imprecision (direction not consistent, wide confidence intervals and few patients). Certainty is very low for hospitalisation and clinical deterioration due to very serious risk of bias and imprecision (studies stopped early, wide confidence intervals, few patients and single study).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
Common side effects and harms associated with vitamin C are nausea, vomiting, diarrhoea, heartburn, stomach cramps, bloating, fatigue, insomnia, headache and skin flushing.

Limited information suggests that vitamin C is not associated with harm **during pregnancy**. Vitamin C may be used in women who are **breastfeeding**.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Vitamin C | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 28 days of commencing treatment<br><br>9 Critical | Relative risk 0.72<br>(CI 95% 0.31 — 1.66)<br>Based on data from 154 participants in 2 studies. [1]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious risk of bias, serious inconsistency and serious imprecision [2] | We are uncertain whether vitamin C increases or decreases risk of death (17 deaths). |
| **All-cause mortality**<br>End of follow-up<br><br>9 Critical | Relative risk 0.71<br>(CI 95% 0.33 — 1.54)<br>Based on data from 210 participants in 2 studies. [3]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision, serious inconsistency and serious risk of bias. [4] | We are uncertain whether vitamin C increases risk of death (24 deaths). |
| **Invasive mechanical ventilation** | Relative risk 0.89<br>(CI 95% 0.49 — 1.62)<br>Based on data from 210 participants in 2 studies. [5] | | | **Very low**<br>Due to serious risk of bias, serious inconsistency and | We are uncertain whether vitamin C increases or decreases invasive mechanical ventilation (36 |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Vitamin C | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| End of follow-up<br>9 Critical | (Randomized controlled) | | | serious imprecision [6] | events). |
| **Invasive mechanical ventilation**<br>Day 7 of treatment<br>9 Critical | Relative risk 0.98<br>(CI 95% 0.5 — 1.92)<br>Based on data from 56 participants in 1 studies. [7]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious risk of bias and serious imprecision [8] | We are uncertain whether vitamin C increases or decreases invasive mechanical ventilation (21 events). |
| **Hospitalisation**<br>6 Important | Relative risk 0.69<br>(CI 95% 0.12 — 3.98)<br>Based on data from 98 participants in 1 studies. [9]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious risk of bias and very serious imprecision [10] | We are uncertain whether vitamin C increases or decreases hospitalisation (5 events). |
| **Clinical deterioration**<br>6 Important | Relative risk 0.64<br>(CI 95% 0.17 — 2.44)<br>Based on data from 56 participants in 1 studies. [11]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious risk of bias and very serious imprecision [12] | We are uncertain whether vitamin C increases or decreases clinical deterioration (8 events). |

1. Systematic review [121] with included studies: Zhang 2021, Thomas 2021.
2. **Risk of Bias: very serious.** Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. **Indirectness: no serious. Imprecision: serious.** Wide confidence intervals, Low number of patients. **Publication bias: no serious.**
3, 5. Systematic review [121] with included studies: JamaliMoghadamSiahkali 2021, Kumari 2020.
4. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. **Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals, Low number of patients. **Publication bias: no serious.**
6. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. **Imprecision: serious.** Low number of patients.
7, 11. Systematic review [121] with included studies: Zhang 2021.
8. **Risk of Bias: very serious.** Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Imprecision: serious.** Wide confidence intervals, Low number of patients, Only data from one study.
9. Systematic review [121] with included studies: Thomas 2021.
10. **Risk of Bias: very serious.** Trials stopping earlier than scheduled, resulting in potential for overestimating benefits, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study.
12. **Risk of Bias: very serious.** Trials stopping earlier than scheduled, resulting in potential for overestimating benefits. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study.

## References

121. [Vitamin C] for [COVID-19].

123. Zhang J, Rao X, Li Y, Zhu Y, Liu F, Guo G, et al. Pilot trial of high-dose vitamin C in critically ill COVID-19 patients. Annals of Intensive Care 2021;11(1):5 Pubmed Journal

191. Kumari P, Dembra S, Dembra P, Bhawna F, Gul A, Ali B, et al. The role of vitamin C as adjuvant therapy in COVID-19. Cureus 2020;12(11):e11779 Pubmed Journal

195. Thomas S, Patel D, Bittel B, Wolski K, Wang Q, Kumar A, et al. Effect of high-dose zinc and ascorbic acid supplementation vs usual care on symptom length and reduction among ambulatory patients with SARS-CoV-2 infection: the COVID A to Z randomized clinical trial. JAMA Network Open 2021;4(2):e210369 Pubmed Journal

197. JamaliMoghadamSiahkali S, Zarezade B, Koolaji S, SeyedAlinaghi S, Zendehdel A, Tabarestani M, et al. Safety and effectiveness of high-dose vitamin C in patients with COVID-19: a randomized open-label clinical trial. European Journal of Medical Research 2021;26(1):20 Pubmed Journal

## 2.12.4 Vitamin D analogues (calcifediol/cholecalciferol)

Only in research settings

Do not use vitamin D analogues for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Vitamin D analogues should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use vitamin D analogues to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### Evidence to decision

**Benefits and harms**

Small net benefit, or little difference between alternatives

**General adult population**
There are limited harms associated with calcifediol, a vitamin D analog, at the doses specified in the included study. However, there remains significant uncertainty around benefits for patients with COVID-19.

**Certainty of the evidence**

Very low

**General adult population**
Certainty of the evidence for all outcomes is low due to very serious imprecision (low patient numbers and/or observed events, incomplete data and/or large loss to follow-up).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the study.

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected information regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

**General adult population**
There is currently limited evidence about the impact of vitamin D analogues on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that vitamin D analogues should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of vitamin D analogues to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Vitamin D analogues
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether vitamin D analogues (calcifediol/cholecalciferol) are more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from three randomised trials comparing vitamin D analogues with standard care or placebo in 353 adults hospitalised with COVID-19 *[198][124][200]*.

**Study characteristics**
Mean age of participants ranged from 48 to 57 years and the proportion of women ranged from 31 to 62%. Pregnant women were ineligible.

**What are the main results?**
For the critical outcomes of death and requirement of invasive mechanical ventilation, we are unsure if vitamin D analogues make a difference. Vitamin D analogues may reduce intensive care unit (ICU) admissions compared with standard care (211 fewer per 1000 patients; RR 0.20, CI 95% 0.01 to 3.50; 308 patients in 2 studies). We are uncertain whether vitamin D analogues make a difference with regards to discharge from hospital or time to discharge from hospital.

**Our confidence in the results**
Certainty of the evidence for all outcomes is low due to very serious imprecision (low patient numbers and/or observed events, incomplete data and/or large loss to follow-up).

For children and adolescents and pregnant and breastfeeding women, certainty is further downgraded due to serious indirectness (absence or

limited inclusion of these populations in the included studies).

**Additional information**
As a vitamin D analogue, there are limited harms associated with calcifediol at the doses specified in the study.

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Standard care | **Intervention** Vitamin D analogues | **Certainty of the evidence** (Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality** End of follow-up 9 Critical | Relative risk 0.58 (CI 95% 0.05 — 7.18) Based on data from 313 participants in 2 studies. [1] (Randomized controlled) | **56** per 1000 Difference: | **32** per 1000 **24 fewer per 1000** ( CI 95% 53 fewer — 346 more ) | **Low** Due to very serious imprecision [2] | We are uncertain whether vitamin D analogues decrease death (16 deaths). |
| **Invasive mechanical ventilation** End of follow-up 6 Important | Relative risk 0.47 (CI 95% 0.21 — 1.04) Based on data from 237 participants in 1 studies. [3] (Randomized controlled) | **144** per 1000 Difference: | **68** per 1000 **76 fewer per 1000** ( CI 95% 114 fewer — 6 more ) | **Low** Due to very serious imprecision [4] | We are uncertain whether vitamin D analogues decrease the requirement of invasive mechanical ventilation (25 events). |
| **ICU admission** End of follow-up 6 Important | Relative risk 0.2 (CI 95% 0.01 — 3.29) Based on data from 313 participants in 2 studies. [5] (Randomized controlled) | **264** per 1000 Difference: | **53** per 1000 **211 fewer per 1000** ( CI 95% 261 fewer — 605 more ) | **Low** Due to very serious imprecision [6] | Vitamin D analogues may decrease the requirement of ICU admission (57 events). |
| **Discharge from hospital** End of follow-up 6 Important | Relative risk 1.09 (CI 95% 0.96 — 1.23) Based on data from 76 participants in 1 studies. [7] (Randomized controlled) | **923** per 1000 Difference: | **1,000** per 1000 **83 more per 1000** ( CI 95% 37 fewer — 212 more ) | **Low** Due to very serious imprecision [8] | We are uncertain whether vitamin D analogues increase or decrease discharge from hospital. |
| **Time to discharge from hospital** Days 6 Important | Lower better Based on data from 237 participants in 1 studies. (Randomized controlled) | **7** (Median) | **7** (Median) CI 95% | **Low** Due to very serious imprecision [9] | We are uncertain whether vitamin D analogues increase or decrease time to discharge from hospital. |

1, 5. Systematic review [127] with included studies: Castillo 2020, Murai 2020.
2. **Imprecision: very serious.** Wide confidence intervals, Wide confidence intervals, due to few events.
3. Systematic review [127] with included studies: Murai 2020.
4, 8. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study.

6. **Imprecision: very serious.** Wide confidence intervals.
7. Systematic review [127] with included studies: Castillo 2020.
9. **Imprecision: very serious.** Low number of patients, Only data from one study.

### References

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127. Calcifediol for COVID-19.

198. Castillo ME, Entrenas Costa LM, Vaquero Barrios JM, Alcalá Díaz JF, Miranda JL, Bouillon R, et al. Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: a pilot randomized clinical study. Journal of Steroid Biochemistry and Molecular Biology 2020;105751 Pubmed Journal

200. Murai IH, Fernandes AL, Sales LP, Pinto AJ, Goessler KF, Duran CSC, et al. Effect of a single high dose of vitamin D3 on hospital length of stay in patients with moderate to severe COVID-19: a randomized clinical trial. JAMA 2021. Pubmed Journal

## 2.12.5 Zinc

Only in research settings

Do not use zinc for the treatment of COVID-19 outside of randomised trials with appropriate ethical approval.

***Additional information***

*Zinc should still be considered for other evidence-based indications in people who have COVID-19.*

*Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use zinc to treat COVID-19 in these populations unless they are eligible to be enrolled in trials.*

*This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.*

### Evidence to decision

**Benefits and harms**

Small net benefit, or little difference between alternatives

**General adult population**
There are limited harms associated with zinc at the doses specified in the included studies. However, there remains significant uncertainty around benefits for patients with COVID-19.

**Certainty of the evidence**

Low

**General adult population**
Certainty of the evidence is low for death and discharge from hospital due to very serious imprecision (reliance on a single study with low patient numbers and wide confidence intervals). Certainty is very low for hospitalisation due

to serious risk of bias (issues with randomisation and blinding of participants/personnel and outcome assessors), in addition to very serious imprecision (as described above).

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, certainty of the evidence is considered very low because of indirectness due to limited inclusion (or absence) of these populations in the trials.

**Values and preferences**

Substantial variability is expected or uncertain

**General adult population**
We have no systematically collected information regarding patients' preferences and values. The Consumer Panel believes that as there is uncertainty regarding the benefits of this treatment, most informed patients would prefer to wait until the available evidence is clearer, while other informed patients may choose to participate in clinical trials of this treatment.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
In addition to the concerns in the general adult population, variability may be expected in preferences and values for these populations given the potentially different goals of care.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected information regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

**General adult population**
There is currently limited evidence about the impact of zinc on patient-relevant outcomes in the treatment of COVID-19. The panel has significant concerns regarding the potential harms of unproven treatments. We therefore recommend that zinc should only be used to treat COVID-19 in the context of randomised trials with appropriate ethical approval.

**Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment**
There is an urgent need for trials that include these populations to inform clinical management of COVID-19. Given the limited evidence in the general adult population, use of zinc to treat COVID-19 in these populations should be avoided until evidence becomes available.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Zinc
**Comparator:** Standard care

### Summary

There remains significant uncertainty whether zinc is more effective and safer than standard care in treating patients with COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from two randomised trials. The first compared zinc with placebo in 33 adults hospitalised with COVID-19 *[201]* and the second compared zinc with standard care in 108 adult outpatients *[131]*.

**Removal of studies**
Version 44: Due to inconsistencies in the data reported for Abd-Elsalam et al. (Biol Trace Elem Res, 27 Nov 2020) *[128]*, we have removed this study from the analyses. The study contributed data to four outcomes (death, invasive mechanical ventilation, recovery and duration of hospital stay) and the removal of these data did not change the strength or direction of the recommendation.

**Study characteristics**
Mean age of participants in Thomas et al. was 45 years and 62% were women *[131]*. In Patel et al. mean age was ~62 years and 64% were women *[201]*.

**What are the main results?**
We are uncertain whether zinc increases or decreases death, rate of hospitalisation or discharge from hospital, or clinical recovery.

**Our confidence in the results**
Certainty of the evidence is low for death and discharge from hospital due to very serious imprecision (reliance on a single study with low patient numbers and wide confidence intervals). Certainty is very low for hospitalisation due to serious risk of bias (issues with randomisation and blinding of participants/personnel and outcome assessors), in addition to very serious imprecision (as described above).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
According to the Therapeutic Goods Administration, common side effects of zinc poisoning include hypotension, pulmonary oedema, diarrhoea, vomiting, jaundice and oliguria *[132]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Zinc | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 28 days of commencing treatment<br>9 Critical | Relative risk 0.8<br>(CI 95% 0.15 — 4.18)<br>Based on data from 141 participants in 2 studies. [1]<br>(Randomized controlled) | 44<br>per 1000<br>Difference: | 35<br>per 1000<br>**9 fewer per 1000**<br>( CI 95% 37 fewer — 140 more ) | **Low**<br>Due to serious risk of bias and serious imprecision [2] | We are uncertain whether zinc impacts death (5 events). |
| **Hospitalisation**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 1.44<br>(CI 95% 0.36 — 5.71)<br>Based on data from 108 participants in 1 studies. [3]<br>(Randomized controlled) | 60<br>per 1000<br>Difference: | 86<br>per 1000<br>**26 more per 1000**<br>( CI 95% 38 fewer — 283 more ) | **Very low**<br>Due to serious risk of bias and very serious imprecision [4] | We are uncertain whether zinc increases or decreases hospitalisation (8 events). |
| **Discharged from hospital**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 0.86<br>(CI 95% 0.55 — 1.32)<br>Based on data from 33 participants in 1 studies. [5]<br>(Randomized controlled) | 778<br>per 1000<br>Difference: | 669<br>per 1000<br>**109 fewer per 1000**<br>( CI 95% 350 fewer — 249 more ) | **Low**<br>Due to very serious imprecision [6] | We are uncertain whether zinc increases or decreases number of patients discharged from hospital (24 events). |

1. Systematic review [130] with included studies: Thomas 2021, Patel 2020.
2. **Risk of Bias: serious.** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. **Imprecision: serious.** Wide confidence intervals, due to [reason].
3. Systematic review [202] with included studies: Thomas 2021.

4. **Risk of Bias: serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias. **Imprecision: very serious.** Wide confidence intervals, Only data from one study, due to few events.
5. Systematic review [203] with included studies: Patel 2020.
6. **Imprecision: very serious.** Wide confidence intervals, Only data from one study, Low number of patients.

### References

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202. Zinc for COVID-19.

203. Zinc for COVID-19.

## 2.13 Other drug treatments

## 3. Pregnant and breastfeeding women

Molnupiravir, Paxlovid, baricitinib, sarilumab, Evusheld

### 3.1 Baricitinib for pregnant or breastfeeding women

Only in research settings

Do not use baricitinib for the treatment of COVID-19 in pregnant or breastfeeding women outside randomised trials with appropriate ethical approval.

***Additional information***

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

**Evidence to decision**

**Benefits and harms**

Small net benefit, or little difference between alternatives

There is uncertainty around the benefits and harms of baricitinib for pregnant or breastfeeding women with COVID-19.

In non-pregnant adult patients hospitalised with moderate or severe COVID-19 who require supplemental oxygen, baricitinib probably decreases the incidence of death and the need for invasive mechanical ventilation.

Evidence from randomised trials versus standard care demonstrates that baricitinib has an acceptable safety profile for non-pregnant adults and probably reduces the incidence of serious adverse events. Consideration should be given when administering baricitinib to patients already on other immunosuppressant or immunomodulatory drugs.

Information on use of baricitinib in pregnancy in humans is limited and insufficient (single case report) to assess the drug-associated risks for birth anomalies or pregnancy loss, though placental transfer is expected based on molecular weight *[482][483]*. However, teratogenic effects has been observed in animal studies when used in high doses *[484]*. It is also unknown whether baricitinib is excreted in human milk, though animal data have shown excretion of baricitinib in milk *[484]*.

Decisions about baricitinib administration in pregnancy need to be made with consideration of the potential maternal benefit and the theoretical fetal risks. Factors that may weigh into shared decision-making include severity of maternal status, underlying risk factors and gestational age. Placental transfer of baricitinib may be expected based on molecular weight.

**Certainty of the evidence**

Low

Certainty of the evidence is moderate for death and low for patients requiring invasive mechanical ventilation. Certainty is moderate for adverse and serious adverse events and low for all other outcomes (patients requiring non-invasive ventilation or high-flow oxygen, discontinuation due to adverse events, clinical recovery and time to recovery, and duration of hospitalisation).

**Values and preferences**

Substantial variability is expected or uncertain

We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women at this point. Since there is uncertainty regarding the benefit to harm ratio for women and their babies, the panel believes some women might prefer to wait while others might be more willing to opt for treatment.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. Depending on the treatment, not only should the cost and resource implications be considered but also the impact on potentially reducing access to these treatments by patients currently using them for other indications.

### Rationale

In non-pregnant adults hospitalised with COVID-19 who require supplemental oxygen, baricitinib probably reduces the risk of death.

Information on baricitinib in pregnancy in humans is insufficient to assess the drug-associated risks for birth anomalies or pregnancy loss, though teratogenic effects have been observed in animal studies when used in high doses. It is also unknown whether baricitinib is excreted in human milk, however animal data have shown excretion of baricitinib in milk.

### Clinical question/ PICO

**Population:** Special Populations with COVID-19
**Intervention:** Baricitinib
**Comparator:** Standard care

### Summary

Evidence indicates that baricitinib probably reduces the risk of death in hospitalised adults who require supplemental oxygen, and may reduce the need for invasive mechanical ventilation, non-invasive ventilation and/or high-flow oxygen.

**What is the evidence informing this recommendation?**
Evidence comes from two randomised trials—one that compared baricitinib plus remdesivir with remdesivir alone in 1033 adults hospitalised with suspected COVID-19 (ACTT-2) *[137]*, and one that compared baricitinib with standard care in 1525 adults with mild to severe COVID-19 (COV-BARRIER) *[133]*.

**Study characteristics**
In both studies, mean age of participants was 57 years and 38% were women. In the ACTT-2 trial, patients received either 4 mg baricitinib plus remdesivir (200 mg on day one, 100 mg a day until day 10 or hospital discharge) or remdesivir alone (same regimen as treatment arm). In the COV-BARRIER trial, patients also received 4 mg baricitinib. Pregnant and breastfeeding women were ineligible.

**What are the main results?**
Baricitinib probably decreases death (40 fewer per 1000; RR 0.63, CI 95% 0.48 to 0.81; 2558 patients in 2 studies) and serious adverse events (40 fewer per 1000; RR 0.79, CI 95% 0.67 to 0.94; 2518 patients in 2 studies).

Baricitinib may decrease the need for invasive mechanical ventilation, non-invasive ventilation and high-flow nasal oxygen therapy, and may increase clinical recovery. Baricitinib probably has little impact on incidence of adverse events. We are uncertain whether baricitinib increases or decreases discontinuation due to adverse events, duration of hospitalisation or time to recovery.

**Our confidence in the results**
Certainty of the evidence is moderate for mortality, adverse events and serious adverse events due to serious imprecision (wide confidence intervals). Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
According to the Therapeutic Goods Administration, known harms associated with baricitinib include an increased risk of serious infections, gastrointestinal disorders, thrombosis and headaches *[204]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Baricitinib | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 28 days of commencing treatment<br>9 Critical | Relative risk 0.63<br>(CI 95% 0.48 — 0.81)<br>Based on data from 2,558 participants in 2 studies. [1]<br>(Randomized controlled) | **107**<br>per 1000<br>Difference: | **67**<br>per 1000<br>**40 fewer per 1000**<br>( CI 95% 56 fewer — 20 fewer ) | **Low**<br>Due to serious imprecision and serious indirectness [2] | Baricitinib may decrease incidence of death. |
| **Invasive mechanical ventilation or ECMO**<br>End of follow-up<br>9 Critical | Relative risk 0.66<br>(CI 95% 0.46 — 0.93)<br>Based on data from 922 participants in 1 studies. [3]<br>(Randomized controlled) | **152**<br>per 1000<br>Difference: | **100**<br>per 1000<br>**52 fewer per 1000**<br>( CI 95% 82 fewer — 11 fewer ) | **Very low**<br>Due to very serious imprecision and serious indirectness [4] | We are uncertain whether baricitinib improves or worsens invasive mechanical ventilation or ECMO. |
| **Non-invasive ventilation or HFNO**<br>End of follow-up<br>6 Important | Relative risk 0.83<br>(CI 95% 0.63 — 1.1)<br>Based on data from 706 participants in 1 studies. [5]<br>(Randomized controlled) | **236**<br>per 1000<br>Difference: | **196**<br>per 1000<br>**40 fewer per 1000**<br>( CI 95% 87 fewer — 24 more ) | **Very low**<br>Due to very serious imprecision and serious indirectness [6] | We are uncertain whether baricitinib improves or worsens NIV / HFNO. |
| **Serious adverse events**<br>End of follow-up<br>6 Important | Relative risk 0.79<br>(CI 95% 0.67 — 0.94)<br>Based on data from 2,518 participants in 2 studies. [7]<br>(Randomized controlled) | **192**<br>per 1000<br>Difference: | **152**<br>per 1000<br>**40 fewer per 1000**<br>( CI 95% 63 fewer — 12 fewer ) | **Low**<br>Due to serious imprecision and serious indirectness [8] | Baricitinib may decrease serious adverse events slightly. |
| **Adverse events**<br>End of follow-up<br>6 Important | Relative risk 0.95<br>(CI 95% 0.87 — 1.04)<br>Based on data from 2,535 participants in 2 studies. [9]<br>(Randomized controlled) | **451**<br>per 1000<br>Difference: | **428**<br>per 1000<br>**23 fewer per 1000**<br>( CI 95% 59 fewer — 18 more ) | **Low**<br>Due to serious imprecision and serious indirectness [10] | Baricitinib may make little or no difference to adverse events. |
| **Discontinuation due to adverse events**<br>During treatment<br>6 Important | Relative risk 0.8<br>(CI 95% 0.57 — 1.12)<br>Based on data from 1,502 participants in 1 studies. [11]<br>(Randomized controlled) | **93**<br>per 1000<br>Difference: | **74**<br>per 1000<br>**19 fewer per 1000**<br>( CI 95% 40 fewer — 11 more ) | **Very low**<br>Due to very serious imprecision and serious indirectness [12] | We are uncertain whether baricitinib increases or decreases discontinuation due to adverse events. |
| **Clinical recovery**<br>End of follow-up | Relative risk 1.07<br>(CI 95% 1.01 — 1.14) | **784**<br>per 1000 | **839**<br>per 1000 | **Very low**<br>Due to very serious | We are uncertain whether baricitinib improves or |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Baricitinib | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| 6 Important | Based on data from 1,033 participants in 1 studies. [13] (Randomized controlled) | Difference: | **55 more per 1000** ( CI 95% 8 more — 110 more ) | imprecision and serious indirectness [14] | worsens clinical recovery. |
| **Duration of hospitalisation**<br>Mean (Days)<br>6 Important | Lower better (Randomized controlled) | **13.7**<br>(Mean)<br>Difference: | **12.9**<br>(Mean)<br>**MD 0.8 lower**<br>CI 95% | **Very low**<br>Due to very serious imprecision and serious indirectness [15] | We are uncertain whether baricitinib increases or decreases duration of hospitalisation. |
| **Time to recovery**<br>Median (Days)<br>6 Important | Lower better (Randomized controlled) | **11**<br>(Median) | **10**<br>(Median)<br>CI 95% | **Very low**<br>Due to very serious imprecision and serious indirectness [16] | We are uncertain whether baricitinib increases or decreases time to recovery. |

1, 7. Systematic review [134] with included studies: Marconi 2021, Kalil 2020.
2. **Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: serious.** due to only 2 studies.
3, 5, 13. Systematic review [138] with included studies: Kalil 2020.
4, 6, 14. **Inconsistency: no serious. Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: very serious.** Wide confidence intervals, Low number of patients, Only data from one study. **Publication bias: no serious.**
8. **Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: serious.** due to 2 studies.
9. Systematic review [134] with included studies: Kalil 2020, Marconi 2021.
10. **Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: serious.** Wide confidence intervals.
11. Systematic review [134] with included studies: Marconi 2021.
12, 15. **Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: very serious.** Wide confidence intervals, Only data from one study.
16. **Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: very serious.** Only data from one study, Wide confidence intervals.

### References

133. Marconi VC, Ramanan AV, de Bono S, Kartman CE, Krishnan V, Liao R, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respiratory Medicine 2021. Pubmed Journal

134. [Baricitinib] for [COVID-19].

136. Summary of Product Characteristics - Olumiant. Website

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204. Therapeutic Goods Administration. Australian Product Information - Olumiant (baricitinib). 23 April 2021. Website

205. Gerosa M, Argolini LM, Artusi C, Chighizola CB. The use of biologics and small molecules in pregnant patients with rheumatic diseases. Expert Review of Clinical Pharmacology 2018;11(10):987-998 Pubmed Journal

## 3.2 Molnupiravir (Lagevrio) for pregnant or breastfeeding women

Only in research settings

Do not use molnupiravir for the treatment of COVID-19 in pregnant or breastfeeding women outside of randomised trials with appropriate ethical approval.

***Additional information***

*Currently, there is no direct evidence for the use of molnupiravir (Lagevrio) in pregnant or breastfeeding women. Trials are needed in special populations, including pregnant or breastfeeding women. Until further evidence is available, do not use molnupiravir for the treatment of COVID-19 in pregnant or breastfeeding women unless they are eligible to be enrolled in trials.*

*There are no clinical data on the use of molnupiravir in pregnant or breastfeeding women. It is unknown whether molnupiravir is present in human or animal milk, and the effects on the breastfed newborn/infant, or the effects on milk production. A risk to the newborn/infant cannot be excluded.*

*There are no clinical data on the effects of molnupiravir against the SARS-CoV-2 Omicron variant.*

*Animal reproductive studies indicate that molnupiravir may have embryo-fetal development effects at high doses, which could include embryofetal lethality, teratogenicity, and reduced fetal growth. Animal studies have also shown potential deleterious effects on cartilage and bone growth and it is unclear if these effects are reversible. (TGA Product Information)*

*This is a high priority recommendation and will be updated as soon as new evidence becomes available.*

## 3.3 Nirmatrelvir plus ritonavir (Paxlovid) for pregnant or breastfeeding women

Only in research settings

Do not use nirmatrelvir plus ritonavir in pregnant or breastfeeding women outside of randomised trials with appropriate ethical approval.

***Additional information***

*Currently, there is no direct evidence for the use of nirmatrelvir plus ritonavir (Paxlovid) in pregnant or breastfeeding women. Trials are needed in special populations, including pregnant or breastfeeding women. Until further evidence is available, do not use nirmatrelvir plus ritonavir for the treatment of COVID-19 in pregnant or breastfeeding women unless they are eligible to be enrolled in trials.*

*There are no clinical data on the use of nirmatrelvir plus ritonavir in pregnant or breastfeeding women. It is unknown whether nirmatrelvir plus ritonavir is present in human or animal milk, and the effects on the breastfed newborn/infant, or the effects on milk production. A risk to the newborn/infant cannot be excluded.*

*There are no clinical data on the effects of nirmatrelvir plus ritonavir against the SARS-CoV-2 Omicron variant.*

*Use of ritonavir may reduce the efficacy of combined hormonal contraceptives.*

*Animal reproductive studies indicate that nirmatrelvir plus ritonavir may have embryo-fetal development effects at high doses, which could include early resorptions, decreased fetal body weight and ossification delays and developmental variations (TGA Product Information).*

*This is a high priority recommendation and will be updated as soon as new evidence becomes available.*

### Clinical question/ PICO

**Population:** OLD Patients with COVID-19
**Intervention:** Nirmatrelvir plus ritonavir
**Comparator:** Placebo

### Summary

Evidence indicates that nirmatrelvir plus ritonavir probably reduces the incidence of hospitalisation or death in adults with mild to moderate COVID-19 who have one or more risk factors for disease progression.

**What is the evidence informing this recommendation?**
Evidence comes from a single clinical study report that compared nirmatrelvir plus ritonavir (Paxlovid) with placebo in 1361 adult outpatients with mild-to-moderate COVID-19. Participants were randomised within 5 days of onset of symptoms and had one or more risk factors for disease progression.

**Study characteristics**
Mean age of participants was 45 years and 48% were women. Approximately half the patients were aged between 18 and 44 years (51%), 9% were aged 65–74 years, and 3% were aged over 70 years. Participants received three 100 mg tablets of nirmatrelvir and one 100 mg tablet of ritonavir twice daily for 5 days. Pregnant and breastfeeding women and children and adolescents were ineligible.

**What are the main results?**
Nirmatrelvir plus ritonavir probably reduces the incidence of hospitalisation or death (RR 0.15, CI 95% 0.06 to 0.34; 1219 patients in 1 study) and incidence of serious adverse events (RR 0.28, CI 95% 0.16 to 0.52; 1349 patients in 1 study). Nirmatrelvir plus ritonavir probably has little impact on incidence of adverse events or discontinuation due to adverse events. We are unsure if nirmatrelvir plus ritonavir impacts all-cause mortality.

**Our confidence in the results**
Certainty of the evidence is moderate for the composite outcomes of hospitalisation or death, hospitalisation, adverse or serious adverse events, and discontinuation due to adverse events (reliance on a single study). Certainty is low for all-cause mortality (reliance on a single study and few events).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
The Therapeutic Goods Administration provisionally approved the use of nirmatrelvir plus ritonavir (Paxlovid) for the treatment of COVID-19 on 18 January 2022.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Paxlovid | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Hospitalisation or death**<br>Day 28, ≤5 days symptom onset<br>9 Critical | Relative risk 0.15<br>(CI 95% 0.06 — 0.34)<br>Based on data from 1,219 participants in 1 studies. [1]<br>(Randomized controlled) | **67**<br>per 1000<br>Difference: | **10**<br>per 1000<br>**57 fewer per 1000**<br>( CI 95% 63 fewer — 44 fewer ) | **Moderate**<br>Due to serious imprecision [2] | Paxlovid probably decreases hospitalisation or death (47 events). |
| **All-cause mortality**<br>Day 28, ≤ 5 days symptom onset<br>9 Critical | Relative risk 0.05<br>(CI 95% 0 — 0.82)<br>Based on data from 1,219 participants in 1 studies. [3]<br>(Randomized controlled) | **16**<br>per 1000<br>Difference: | **1**<br>per 1000<br>**15 fewer per 1000**<br>( CI 95% 16 fewer — 3 fewer ) | **Low**<br>Due to very serious imprecision [4] | Paxlovid may decrease all-cause mortality slightly (10 events). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Paxlovid | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Hospitalisation**<br>Day 28, ≤ 5 days symptom onset<br><br>6 Important | Relative risk 0.15<br>(CI 95% 0.06 — 0.34)<br>Based on data from 1,219 participants in 1 studies. [5]<br>(Randomized controlled) | **67**<br>per 1000<br><br>Difference: | **10**<br>per 1000<br><br>**57 fewer per 1000**<br>( CI 95% 63 fewer — 44 fewer ) | **Moderate**<br>Due to serious imprecision [6] | Paxlovid probably decreases hospitalisation (47 events). |
| **Adverse events**<br>Within 28 days of commencing treatment<br><br>6 Important | Relative risk 0.89<br>(CI 95% 0.72 — 1.09)<br>Based on data from 1,349 participants in 1 studies. [7]<br>(Randomized controlled) | **223**<br>per 1000<br><br>Difference: | **198**<br>per 1000<br><br>**25 fewer per 1000**<br>( CI 95% 62 fewer — 20 more ) | **Moderate**<br>Due to serious imprecision [8] | Paxlovid probably has little impact on adverse events (284 events). |
| **Serious adverse events**<br>Within 28 days of commencing treatment<br><br>6 Important | Relative risk 0.28<br>(CI 95% 0.16 — 0.52)<br>Based on data from 1,349 participants in 1 studies. [9]<br>(Randomized controlled) | **68**<br>per 1000<br><br>Difference: | **19**<br>per 1000<br><br>**49 fewer per 1000**<br>( CI 95% 57 fewer — 33 fewer ) | **Moderate**<br>Due to serious imprecision [10] | Paxlovid probably decreases serious adverse events slightly (59 events). |
| **Discontinuation due to adverse events**<br>Within 28 days of commencing treatment<br><br>6 Important | Relative risk 0.56<br>(CI 95% 0.3 — 1.01)<br>Based on data from 1,361 participants in 1 studies. [11]<br>(Randomized controlled) | **42**<br>per 1000<br><br>Difference: | **24**<br>per 1000<br><br>**18 fewer per 1000**<br>( CI 95% 29 fewer — 0 fewer ) | **Moderate**<br>Due to serious imprecision [12] | Paxlovid probably has little impact on discontinuation due to adverse events (45 events). |

1, 3, 5, 7, 9, 11. Systematic review [144] with included studies: Paxlovid interim CSR 12-21.
2, 6, 8, 10, 12. **Imprecision: serious.** Only data from one study.
4. **Imprecision: very serious.** Only data from one study, due to few events.

### References

143. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, et al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. New England Journal of Medicine 2021. Pubmed Journal

144. Paxlovid for COVID-19.

## 3.4 Regdanvimab (Regkirona) for pregnant or breastfeeding women

Only in research settings

New

Do not use regdanvimab for the treatment of COVID-19 in pregnant or breastfeeding women outside randomised trials with appropriate ethical approval.

***Additional information***

*Currently there is no direct evidence evaluating the effectiveness of regdanvimab (Regkirona) in pregnant and breastfeeding women. Until further evidence is available, do not use regdanvimab for the treatment of COVID-19 in pregnant and breastfeeding women unless they are eligible to be enrolled in trials.*

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

### Clinical question/ PICO

**Population:** People with COVID-19 (not requiring oxygen)
**Intervention:** Regdanvimab
**Comparator:** Placebo

### Summary

Evidence indicates that regdanvimab probably reduces the requirement of supplemental oxygen and hospitalisation, and increases clinical recovery in adults with mild COVID-19 who have one or more risk factors for disease progression.

**What is the evidence informing this recommendation?**
Evidence comes from one clinical trial separated into two distinct parts; part 1 consisting of 335 individuals with confirmed COVID-19 *[440]* and part 2 consisting of 1315 individuals with COVID-19. Participants were randomised within 7 days onset of symptoms and the majority had one or more risk factors for disease progression.

**Study characteristics**
Mean age of participants was 48 years and 49% were women. Participants received a single 40 mg/kg intravenous infusion of regdanvimab over 60 minutes or placebo. Pregnant and breastfeeding women and children and adolescents were ineligible.

**What are the main results?**
Regdanvimab probably reduces the requirement of supplemental oxygen (RR 0.34, CI 95% 0.21 to 0.55; 1622 patients in 2 studies), incidence of hospitalisation (RR 0.35 CI 95% 0.22 to 0.56; 1622 patients in 2 studies) and increases clinical recovery (RR 1.14, CI 95% 1.06 to 1.22; 1532 patients in 2 studies). Regdanvimab probably has little impact on incidence of adverse events. We are unsure if regdanvimab impacts all-cause mortality, mechanical ventilation, ICU admission, serious adverse events or discontinuation due to adverse events.

**Our confidence in the results**
Certainty of the evidence is moderate for the requirement of supplemental oxygen, hospitalisation, clinical recovery and adverse events due to wide confidence intervals or reliance on a single study. Certainty is low for all remaining outcomes due to the above in addition to few events.

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
The Therapeutic Goods Administration provisionally approved the use of regdanvimab (Regkirona) for the treatment of COVID-19 on 6 December 2021. Further details of Part 2 of the study are available within the TGA's Australian Public Assessment Report (AusPAR).

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Regdanvimab | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 28 days of commencing treatment<br>9 Critical | Relative risk 0.5<br>(CI 95% 0.05 — 5.53)<br>Based on data from 1,622 participants in 2 studies. [1]<br>(Randomized controlled) | 3<br>per 1000<br>Difference: | 2<br>per 1000<br>**1 fewer per 1000**<br>( CI 95% 3 fewer — 14 more ) | **Low**<br>Due to very serious imprecision [2] | Regdanvimab may have little impact on all-cause mortality (3 events). |
| **Invasive mechanical ventilation**<br>Within 28 days of commencing treatment<br>9 Critical | Relative risk 0.43<br>(CI 95% 0.04 — 4.35)<br>Based on data from 1,622 participants in 2 studies. [3]<br>(Randomized controlled) | 4<br>per 1000<br>Difference: | 2<br>per 1000<br>**2 fewer per 1000**<br>( CI 95% 4 fewer — 13 more ) | **Low**<br>Due to very serious imprecision [4] | Regdanvimab may have little impact on invasive mechanical ventilation (4 events). |
| **Supplemental oxygen**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 0.34<br>(CI 95% 0.21 — 0.55)<br>Based on data from 1,622 participants in 2 studies. [5]<br>(Randomized controlled) | 76<br>per 1000<br>Difference: | 26<br>per 1000<br>**50 fewer per 1000**<br>( CI 95% 60 fewer — 34 fewer ) | **Moderate**<br>Due to serious imprecision [6] | Regdanvimab probably decreases requirement of supplemental oxygen (81 events). |
| **Serious adverse events**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 3.99<br>(CI 95% 0.45 — 35.58)<br>Based on data from 1,302 participants in 1 studies. [7]<br>(Randomized controlled) | 2<br>per 1000<br>Difference: | 8<br>per 1000<br>**6 more per 1000**<br>( CI 95% 1 fewer — 69 more ) | **Low**<br>Due to very serious imprecision [8] | Regdanvimab may have little impact on serious adverse events (5 events). |
| **Adverse events**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 0.96<br>(CI 95% 0.83 — 1.11)<br>Based on data from 1,627 participants in 2 studies. [9]<br>(Randomized controlled) | 311<br>per 1000<br>Difference: | 299<br>per 1000<br>**12 fewer per 1000**<br>( CI 95% 53 fewer — 34 more ) | **Moderate**<br>Due to serious imprecision [10] | Regdanvimab probably has little impact on adverse events (482 events). |
| **Discontinuation due to an adverse event**<br>Within 28 days of commencing treatment | Based on data from 1,311 participants in 1 studies. [11]<br>(Randomized controlled) | | | **Low**<br>Due to very serious imprecision [12] | No patients discontinued due to an adverse event. |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Regdanvimab | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| 6 Important | | | | | |
| **Hospitalisation**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 0.35<br>(CI 95% 0.22 — 0.56)<br>Based on data from 1,622 participants in 2 studies. [13]<br>(Randomized controlled) | **80**<br>per 1000<br>Difference: | **28**<br>per 1000<br>**52 fewer per 1000**<br>( CI 95% 62 fewer — 35 fewer ) | **Moderate**<br>Due to serious imprecision [14] | Regdanvimab probably decreases hospitalisation (86 events). |
| **ICU admission**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 0.09<br>(CI 95% 0.01 — 1.65)<br>Based on data from 1,622 participants in 2 studies. [15]<br>(Randomized controlled) | **7**<br>per 1000<br>Difference: | **1**<br>per 1000<br>**6 fewer per 1000**<br>( CI 95% 7 fewer — 5 more ) | **Low**<br>Due to very serious imprecision [16] | Regdanvimab may have little impact on ICU admission (5 events). |
| **Clinical recovery**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 1.14<br>(CI 95% 1.06 — 1.22)<br>Based on data from 1,532 participants in 2 studies. [17]<br>(Randomized controlled) | **712**<br>per 1000<br>Difference: | **812**<br>per 1000<br>**100 more per 1000**<br>( CI 95% 43 more — 157 more ) | **Moderate**<br>Due to serious imprecision [18] | Regdanvimab probably increases clinical recovery. |
| **Time to recovery**<br>Days<br>6 Important | Based on data from 1,302 participants in 1 studies. [19]<br>(Randomized controlled) | **13.29**<br>(Mean)<br>Difference: | **8.39**<br>(Mean)<br>**MD 4.9 lower**<br>CI 95% | **Low**<br>Due to very serious imprecision [20] | Regdanvimab may decrease time to recovery. |

1, 3, 9, 13, 17. Systematic review [199] with included studies: Eom 2021 - Part I CSR, Part II CSR.
2, 4, 16. **Imprecision: very serious.** Wide confidence intervals, due to few events.
5, 15. Systematic review [199] with included studies: Part II CSR, Eom 2021 - Part I CSR.
6, 14, 18. **Imprecision: serious.** Data derived from two studies from the same study group (phase I and II).
7, 11, 19. Systematic review [199] with included studies: Part II CSR.
8, 20. **Imprecision: very serious.** Wide confidence intervals, Only data from one study.
10. **Imprecision: serious.** Wide confidence intervals.
12. **Imprecision: very serious.** Only data from one study, due to no events.

### References

199. [Intervention] for [COVID-19].

## 3.5 Sarilumab for pregnant or breastfeeding women

Only in research settings

Do not use sarilumab for the treatment of COVID-19 in pregnant or breastfeeding women outside randomised trials with appropriate ethical approval.

***Additional information***

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

### Evidence to decision

**Benefits and harms**

Small net benefit, or little difference between alternatives

There is uncertainty around the benefits and harms of sarilumab for pregnant or breastfeeding women with COVID-19.

In non-pregnant adult patients hospitalised with critical COVID-19 who require supplemental oxygen, sarilumab probably decreases the incidence of death.

Evidence from randomised trials versus standard care in non-pregnant adults demonstrates that sarilumab does not increase the risk of serious adverse events, however it probably increases the risk of non-serious adverse events. According to the Therapeutic Goods Administration, common side effects and harms associated with sarilumab include upper respiratory tract infections, neutropaenia and injection site reactions *[307]*.

**Certainty of the evidence**

Low

Certainty of the evidence ismoderate for mortality, adverse and serious adverse events due to serious imprecision (wide confidence intervals). Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children & adolescents and pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Values and preferences**

Substantial variability is expected or uncertain

We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women at this point. Since there is uncertainty regarding the benefit-to-harm ratio for women and their babies, the panel believes some women might prefer to wait while others might be more willing to opt for treatment.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit.

### Rationale

There is no information on the use of sarilumab during pregnancy and breastfeeding in humans. Limited data are available from animal studies, where the possibility that sarilumab increases stillbirth or pregnancy loss rates cannot be ruled out. It is not known if sarilumab is present in breast milk.

In non-pregnant adult patients hospitalised with COVID-19 who require supplemental oxygen, sarilumab probably reduces the risk of death.

Because of this, the Taskforce has given a conditional recommendation for sarilumab in non-pregnant adult patients both within and outside the context of a randomised trial.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Sarilumab
**Comparator:** Standard care

### Summary

Evidence indicates that sarilumab probably reduces the risk of death in hospitalised adults who require high-flow oxygen, non-invasive ventilation and invasive mechanical ventilation.

**What is the evidence informing this recommendation?**
Evidence comes from seven randomised trials that compared sarilumab with standard care in 970 adults hospitalised with critical COVID-19 *[153][151]*, 2238 patients hospitalised with severe to critical COVID-19 *[146][149]* and 460 patients with moderate to critical COVID-19 *[154][155][206]*.

**Study characteristics**
Mean age of participants ranged from 58 to 63 years, and the proportion of women ranged from 19 to 36%. Pregnant and breastfeeding women were ineligible.

Consideration was given to separating data based on severity of illness (severe and critical subgroups); however it was considered inappropriate to do so due to limited data and a non-significant test for subgroup differences.

**What are the main results?**
Sarilumab probably decreases death slightly (28 fewer per 1000; RR 0.79, CI 95% 0.73 to 1.02; 3291 patients in 6 studies). Sarilumab probably has little impact on serious adverse events or discharge from hospital, but probably increases adverse events slightly (38 more per 1000; RR 1.07, CI 95% 0.98 to 1.18; 1946 patients in 3 studies). We are unsure whether sarilumab increases or decreases the requirement for ventilation, admission to ICU, clinical improvement or clinical recovery.

**Our confidence in the results**
Certainty of the evidence is moderate for death, serious adverse events and adverse events due to serious imprecision (wide confidence intervals). Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
According to the Australian Therapeutic Goods Administration, side effects associated with sarilumab include upper respiratory tract infections, neutropaenia, increased alanine aminotransferase (ALT) and injection site redness *[157]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Sarilumab | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 21-29 days of commencing treatment<br><br>9 Critical | Relative risk 0.89<br>(CI 95% 0.79 — 1.02)<br>Based on data from 3,291 participants in 7 studies. [1]<br>(Randomized controlled) | **259**<br>per 1000<br><br>Difference: | **231**<br>per 1000<br><br>**28 fewer per 1000**<br>( CI 95% 54 fewer — 5 more ) | **Moderate**<br>Due to serious imprecision [2] | Sarilumab probably decreases death slightly (775 events) |
| **Mechanical ventilation**<br>Within 28 days of | Relative risk 1.15<br>(CI 95% 0.38 — 3.51)<br>Based on data from 115 | **103**<br>per 1000 | **118**<br>per 1000 | **Very low**<br>Due to extremely serious imprecision | We are uncertain whether sarilumab increases or decreases need for mechanical ventilation (13 |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Sarilumab | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| treatment<br><br>9 Critical | participants in 1 studies. [3]<br>(Randomized controlled) | Difference: | **15 more per 1000**<br>( CI 95% 64 fewer — 259 more ) | [4] | events) |
| **Respiratory failure**<br>Within 28 days of treatment<br><br>9 Critical | Relative risk 1.03<br>(CI 95% 0.55 — 1.94)<br>Based on data from 201 participants in 1 studies. [5]<br>(Randomized controlled) | **157**<br>per 1000<br><br>Difference: | **162**<br>per 1000<br><br>**5 more per 1000**<br>( CI 95% 71 fewer — 148 more ) | **Low**<br>Due to very serious imprecision [6] | Sarilumab may have little or no difference on respiratory failure |
| **Requiring ventilation (HFNO, NIV, MV)**<br>End of follow-up<br><br>6 Important | Relative risk 0.93<br>(CI 95% 0.58 — 1.51)<br>Based on data from 531 participants in 2 studies. [7]<br>(Randomized controlled) | **195**<br>per 1000<br><br>Difference: | **181**<br>per 1000<br><br>**14 fewer per 1000**<br>( CI 95% 82 fewer — 99 more ) | **Low**<br>Due to serious inconsistency and serious imprecision [8] | Sarilumab may have little impact on number of patients requiring ventilation (98 events) |
| **Serious adverse events**<br>End of follow-up<br><br>6 Important | Relative risk 1.04<br>(CI 95% 0.91 — 1.18)<br>Based on data from 2,396 participants in 4 studies. [9]<br>(Randomized controlled) | **214**<br>per 1000<br><br>Difference: | **223**<br>per 1000<br><br>**9 more per 1000**<br>( CI 95% 19 fewer — 39 more ) | **Moderate**<br>Due to serious imprecision [10] | Sarilumab probably has little impact on serious adverse events. |
| **Adverse events**<br>End of follow-up<br><br>6 Important | Relative risk 1.07<br>(CI 95% 0.98 — 1.18)<br>Based on data from 1,946 participants in 3 studies. [11]<br>(Randomized controlled) | **549**<br>per 1000<br><br>Difference: | **587**<br>per 1000<br><br>**38 more per 1000**<br>( CI 95% 11 fewer — 99 more ) | **Moderate**<br>Due to serious imprecision [12] | Sarilumab probably increases adverse events slightly. |
| **Admission to ICU**<br>Within 28 days of treatment<br><br>6 Important | Relative risk 0.9<br>(CI 95% 0.5 — 1.63)<br>Based on data from 469 participants in 2 studies. [13]<br>(Randomized controlled) | **108**<br>per 1000<br><br>Difference: | **97**<br>per 1000<br><br>**11 fewer per 1000**<br>( CI 95% 54 fewer — 68 more ) | **Moderate**<br>Due to serious imprecision [14] | Sarilumab probably has little or no impact on admission to ICU (52 events) |
| **Clinical improvement**<br>Within 22 days of commencing treatment<br><br>6 Important | Relative risk 0.98<br>(CI 95% 0.87 — 1.1)<br>Based on data from 1,097 participants in 1 studies. [15]<br>(Randomized controlled) | **608**<br>per 1000<br><br>Difference: | **596**<br>per 1000<br><br>**12 fewer per 1000**<br>( CI 95% 79 fewer — 61 more ) | **Low**<br>Due to very serious imprecision [16] | Sarilumab may have little impact on clinical improvement. |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Sarilumab | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Clinical recovery**<br>Within 22 days of commencing treatment<br><br>6 Important | Relative risk 0.99<br>(CI 95% 0.89 — 1.1)<br>Based on data from 1,449 participants in 1 studies. [17]<br>(Randomized controlled) | **589**<br>per 1000<br><br>Difference: | **583**<br>per 1000<br><br>**6 fewer per 1000**<br>( CI 95% 65 fewer — 59 more ) | **Low**<br>Due to very serious imprecision [18] | Sarilumab may have little impact on clinical recovery. |
| **Discharged from hospital**<br>End of follow-up<br><br>6 Important | Relative risk 0.99<br>(CI 95% 0.95 — 1.05)<br>Based on data from 1,973 participants in 5 studies. [19]<br>(Randomized controlled) | **636**<br>per 1000<br><br>Difference: | **630**<br>per 1000<br><br>**6 fewer per 1000**<br>( CI 95% 32 fewer — 32 more ) | **Moderate**<br>Due to serious imprecision [20] | Sarilumab probably has little impact on discharge from hospital. |

1. Systematic review [207] with included studies: Sancho-Lopez 2021, CORIMUNDO 2022, Merchante et al. 2022, Lescure 2021, Sivapalasingam 2021, Hermine 2022, REMAP-CAP sarilumab FINAL.
2, 10, 12, 14, 20. **Imprecision: serious.** Wide confidence intervals.
3. Systematic review [207] with included studies: Merchante et al. 2022.
4. **Imprecision: extremely serious.** Wide confidence intervals, Low number of patients, Only data from one study, due to few events.
5. Systematic review [207] with included studies: Sancho-Lopez 2021.
6, 16, 18. **Imprecision: very serious.** Wide confidence intervals, Only data from one study.
7. Systematic review [207] with included studies: Merchante et al. 2022, Lescure 2021.
8. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies, Point estimates vary widely. **Imprecision: serious.** Wide confidence intervals.
9. Systematic review [207] with included studies: Lescure 2021, Sivapalasingam 2021, Hermine 2022, REMAP-CAP sarilumab.
11. Systematic review [207] with included studies: Lescure 2021, Sivapalasingam 2021, Hermine 2022.
13. Systematic review [207] with included studies: Sancho-Lopez 2021, Lescure 2021.
15, 17. Systematic review [152] with included studies: Sivapalasingam 2021.
19. Systematic review [207] with included studies: Merchante et al. 2022, Lescure 2021, Sancho-Lopez 2021, CORIMUNDO 2022, Sivapalasingam 2021.

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152. Sarilumab for COVID-19.

153. REMAP-CAP. Effectiveness of Tocilizumab, Sarilumab, and Anakinra for critically ill patients with COVID-19. medRxiv 25 June 2021. Journal Website

154. CORIMUNO-19 Collaborative Group. Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild to moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial. Lancet Respiratory Medicine 2020. Pubmed Journal Website

155. Merchante N, Cárcel S, Garrido-Gracia JC, Trigo-Rodríguez M, Moreno MÁE, León-López R, et al. Early use of sarilumab in patients hospitalized with COVID-19 pneumonia and features of systemic inflammation: the SARICOR randomized clinical trial. Antimicrobial Agents and Chemotherapy 2022;66(2):e0210721 Pubmed Journal

157. Therapeutic Goods Administration. Australian Product Information: Kevzara (Sarilumab) pre-filled pen and pre-filled syringe. 2018. Website

158. Australian Public Assessment Report for Sarilumab. Australian Government Department of Health - Therapeutic Goods Administration 2018. Website

206. Sancho-López A, Caballero-Bermejo AF, Ruiz-Antorán B, Múñez Rubio E, García Gasalla M, Buades J, et al. Efficacy and safety of sarilumab in patients with COVID19 pneumonia: a randomized, phase III clinical trial (SARTRE Study). Infectious Diseases and Therapy 2021;10(4):2735-2748 Pubmed Journal

207. Sarilumab for COVID-19.

## 3.6 Tixagevimab plus cilgavimab (Evusheld) for pregnant or breastfeeding women

Only in research settings

Do not use tixagevimab plus cilgavimab for the treatment of COVID-19 in pregnant or breastfeeding women outside of randomised trials with appropriate ethical approval.

***Additional information***

*Currently, there is no direct evidence for the use of tixagevimab plus cilgavimab (Evusheld) in pregnant or breastfeeding women. Trials are needed in special populations, including pregnant or breastfeeding women. Until further evidence is available, do not routinely use tixagevimab plus cilgavimab for the treatment of COVID-19 in pregnant or breastfeeding women unless they are eligible to be enrolled in trials.*

*This is a high priority recommendation and will be updated as soon as new evidence becomes available.*

# 4. Children and adolescents

Ronapreve, molnupiravir, Paxlovid (under 12 years), sarilumab, sotrovimab (under 12 years), Evusheld (under 12 years)

## 4.1 All children and adolescents

### 4.1.1 Casirivimab plus imdevimab (Ronapreve) for children and adolescents

Only in research settings

Do not use casirivimab plus imdevimab in children under 12 years of age without risk factors for deterioration who have **mild or asymptomatic COVID-19** outside of randomised trials with appropriate ethical approval.

***Additional information***

*Please note: Two consensus recommendations for the use of casirivimab plus imdevimab in children and adolescents are available in the primary Taskforce guideline (children who do not require oxygen; children who require oxygen)*

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

**Clinical question/ PICO**

**Population:** Children or adolescents outpatients with mild or asymptomatic COVID-19
**Intervention:** Casirivimab plus imdevimab
**Comparator:** Placebo

**Summary**

There remains significant uncertainty whether casirivimab plus imdevimab is more effective and safer than standard care in treating patients with mild or asymptomatic COVID-19.

**What is the evidence informing this recommendation?**
Evidence comes from three randomised trials that compared casirivimab plus imdevimab with placebo in 4856 adult outpatients with mild COVID-19 *[160][165]* and 207 asymptomatic outpatients *[163]*. Two trials are linked—one presents results from the phase I-II portion *[160]* and the second from the phase III portion of the study *[165]*. The third study included asymptomatic patients who had close contacts with confirmed COVID-19 individuals *[163]*.

**Publication status**
One study is only available as a preprint (Weinreich et al. posted to medRxiv on 12 June 2021 *[160]*) and has therefore not been peer reviewed.

**Study characteristics**
Median age of participants ranged from 41 to 50 years and the proportion of women ranged from 51 to 55%. Patients in the phase I and II portions of the study by Weinreich et al. received a dose of either 1200 mg or 2400 mg REGEN-COV (1:1 casirivimab:imdevimab), however the larger phase III portion randomised patients to receive either one 2400 mg or one 8000 mg dose. In O'Brien et al. patients received a single dose of 1200 mg. Pregnant and breastfeeding patients were ineligible.

**What are the main results?**
There were too few patients who died or required mechanical ventilation to determine whether casirivimab plus imdevimab makes a difference. Casirivimab plus imdevimab may decrease the incidence of adverse events and number of patients requiring hospitalisation slightly, and may have little impact on incidence of serious adverse events. We are uncertain if casirivimab plus imdevimab affects the incidence of ICU admission or discontinuation of treatment due to adverse events.

**Our confidence in the results**

Certainty of evidence is low for the critical outcomes of all-cause mortality and mechanical ventilation due to serious risk of bias (significant loss to follow-up) and serious imprecision (few events). Certainty is low for all other outcomes due to serious risk of bias, serious imprecision and serious publication bias (commercial funding), with the exception of discontinuation due to adverse events, which is very low certainty (due to very serious imprecision and serious publication bias).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
As of 25 June 2021, REGN-COV2 (casirivimab plus imdevimab) is not listed in the Australian Register of Therapeutic Goods and is not approved for use in Australia.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>REGEN-COV | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 28 days of commencing treatment<br>9 Critical | Relative risk 3.07<br>(CI 95% 0.87 — 10.85)<br>Based on data from 5,347 participants in 2 studies. [1]<br>(Randomized controlled) | 1<br>per 1000<br>Difference: | 3<br>per 1000<br>**2 more per 1000**<br>( CI 95% 0 fewer — 10 more ) | **Very low**<br>Due to serious risk of bias and serious imprecision, Due to serious indirectness [2] | Casirivimab plus imdevimab may have little impact on death (10 events). |
| **Mechanical ventilation**<br>Within 28 days of commencing treatment<br>9 Critical | Relative risk 0.21<br>(CI 95% 0.04 — 1.06)<br>Based on data from 3,432 participants in 1 studies. [3]<br>(Randomized controlled) | 4<br>per 1000<br>Difference: | 1<br>per 1000<br>**3 fewer per 1000**<br>( CI 95% 4 fewer — 0 fewer ) | **Very low**<br>Due to serious risk of bias and serious imprecision, Due to very serious indirectness [4] | Casirivimab plus imdevimab may have little impact on mechanical ventilation (8 events). |
| **ICU admission**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 0.32<br>(CI 95% 0.14 — 0.71)<br>Based on data from 3,432 participants in 1 studies. [5]<br>(Randomized controlled) | 13<br>per 1000<br>Difference: | 4<br>per 1000<br>**9 fewer per 1000**<br>( CI 95% 11 fewer — 4 fewer ) | **Very low**<br>Due to serious risk of bias and serious imprecision, Due to serious indirectness [6] | Casirivimab plus imdevimab may have little impact on ICU admission (27 events). |
| **Adverse events**<br>End of follow-up<br>6 Important | Relative risk 0.74<br>(CI 95% 0.64 — 0.86)<br>Based on data from 5,842 participants in 2 studies. [7]<br>(Randomized controlled) | 132<br>per 1000<br>Difference: | 98<br>per 1000<br>**34 fewer per 1000**<br>( CI 95% 48 fewer — 18 fewer ) | **Very low**<br>Due to serious risk of bias and serious publication bias, Due to serious indirectness [8] | We are uncertain whether regen-cov improves or worsen adverse events |
| **Serious adverse event**<br>End of follow-up | Relative risk 0.34<br>(CI 95% 0.25 — 0.48)<br>Based on data from 6,622 participants in 3 studies. [9]<br>(Randomized controlled) | 37<br>per 1000<br>Difference: | 13<br>per 1000<br>**24 fewer per 1000** | **Very low**<br>Due to serious risk of bias and serious publication bias, Due to serious | Casirivimab plus imdevimab may have little impact on serious adverse events (140 events). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>REGEN-COV | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| 6 Important | | | ( CI 95% 28 fewer — 19 fewer ) | indirectness [10] | |
| **Discontinuation due to adverse event**<br>During treatment<br>6 Important | Based on data from 780 participants in 1 studies. [11]<br>(Randomized controlled) | | | **Very low**<br>Due to very serious imprecision and serious publication bias [12] | We are uncertain whether casirivimab plus imdevimab increases or decreases discontinuation due to adverse events (1 event). |
| **Hospitalisation**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 0.3<br>(CI 95% 0.2 — 0.45)<br>Based on data from 4,057 participants in 1 studies. [13]<br>(Randomized controlled) | **44**<br>per 1000<br>Difference: | **13**<br>per 1000<br>**31 fewer per 1000**<br>( CI 95% 35 fewer — 24 fewer ) | **Very low**<br>Due to serious risk of bias and serious imprecision, Due to serious indirectness [14] | We are uncertain whether regen-cov improves or worsen hospitalisation |

1. Systematic review [161] with included studies: Weinreich 2021 p III, Weinreich 2021 p I-II.
2. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias. **Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: serious.** Only data from one study, due to few events.
3, 5, 13. Systematic review [161] with included studies: Weinreich 2021 p III.
4. **Risk of Bias: serious.** Incomplete data and/or large loss to follow up, Inadequate concealment of allocation during randomization process, resulting in potential for selection bias. **Indirectness: very serious.** Differences between the population of interest and those studied. **Imprecision: serious.** Only data from one study, due to few events.
6, 14. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Incomplete data and/or large loss to follow up. **Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: serious.** Only data from one study.
7. Systematic review [161] with included studies: Weinreich 2021 p III, O'Brien 2021.
8, 10. **Risk of Bias: serious.** Inadequate concealment of allocation during randomization process, resulting in potential for selection bias, Incomplete data and/or large loss to follow up. **Indirectness: serious.** Differences between the population of interest and those studied. **Publication bias: serious.** Mostly commercially funded studies.
9. Systematic review [161] with included studies: O'Brien 2021, Weinreich 2021 p III, Weinreich 2021 p I-II.
11. Systematic review [161] with included studies: Weinreich 2021 p I-II.
12. **Imprecision: very serious.** due to few events, Only data from one study, Wide confidence intervals. **Publication bias: serious.** Mostly commercially funded studies.

### References

160. Weinreich D, Sivapalasingam S, Norton T. REGEN-COV antibody cocktail in outpatients with COVID-19. medRxiv 2021. Journal Website

161. [REGN-COV2] for [COVID-19].

163. O'Brien MP, Forleo-Neto E, Sarkar N, Isa F, Hou P, Chan K-C, et al. Effect of subcutaneous casirivimab and imdevimab antibody combination vs placebo on development of symptomatic COVID-19 in early asymptomatic SARS-CoV-2 infection: A randomized clinical trial. JAMA 2022. Pubmed Journal

165. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGEN-COV antibody combination and outcomes in outpatients with Covid-19. New England Journal of Medicine 2021. Pubmed Journal

208. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. New England Journal of Medicine 2021;384(3):238-251 Pubmed Journal

## 4.1.2 Molnupiravir (Lagevrio) for children and adolescents

Only in research settings

Do not use molnupiravir for the treatment of COVID-19 in children and adolescents outside of randomised trials with appropriate ethical approval.

***Additional information***

*Currently, there is no direct evidence for the use of molnupiravir (Lagevrio) in children and adolescents. Trials are needed in special populations, including children and adolescents. Until further evidence is available, do not routinely use molnupiravir for the treatment of COVID-19 in children and adolescents unless they are eligible to be enrolled in trials.*

*Animal studies have shown potential deleterious effects on cartilage and bone growth, and it is unclear if these effects are reversible.*

*Currently molnupiravir is not approved for use in people under 18 years of age.*

*This is a high priority recommendation and will be updated as soon as new evidence becomes available.*

### Evidence to decision

**Benefits and harms**

Small net benefit, or little difference between alternatives

Molnupiravir may decrease the incidence of hospitalisation or death, and probably has little impact on the incidence of adverse or serious adverse events. We are unsure if molnupiravir has an impact on mortality, discontinuation due to adverse events, and the composite outcome of hospitalisation or death within subgroups based on SARS-CoV-2 variant.

Studies in animal models suggest potential embryolethal and teratogenic effects and deleterious effects on cartilage and bone growth at very high doses.

**Certainty of the evidence**

Low

Certainty of the evidence is low for the composite outcome of hospitalisation or death, adverse events and serious adverse events (due to reliance on a single study) and very low for all-cause mortality and discontinuation due to adverse events (due to reliance on a single study and few events). Certainty is low or very low for all subgroup analyses focused on SARS-CoV-2 variant.

**Values and preferences**

Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values.

**Pregnant or breastfeeding patients**
We have no systematically collected information regarding the preferences and values of pregnant or breastfeeding women at this point. Although there is uncertainty regarding the benefit to harm ratio for women and their babies, evidence demonstrates embryolethality and reduced fetal growth in rats when administered at seven and three times the therapeutic dose. As such, the panel believes most women would not opt for treatment.

**Children and adolescents**
We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for treatment.

**Resources and other considerations**

Important issues, or potential issues not investigated

The limited availability of molnupiravir, as well as the cost of treatment, are limiting factors preventing widespread use of this treatment.

### Rationale

**General adult population**

In adult outpatients with mild COVID-19, molnupiravir probably reduces the risk of hospitalisation or death slightly. Because of this, the Taskforce gives a consensus recommendation for molnupiravir both within and outside a randomised trial, only where other treatments (such as sotrovimab or nirmatrelvir plus ritonavir) are not suitable or available.

### Clinical question/ PICO

**Population:** Special populations with COVID-19
**Intervention:** Molnupiravir
**Comparator:** Placebo

### Summary

Evidence indicates that molnupiravir probably reduces the incidence of hospitalisation or death in adults with mild-to-moderate COVID-19 who have one or more risk factors for disease progression.

**What is the evidence informing this recommendation?**

Evidence comes from a single clinical study report (MOVe-OUT) that compared molnupiravir with placebo in 1433 adult outpatients with mild to moderate COVID-19 *[209]*. Participants were randomised within 5 days of onset of symptoms and had one or more risk factors for disease progression.

**Study characteristics**

Median age of participants was 43 years and 51% were women. Two-thirds of participants were aged 18 to 49 years. Participants received four 200 mg tablets of molnupiravir or placebo twice daily for five days. Pregnant & breastfeeding women and children & adolescents were ineligible.

**What are the main results?**

Molnupiravir probably reduces the incidence of hospitalisation or death slightly (RR 0.70, CI 95% 0.49 to 0.99; 1408 patients in 1 study). Molnupiravir probably has little impact on incidence of adverse or serious adverse events, and may have little impact on discontinuation due to adverse events. We are unsure if molnupiravir has an impact on mortality.

**Our confidence in the results**

Certainty of the evidence is moderate for the composite outcome of hospitalisation or death, adverse events and serious adverse events (due to reliance on a single study) and low for all-cause mortality and discontinuation due to adverse events (due to reliance on a single study and few events). Certainty is low or very low for all subgroup analyses focused on SARS-CoV-2 variant.

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**

The Therapeutic Goods Administration provisionally approved the use of molnupiravir (Lagevrio) for the treatment of COVID-19 on 18 January 2022.

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Placebo | **Intervention** Molnupiravir | **Certainty of the evidence** (Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality** Within 29 days of commencing | Relative risk 0.11 (CI 95% 0.01 — 0.86) Based on data from 1,408 participants in 1 studies. [1] | **13** per 1000 | **1** per 1000 | **Very low** Due to very serious imprecision, Due to serious | Molnupiravir may have little impact on death (10 events). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Molnupiravir | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| treatment<br><br>9 Critical | (Randomized controlled) | Difference: | **12 fewer per 1000**<br>( CI 95% 13 fewer — 2 fewer ) | indirectness [2] | |
| **All-cause mortality or hospitalisation [FINAL - INTERIM]**<br>Within 29 days of commencing treatment<br><br>9 Critical | Relative risk 1.33<br>(CI 95% 0.69 — 2.54)<br>Based on data from 646 participants in 1 studies. [3] | **47**<br>per 1000<br><br>Difference: | **63**<br>per 1000<br><br>**16 more per 1000**<br>( CI 95% 15 fewer — 72 more ) | | |
| **All-cause mortality or hospitalisation [FINAL]**<br>Within 29 days of commencing treatment<br><br>9 Critical | Relative risk 0.7<br>(CI 95% 0.49 — 0.99)<br>Based on data from 1,408 participants in 1 studies. [4]<br>(Randomized controlled) | **97**<br>per 1000<br><br>Difference: | **68**<br>per 1000<br><br>**29 fewer per 1000**<br>( CI 95% 49 fewer — 1 fewer ) | **Low**<br>Due to serious imprecision, Due to serious indirectness [5] | Molnupiravir may reduce all-cause mortality or hospitalisation slightly [final] (116 events). |
| **All-cause mortality or hospitalisation [INTERIM]**<br>Within 29 days of commencing treatment<br><br>9 Critical | Relative risk 0.52<br>(CI 95% 0.33 — 0.8)<br>Based on data from 762 participants in 1 studies. [6]<br>(Randomized controlled) | **141**<br>per 1000<br><br>Difference: | **73**<br>per 1000<br><br>**68 fewer per 1000**<br>( CI 95% 94 fewer — 28 fewer ) | **Low**<br>Due to serious imprecision, Due to serious indirectness [7] | Molnupiravir may reduce all-cause mortality of hospitalisation [interim] (81 events) |
| **Mortality or hospitalisation [DELTA]**<br>Within 29 days of commencing treatment<br><br>9 Critical | Relative risk 0.76<br>(CI 95% 0.42 — 1.38)<br>Based on data from 458 participants in 1 studies. [8]<br>(Randomized controlled) | **100**<br>per 1000<br><br>Difference: | **76**<br>per 1000<br><br>**24 fewer per 1000**<br>( CI 95% 58 fewer — 38 more ) | **Very low**<br>Due to very serious imprecision, Due to serious indirectness [9] | Molnupiravir may have little impact on mortality or hospitalisation [Delta variant] (40 events). |
| **Mortality or hospitalisation [GAMMA]**<br>Within 29 days of | Relative risk 0.07<br>(CI 95% 0 — 1.11)<br>Based on data from 84 participants in 1 studies. [10]<br>(Randomized controlled) | **191**<br>per 1000<br><br>Difference: | **13**<br>per 1000<br><br>**178 fewer per** | **Very low**<br>Due to extremely serious imprecision, Due to serious | We are uncertain whether molnupiravir increases or decreases mortality or hospitalisation [Gamma variant] (9 events). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Molnupiravir | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| commencing treatment<br><br>9 Critical | | | **1000**<br>( CI 95% 191 fewer — 21 more ) | indirectness [11] | |
| **Mortality or hospitalisation [MU]**<br>Within 29 days of commencing treatment<br><br>9 Critical | Relative risk 0.5<br>(CI 95% 0.2 — 1.26)<br>Based on data from 157 participants in 1 studies. [12]<br>(Randomized controlled) | **159**<br>per 1000<br><br>Difference: | **80**<br>per 1000<br><br>**80 fewer per 1000**<br>( CI 95% 127 fewer — 41 more ) | **Very low**<br>Due to extremely serious imprecision, Due to serious indirectness [13] | We are uncertain whether molnupiravir increases or decreases mortality or hospitalisation [Mu variant] (19 events). |
| **Mortality or hospitalisation [OTHER]**<br>Within 29 days of commencing treatment<br><br>9 Critical | Relative risk 0.58<br>(CI 95% 0.2 — 1.68)<br>Based on data from 85 participants in 1 studies. [14]<br>(Randomized controlled) | **184**<br>per 1000<br><br>Difference: | **107**<br>per 1000<br><br>**77 fewer per 1000**<br>( CI 95% 147 fewer — 125 more ) | **Very low**<br>Due to extremely serious imprecision, Due to serious indirectness [15] | We are uncertain whether molnupiravir increases or decreases mortality or hospitalisation [other variants] (12 events). |
| **Mortality or hospitalisation [UNKNOWN]**<br>Within 29 days of commencing treatment<br><br>9 Critical | Relative risk 1.18<br>(CI 95% 0.62 — 2.25)<br>Based on data from 624 participants in 1 studies. [16]<br>(Randomized controlled) | **51**<br>per 1000<br><br>Difference: | **60**<br>per 1000<br><br>**9 more per 1000**<br>( CI 95% 19 fewer — 64 more ) | **Very low**<br>Due to very serious imprecision, Due to serious indirectness [17] | Molnupiravir may have little impact on mortality or hospitalisation [unknown variant] (35 events). |
| **Adverse events**<br>Within 29 days of commencing treatment<br><br>6 Important | Relative risk 0.92<br>(CI 95% 0.79 — 1.08)<br>Based on data from 1,411 participants in 1 studies. [18]<br>(Randomized controlled) | **330**<br>per 1000<br><br>Difference: | **304**<br>per 1000<br><br>**26 fewer per 1000**<br>( CI 95% 69 fewer — 26 more ) | **Low**<br>Due to serious imprecision, Due to serious indirectness [19] | Molnupiravir may have little impact on adverse events (447 events). |
| **Serious adverse events**<br>Within 29 days of commencing treatment<br><br>6 Important | Relative risk 0.72<br>(CI 95% 0.51 — 1.03)<br>Based on data from 1,411 participants in 1 studies. [20]<br>(Randomized controlled) | **96**<br>per 1000<br><br>Difference: | **69**<br>per 1000<br><br>**27 fewer per 1000**<br>( CI 95% 47 fewer — 3 more ) | **Low**<br>Due to serious imprecision, Due to serious indirectness [21] | Molnupiravir may have little impact on serious adverse events (116 events). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Molnupiravir | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Discontinuation due to AEs**<br>Within 29 days of commencing treatment<br><br>6 Important | Relative risk 0.49<br>(CI 95% 0.23 — 1.05)<br>Based on data from 1,411 participants in 1 studies. [22]<br>(Randomized controlled) | **29**<br>per 1000<br><br>Difference: | **14**<br>per 1000<br><br>**15 fewer per 1000**<br>( CI 95% 22 fewer — 1 more ) | **Very low**<br>Due to very serious imprecision, Due to serious indirectness [23] | We are uncertain whether molnupiravir increases or decreases discontinuation due to adverse events (30 events). |

1. Systematic review [212] with included studies: Bernal 2021.
2. **Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: very serious.** Only data from one study, due to few events.
3, 4. Systematic review [167] with included studies: Bernal 2021.
5, 7, 19, 21. **Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: serious.** Only data from one study.
6. Systematic review [171] with included studies: Bernal 2021.
8, 10, 12, 14, 18, 20, 22. Systematic review [210] with included studies: Bernal 2021.
9. **Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: very serious.** Only data from one study, Low number of patients.
11. **Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: extremely serious.** Only data from one study, Low number of patients, Wide confidence intervals, due to few events.
13. **Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: extremely serious.** Only data from one study, Low number of patients, due to few events, Wide confidence intervals.
15. **Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: extremely serious.** Only data from one study, due to few events, Wide confidence intervals, Low number of patients.
16. Systematic review [169] with included studies: Bernal 2021.
17. **Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: very serious.** Only data from one study, Wide confidence intervals.
23. **Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: very serious.** due to few events, Only data from one study.

### References

166. Weinreich D, Sivapalasingam S, Norton T. REGEN-COV antibody cocktail in outpatients with COVID-19. medRxiv 2021. Journal Website

167. Molnupiravir for COVID-19.

169. Molnupiravir for COVID-19.

171. Molnupiravir for COVID-19.

209. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, et al. Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. New England Journal of Medicine 2021. Pubmed Journal

210. Molnupiravir for COVID-19.

211. Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGEN-COV antibody combination and outcomes in outpatients with Covid-19. New England Journal of Medicine 2021. Pubmed Journal

212. Molnupiravir for COVID-19.

## 4.1.3 Regdanvimab (Regkirona) for children and adolescents

Only in research settings

New

Do not use regdanvimab for the treatment of COVID-19 in children and adolescents outside of randomised trials with appropriate ethical approval.

***Additional information***

*Currently, there is no direct evidence evaluating the effectiveness of regdanvimab (Regkirona) in children and adolescents. Until further evidence is available, do not use regdanvimab for the treatment of COVID-19 in children and adolescents unless they are eligible to be enrolled in trials.*

*Currently regdanvimab is not approved for use in people under 18 years of age.*

*This is a high priority recommendation and will be updated as soon as new evidence becomes available.*

### Evidence to decision

**Benefits and harms**

Substantial net benefits of the recommended alternative

Regdanvimab probably reduces the requirement of supplemental oxygen (RR 0.34, CI 95% 0.21 to 0.55; 1622 patients in 2 studies), incidence of hospitalisation (RR 0.35 CI 95% 0.22 to 0.56; 1622 patients in 2 studies) and increases clinical recovery (RR 1.14, CI 95% 1.06 to 1.22; 1532 patients in 2 studies).

Regdanvimab probably has little impact on incidence of adverse events. We are unsure if regdanvimab impacts all-cause mortality, mechanical ventilation, ICU admission, serious adverse events or discontinuation due to adverse events.

**Certainty of the evidence**

Moderate

Certainty of the evidence is moderate for the requirement of supplemental oxygen, hospitalisation, clinical recovery and adverse events due to wide confidence intervals or reliance on a single study. Certainty is low for all remaining outcomes due to the above in addition to few events.

**Values and preferences**

Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values.

**Resources**

Important negative issues

The unavailability of regdanvimab within Australia is a limiting factor preventing widespread use of this treatment.

**Equity**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding impact on equity.

**Acceptability**

Important issues, or potential issues not investigated

Although we have no systematically collected evidence regarding acceptability, treatment is probably acceptable to both patients and clinicians.

**Feasibility**

Intervention is likely difficult to implement

Regdanvimab was approved for the treatment of people with COVID-19 who do not require oxygen on 6 December 2021; however at this time, regdanvimab is not available within Australia.

## Clinical question/ PICO

**Population:** People with COVID-19 (not requiring oxygen)
**Intervention:** Regdanvimab
**Comparator:** Placebo

## Summary

Evidence indicates that regdanvimab probably reduces the requirement of supplemental oxygen and hospitalisation, and increases clinical recovery in adults with mild COVID-19 who have one or more risk factors for disease progression.

**What is the evidence informing this recommendation?**
Evidence comes from one clinical trial separated into two distinct parts; part 1 consisting of 335 individuals with confirmed COVID-19 *[221]* and part 2 consisting of 1315 individuals with COVID-19. Participants were randomised within 7 days onset of symptoms and the majority had one or more risk factors for disease progression.

**Study characteristics**
Mean age of participants was 48 years and 49% were women. Participants received a single 40 mg/kg intravenous infusion of regdanvimab over 60 minutes or placebo. Pregnant and breastfeeding women and children and adolescents were ineligible.

**What are the main results?**
Regdanvimab probably reduces the requirement of supplemental oxygen (RR 0.34, CI 95% 0.21 to 0.55; 1622 patients in 2 studies), incidence of hospitalisation (RR 0.35 CI 95% 0.22 to 0.56; 1622 patients in 2 studies) and increases clinical recovery (RR 1.14, CI 95% 1.06 to 1.22; 1532 patients in 2 studies). Regdanvimab probably has little impact on incidence of adverse events. We are unsure if regdanvimab impacts all-cause mortality, mechanical ventilation, ICU admission, serious adverse events or discontinuation due to adverse events.

**Our confidence in the results**
Certainty of the evidence is moderate for the requirement of supplemental oxygen, hospitalisation, clinical recovery and adverse events due to wide confidence intervals or reliance on a single study. Certainty is low for all remaining outcomes due to the above in addition to few events.

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
The Therapeutic Goods Administration provisionally approved the use of regdanvimab (Regkirona) for the treatment of COVID-19 on 6 December 2021. Further details of Part 2 of the study are available within the TGA's Australian Public Assessment Report (AusPAR).

| **Outcome** Timeframe | **Study results and measurements** | **Comparator** Placebo | **Intervention** Regdanvimab | **Certainty of the evidence** (Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality** Within 28 days of commencing treatment | Relative risk 0.5 (CI 95% 0.05 — 5.53) Based on data from 1,622 participants in 2 studies. [1] (Randomized controlled) | 3 per 1000 Difference: | 2 per 1000 **1 fewer per 1000** ( CI 95% 3 fewer — 14 more ) | **Low** Due to very serious imprecision [2] | Regdanvimab may have little impact all-cause mortality (3 events). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Regdanvimab | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| 9 Critical | | | | | |
| **Invasive mechanical ventilation**<br>Within 28 days of commencing treatment<br>9 Critical | Relative risk 0.43<br>(CI 95% 0.04 — 4.35)<br>Based on data from 1,622 participants in 2 studies. [3]<br>(Randomized controlled) | **4**<br>per 1000<br>Difference: | **2**<br>per 1000<br>**2 fewer per 1000**<br>( CI 95% 4 fewer — 13 more ) | **Low**<br>Due to very serious imprecision [4] | Regdanvimab may have little impact on invasive mechanical ventilation (4 events). |
| **Supplemental oxygen**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 0.34<br>(CI 95% 0.21 — 0.55)<br>Based on data from 1,622 participants in 2 studies. [5]<br>(Randomized controlled) | **76**<br>per 1000<br>Difference: | **26**<br>per 1000<br>**50 fewer per 1000**<br>( CI 95% 60 fewer — 34 fewer ) | **Moderate**<br>Due to serious imprecision [6] | Regdanvimab probably decreases requirement of supplemental oxygen (81 events). |
| **Serious adverse events**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 3.99<br>(CI 95% 0.45 — 35.58)<br>Based on data from 1,302 participants in 1 studies. [7]<br>(Randomized controlled) | **2**<br>per 1000<br>Difference: | **8**<br>per 1000<br>**6 more per 1000**<br>( CI 95% 1 fewer — 69 more ) | **Low**<br>Due to very serious imprecision [8] | Regdanvimab may have little impact on serious adverse events (5 events). |
| **Adverse events**<br>Within 28 days of commencing treatment<br>6 Important | Relative risk 0.96<br>(CI 95% 0.83 — 1.11)<br>Based on data from 1,627 participants in 2 studies. [9]<br>(Randomized controlled) | **311**<br>per 1000<br>Difference: | **299**<br>per 1000<br>**12 fewer per 1000**<br>( CI 95% 53 fewer — 34 more ) | **Moderate**<br>Due to serious imprecision [10] | Regdanvimab probably has little impact on adverse events (482 events). |
| **Discontinuation due to an adverse event**<br>Within 28 days of commencing treatment<br>6 Important | Based on data from 1,311 participants in 1 studies. [11]<br>(Randomized controlled) | | | **Low**<br>Due to very serious imprecision [12] | No patients discontinued due to an adverse event. |
| **Hospitalisation**<br>Within 28 days of commencing | Relative risk 0.35<br>(CI 95% 0.22 — 0.56)<br>Based on data from 1,622 | **80**<br>per 1000 | **28**<br>per 1000 | **Moderate**<br>Due to serious imprecision [14] | Regdanvimab probably decreases hospitalisation (86 events). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Regdanvimab | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| treatment<br><br>6 Important | participants in 2 studies. [13]<br>(Randomized controlled) | Difference: | **52 fewer per 1000**<br>( CI 95% 62 fewer — 35 fewer ) | | |
| **ICU admission**<br>Within 28 days of commencing treatment<br><br>6 Important | Relative risk 0.09<br>(CI 95% 0.01 — 1.65)<br>Based on data from 1,622 participants in 2 studies. [15]<br>(Randomized controlled) | **7**<br>per 1000<br><br>Difference: | **1**<br>per 1000<br><br>**6 fewer per 1000**<br>( CI 95% 7 fewer — 5 more ) | **Low**<br>Due to very serious imprecision [16] | Regdanvimab may have little impact on ICU admission (5 events). |
| **Clinical recovery**<br>Within 28 days of commencing treatment<br><br>6 Important | Relative risk 1.14<br>(CI 95% 1.06 — 1.22)<br>Based on data from 1,532 participants in 2 studies. [17]<br>(Randomized controlled) | **712**<br>per 1000<br><br>Difference: | **812**<br>per 1000<br><br>**100 more per 1000**<br>( CI 95% 43 more — 157 more ) | **Moderate**<br>Due to serious imprecision [18] | Regdanvimab probably increases clinical recovery. |
| **Time to recovery**<br>Days<br><br>6 Important | Based on data from 1,302 participants in 1 studies. [19]<br>(Randomized controlled) | **13.29**<br>(Mean)<br><br>Difference: | **8.39**<br>(Mean)<br><br>**MD 4.9 lower**<br>CI 95% | **Low**<br>Due to very serious imprecision [20] | Regdanvimab may decrease time to recovery. |

1. Systematic review [199] with included studies: Part II CSR, Eom 2021 - Part I CSR.
2, 4, 16. **Imprecision: very serious.** Wide confidence intervals, due to few events.
3, 5, 9, 13, 15, 17. Systematic review [199] with included studies: Eom 2021 - Part I CSR, Part II CSR.
6, 14, 18. **Imprecision: serious.** Data derived from two studies from the same study group (phase I and II).
7, 11, 19. Systematic review [199] with included studies: Part II CSR.
8, 20. **Imprecision: very serious.** Wide confidence intervals, Only data from one study.
10. **Imprecision: serious.** Wide confidence intervals.
12. **Imprecision: very serious.** Only data from one study, due to no events.

### References

199. [Intervention] for [COVID-19].

221. Streinu-Cercel A, Săndulescu O, Preotescu L-L, Kim JY, Kim Y-S, Cheon S, et al. Efficacy and safety of regdanvimab (CT-P59): a phase 2/3 randomized, double-blind, placebo-controlled trial in outpatients with mild-to-moderate Coronavirus disease 2019. Open Forum Infectious Diseases 2022;9(4):ofac053 Pubmed Journal

222. Eom J, Ison M, Streinu-Cercel A. Efficacy and safety of CT-P59 plus standard of care: a phase 2/3 randomized, double-blind, placebo-controlled trial in outpatients with mild-to-moderate SARS-CoV-2 infection. Research Square 15 March 2021. Journal Website

## 4.1.4 Sarilumab for children and adolescents

Only in research settings

Do not use sarilumab for the treatment of COVID-19 in children and adolescents outside randomised trials with appropriate ethical approval.

***Additional information***

*This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.*

### Evidence to decision

**Benefits and harms**

Small net benefit, or little difference between alternatives

In adult patients hospitalised with critical COVID-19 who require supplemental oxygen, sarilumab probably decreases the incidence of death.

Evidence from randomised trials versus standard care in adult patients demonstrates that sarilumab does not increase the risk of serious adverse events, however it probably increases the risk of non-serious adverse events. According to the Therapeutic Goods Administration, common side effects and harms associated with sarilumab include upper respiratory tract infections, neutropaenia and injection site reactions *[307]*.

Currently there is insufficient evidence for the safety of sarilumab in children and adolescents, as it has not been approved previously for any other indication. Phase II trials are currently being conducted to assess this in children and adolescents for other indications.

**Certainty of the evidence**

Low

Certainty of the evidence is moderate for mortality, adverse and serious adverse events due to serious imprecision (wide confidence intervals). Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children & adolescents and pregnant & breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Values and preferences**

Substantial variability is expected or uncertain

We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians. The panel believes that since there is uncertainty regarding the benefit-to-harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for treatment.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit.

### Rationale

Currently, sarilumab is not approved in children or adolescents for any other indication. Given this, uncertainties remain regarding the potential benefits and harms of this drug in this population.

### Clinical question/ PICO

**Population:** Patients with COVID-19
**Intervention:** Sarilumab
**Comparator:** Standard care

### Summary

Evidence indicates that sarilumab probably reduces the risk of death in hospitalised adults who require high-flow oxygen, non-invasive ventilation and invasive mechanical ventilation.

**What is the evidence informing this recommendation?**
Evidence comes from seven randomised trials that compared sarilumab with standard care in 970 adults hospitalised with critical COVID-19 *[179][213]*, 2238 patients hospitalised with severe to critical COVID-19 *[174][177]* and 460 patients with moderate to critical COVID-19 *[215][180][178]*.

**Study characteristics**
Mean age of participants ranged from 58 to 63 years, and the proportion of women ranged from 19 to 36%. Pregnant and breastfeeding women were ineligible.

Consideration was given to separating data based on severity of illness (severe and critical subgroups); however it was considered inappropriate to do so due to limited data and a non-significant test for subgroup differences.

**What are the main results?**
Sarilumab probably decreases death slightly (28 fewer per 1000; RR 0.79, CI 95% 0.73 to 1.02; 3291 patients in 6 studies). Sarilumab probably has little impact on serious adverse events or discharge from hospital, but probably increases adverse events slightly (38 more per 1000; RR 1.07, CI 95% 0.98 to 1.18; 1946 patients in 3 studies). We are unsure whether sarilumab increases or decreases the requirement for ventilation, admission to ICU, clinical improvement or clinical recovery.

**Our confidence in the results**
Certainty of the evidence is moderate for death, serious adverse events and adverse events due to serious imprecision (wide confidence intervals). Certainty is low for all remaining outcomes due to very serious imprecision (wide confidence intervals and reliance on a single study).

For children and adolescents and pregnant and breastfeeding women, certainty is also downgraded for serious indirectness (absence or limited inclusion of these populations in the included studies).

**Additional information**
According to the Australian Therapeutic Goods Administration, side effects associated with sarilumab include upper respiratory tract infections, neutropaenia, increased alanine aminotransferase (ALT) and injection site redness *[181]*.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Sarilumab | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **All-cause mortality**<br>Within 21-29 days of commencing treatment<br>9 Critical | Relative risk 0.89<br>(CI 95% 0.79 — 1.02)<br>Based on data from 3,291 participants in 7 studies. [1]<br>(Randomized controlled) | **259**<br>per 1000<br>Difference: | **231**<br>per 1000<br>**28 fewer per 1000**<br>( CI 95% 54 fewer — 5 more ) | **Moderate**<br>Due to serious imprecision [2] | Sarilumab probably decreases death slightly (775 events) |
| **Mechanical ventilation**<br>Within 28 days of treatment | Relative risk 1.15<br>(CI 95% 0.38 — 3.51)<br>Based on data from 115 participants in 1 studies. [3]<br>(Randomized controlled) | **103**<br>per 1000<br>Difference: | **118**<br>per 1000<br>**15 more per 1000**<br>( CI 95% 64 fewer | **Very low**<br>Due to extremely serious imprecision [4] | We are uncertain whether sarilumab increases or decreases need for mechanical ventilation (13 events) |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Sarilumab | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| 9 Critical | | | — 259 more ) | | |
| **Respiratory failure**<br>Within 28 days of treatment<br>9 Critical | Relative risk 1.03<br>(CI 95% 0.55 — 1.94)<br>Based on data from 201 participants in 1 studies. [5]<br>(Randomized controlled) | **157**<br>per 1000<br>Difference: | **162**<br>per 1000<br>**5 more per 1000**<br>( CI 95% 71 fewer — 148 more ) | **Low**<br>Due to very serious imprecision [6] | Sarilumab may have little or no difference on respiratory failure |
| **Requiring ventilation (HFNO, NIV, MV)**<br>End of follow-up<br>6 Important | Relative risk 0.93<br>(CI 95% 0.58 — 1.51)<br>Based on data from 531 participants in 2 studies. [7]<br>(Randomized controlled) | **195**<br>per 1000<br>Difference: | **181**<br>per 1000<br>**14 fewer per 1000**<br>( CI 95% 82 fewer — 99 more ) | **Low**<br>Due to serious inconsistency and serious imprecision [8] | Sarilumab may have little impact on number of patients requiring ventilation (98 events) |
| **Serious adverse events**<br>End of follow-up<br>6 Important | Relative risk 1.04<br>(CI 95% 0.91 — 1.18)<br>Based on data from 2,396 participants in 4 studies. [9]<br>(Randomized controlled) | **214**<br>per 1000<br>Difference: | **223**<br>per 1000<br>**9 more per 1000**<br>( CI 95% 19 fewer — 39 more ) | **Moderate**<br>Due to serious imprecision [10] | Sarilumab probably has little impact on serious adverse events. |
| **Adverse events**<br>End of follow-up<br>6 Important | Relative risk 1.07<br>(CI 95% 0.98 — 1.18)<br>Based on data from 1,946 participants in 3 studies. [11]<br>(Randomized controlled) | **549**<br>per 1000<br>Difference: | **587**<br>per 1000<br>**38 more per 1000**<br>( CI 95% 11 fewer — 99 more ) | **Moderate**<br>Due to serious imprecision [12] | Sarilumab probably increases adverse events slightly. |
| **Admission to ICU**<br>Within 28 days of treatment<br>6 Important | Relative risk 0.9<br>(CI 95% 0.5 — 1.63)<br>Based on data from 469 participants in 2 studies. [13]<br>(Randomized controlled) | **108**<br>per 1000<br>Difference: | **97**<br>per 1000<br>**11 fewer per 1000**<br>( CI 95% 54 fewer — 68 more ) | **Moderate**<br>Due to serious imprecision [14] | Sarilumab probably has little or no impact on admission to ICU (52 events) |
| **Clinical improvement**<br>Within 22 days of commencing treatment<br>6 Important | Relative risk 0.98<br>(CI 95% 0.87 — 1.1)<br>Based on data from 1,097 participants in 1 studies. [15]<br>(Randomized controlled) | **608**<br>per 1000<br>Difference: | **596**<br>per 1000<br>**12 fewer per 1000**<br>( CI 95% 79 fewer — 61 more ) | **Low**<br>Due to very serious imprecision [16] | Sarilumab may have little impact on clinical improvement. |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Standard care | **Intervention**<br>Sarilumab | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Clinical recovery**<br>Within 22 days of commencing treatment<br><br>6 Important | Relative risk 0.99<br>(CI 95% 0.89 — 1.1)<br>Based on data from 1,449 participants in 1 studies. [17]<br>(Randomized controlled) | **589**<br>per 1000<br><br>Difference: | **583**<br>per 1000<br><br>**6 fewer per 1000**<br>( CI 95% 65 fewer — 59 more ) | **Low**<br>Due to very serious imprecision [18] | Sarilumab may have little impact on clinical recovery. |
| **Discharged from hospital**<br>End of follow-up<br><br>6 Important | Relative risk 0.99<br>(CI 95% 0.95 — 1.05)<br>Based on data from 1,973 participants in 5 studies. [19]<br>(Randomized controlled) | **636**<br>per 1000<br><br>Difference: | **630**<br>per 1000<br><br>**6 fewer per 1000**<br>( CI 95% 32 fewer — 32 more ) | **Moderate**<br>Due to serious imprecision [20] | Sarilumab probably has little impact on discharge from hospital. |

1. Systematic review [216] with included studies: Merchante et al. 2022, Sancho-Lopez 2021, Lescure 2021, Hermine 2022, Sivapalasingam 2021, CORIMUNDO 2022, REMAP-CAP sarilumab FINAL.
2, 10, 12, 14, 20. **Imprecision: serious.** Wide confidence intervals.
3. Systematic review [216] with included studies: Merchante et al. 2022.
4. **Imprecision: extremely serious.** Wide confidence intervals, Low number of patients, Only data from one study, due to few events.
5. Systematic review [216] with included studies: Sancho-Lopez 2021.
6, 16, 18. **Imprecision: very serious.** Wide confidence intervals, Only data from one study.
7. Systematic review [216] with included studies: Lescure 2021, Merchante et al. 2022.
8. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies, Point estimates vary widely. **Imprecision: serious.** Wide confidence intervals.
9. Systematic review [216] with included studies: Hermine 2022, Lescure 2021, REMAP-CAP sarilumab, Sivapalasingam 2021.
11. Systematic review [216] with included studies: Sivapalasingam 2021, Hermine 2022, Lescure 2021.
13. Systematic review [216] with included studies: Lescure 2021, Sancho-Lopez 2021.
15, 17. Systematic review [214] with included studies: Sivapalasingam 2021.
19. Systematic review [216] with included studies: Sancho-Lopez 2021, Merchante et al. 2022, Sivapalasingam 2021, Lescure 2021, CORIMUNDO 2022.

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178. Sancho-López A, Caballero-Bermejo AF, Ruiz-Antorán B, Múñez Rubio E, García Gasalla M, Buades J, et al. Efficacy and safety of sarilumab in patients with COVID19 pneumonia: a randomized, phase III clinical trial (SARTRE Study). Infectious Diseases and Therapy 2021;10(4):2735-2748 Pubmed Journal

179. REMAP-CAP. Effectiveness of Tocilizumab, Sarilumab, and Anakinra for critically ill patients with COVID-19. medRxiv 25 June 2021. Journal Website

180. Merchante N, Cárcel S, Garrido-Gracia JC, Trigo-Rodríguez M, Moreno MÁE, León-López R, et al. Early use of sarilumab in patients hospitalized with COVID-19 pneumonia and features of systemic inflammation: the SARICOR randomized clinical trial. Antimicrobial Agents and Chemotherapy 2022;66(2):e0210721 Pubmed Journal

181. Therapeutic Goods Administration. Australian Product Information: Kevzara (Sarilumab) pre-filled pen and pre-filled syringe. 2018. Website

213. Hermine O, Mariette X, Porcher R, Resche-Rigon M, Tharaux P-L, Ravaud P. Effect of Interleukin-6 Receptor Antagonists in Critically Ill Adult Patients with COVID-19 Pneumonia: two Randomised Controlled Trials of the CORIMUNO-19 Collaborative Group. European Respiratory Journal 2022. Pubmed Journal

214. Sarilumab for COVID-19.

215. CORIMUNO-19 Collaborative Group. Effect of anakinra versus usual care in adults in hospital with COVID-19 and mild to moderate pneumonia (CORIMUNO-ANA-1): a randomised controlled trial. Lancet Respiratory Medicine 2020. Pubmed Journal Website

216. Sarilumab for COVID-19.

217. Australian Public Assessment Report for Sarilumab. Australian Government Department of Health - Therapeutic Goods Administration 2018. Website

## 4.2 Children aged < 12 years weighing < 40 kg

### 4.2.1 Nirmatrelvir plus ritonavir (Paxlovid) for children and adolescents

Only in research settings

Do not use nirmatrelvir plus ritonavir for the treatment of COVID-19 in children under 12 years of age without risk factors for deterioration who do not require oxygen, outside of randomised trials with appropriate ethical approval.

***Additional information***

*Please note: A consensus recommendation for the use of nirmatrelvir plus ritonavir in children and adolescents is available in the primary Taskforce guideline.*

*This is a high priority recommendation and will be updated as soon as new evidence becomes available.*

## 4.2.2 Sotrovimab (Xevudy) for children and adolescents

Only in research settings

Do not routinely use sotrovimab outside of randomised trials with appropriate ethical approval for the treatment of COVID-19 in children and adolescents under 12 years of age and without high risk factors for deterioration.

Where infection with Omicron BA.2 is confirmed or considered likely, use of sotrovimab should only be considered where other treatments are not suitable or available.

***Additional information***

*Please note: A consensus recommendation for the use of sotrovimab in children and adolescents is available in the primary Taskforce guideline.*

*Where infection with Omicron BA.2 is confirmed or considered likely, use of sotrovimab in children and adolescents should only be considered where other treatments are not suitable or available. There are limited evidence-based alternatives for children and adolescents currently (e.g. inhaled corticosteroids)*

*While the clinical evidence supports use of sotrovimab to treat mild COVID-19 (in adults at high risk of severe disease), there is no clinical evidence to evaluate its effectiveness against the Omicron variant or BA.1 or BA.2 sub-variants. The Taskforce is aware of in vitro data that suggest potentially reduced efficacy against these variants and while the clinical implications of this are not certain, given the availability of other treatments, where infection with Omicron BA.2 is confirmed or considered likely, use of sotrovimab should not be considered unless other treatments are unsuitable or unavailable.*

*Children and adolescents were not included in the COMET-ICE trial. However trials are underway in which children over 12 years of age are eligible for inclusion (OPTIMISE-C19, NCT04913675).*

*The efficacy of sotrovimab (Xevudy) in vaccinated or immunocompromised patients is unknown.*

### Evidence to decision

**Benefits and harms**

Small net benefit, or little difference between alternatives

In non-hospitalised adults with mild COVID-19 who receive treatment within 5 days of symptom onset, sotrovimab probably decreases hospitalisation and serious adverse events. Based on the results of the COMET-ICE trial, sotrovimab has an acceptable safety profile.

**Older people living with frailty or cognitive impairment**
People aged over 65 years were included in the trial but no details were reported for frailty or cognitive impairment.

**People requiring palliative care**
There is uncertainty regarding benefits and harms for people requiring palliative care as no details were reported in the trial for this population. In particular, the benefits for symptom management are uncertain.

**Pregnant and breastfeeding women**
There is uncertainty around the benefits and harms of sotrovimab for pregnant or breastfeeding women as they were excluded from the trial.

**Children and adolescents**
There is uncertainty around the benefits and harms of sotrovimab for children or adolescents as they were excluded from the trial. There are presently two randomised trials underway in which children aged 12 years and over are eligible for inclusion (OPTIMISE-C19, NCT04913675).

**Certainty of the evidence**

Low

Certainty of the evidence for the composite outcome of hospitalisation (for longer than 24 hours) or death, hospitalisation, ICU admission, the requirement of non-invasive ventilation or HFNO and serious adverse events is moderate due to serious imprecision (reliance on a single study). Certainty for all-cause mortality and the requirement of invasive mechanical ventilation is low due to very serious imprecision (reliance on a single study and low number of events).

For children and adolescents, certainty has been downgraded further due to serious indirectness (absence of inclusion of these populations in the study).

**Values and preferences**

Substantial variability is expected or uncertain

We have no systematically collected information regarding patients' preferences and values.

**Children and adolescents**
We have no systematically collected information regarding the preferences and values of patients, parents, carers, families and guardians. The panel believes that since there is uncertainty regarding the benefit to harm ratio some patients (and their parents/caregivers/guardians) may prefer to wait while others might be more willing to opt for treatment.

**Resources and other considerations**

Important issues, or potential issues not investigated

We have no systematically collected evidence regarding cost-benefit. At this point, sotrovimab remains an experimental therapy so the potential costs for this therapy outside a research setting are unclear.

### Clinical question/ PICO

**Population:** Special populations with mild or moderate COVID-19
**Intervention:** Sotrovimab
**Comparator:** Placebo

### Summary

Evidence indicates that sotrovimab probably reduces incidence of hospitalisation in patients with mild COVID-19 illness who have one or more risk factors for disease progression, if received within 5 days of symptom onset.

**What is the evidence informing this recommendation?**
Evidence comes from one randomised trial (COMET-ICE) that compared sotrovimab with placebo in 1057 adult outpatients with mild-to-moderate COVID-19 *[183]*.

**Study characteristics**
Median age of participants was 52 years and 54% were women. All eligible patients required one or more risk factors for disease progression, including diabetes (requiring medication), obesity, chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, moderate to severe asthma or adults over 55 years of age. Pregnant women were ineligible, and only six patients were aged under 19 years.

**What are the main results?**
Sotrovimab probably decreases the incidence of hospitalisation (42 fewer per 1000; RR 0.24, CI 95% 0.11 to 0.55; 1057 patients in 1 study), the composite outcome of hospitalisation (for longer than 24 hours) or death (46 fewer per 1000; RR 0.20, CI 95% 0.08 to 0.48; 1057 patients in 1 study) and serious adverse events (40 fewer per 1000; RR 0.35, CI 95% 0.18 to 0.68; 1049 patients from 1 study). We are unsure if sotrovimab impacts death or the requirement for invasive mechanical ventilation.

Sotrovimab probably has little impact on intensive care unit (ICU) admission, the requirement of non-invasive ventilation or high-flow nasal oxygenation (HFNO), or adverse events.

**Our confidence in the results**

Certainty of the evidence for the composite outcome of hospitalisation (for longer than 24 hours) or death, hospitalisation, ICU admission, requirement for non-invasive ventilation or HFNO, and serious adverse events is moderate due to serious imprecision (reliance on a single study). Certainty for all-cause mortality and the requirement for invasive mechanical ventilation is low due to very serious imprecision (reliance on a single study and few events).

For children and adolescents and pregnant and breastfeeding women, certainty has been downgraded further due to serious indirectness (absence or limited of inclusion of these populations in the included study).

**Additional information**
There is currently limited supply of sotrovimab available for use within Australia and this may affect the feasibility of widespread treatment in this population.

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Sotrovimab | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| **Hospitalisation (≥ 24 hours) or death [composite]**<br>Within 29 days of treatment<br>9 Critical | Relative risk 0.2<br>(CI 95% 0.08 — 0.48)<br>Based on data from 1,057 participants in 1 studies. [1]<br>(Randomized controlled) | **57**<br>per 1000<br>Difference: | **11**<br>per 1000<br>**46 fewer per 1000**<br>( CI 95% 52 fewer — 30 fewer ) | **Low**<br>Due to serious imprecision, Due to serious indirectness [2] | Sotrovimab may decrease hospitalisation (≥ 24 hours) or death (36 events). |
| **All-cause mortality**<br>Within 29 days of treatment<br>9 Critical | Relative risk 0.2<br>(CI 95% 0.01 — 4.16)<br>Based on data from 1,057 participants in 1 studies. [3]<br>(Randomized controlled) | **4**<br>per 1000<br>Difference: | **1**<br>per 1000<br>**3 fewer per 1000**<br>( CI 95% 4 fewer — 13 more ) | **Very low**<br>Due to very serious imprecision, Due to serious indirectness [4] | We are uncertain whether sotrovimab impacts death (2 events). |
| **Hospitalisation [any cause or duration]**<br>Within 29 days of treatment<br>6 Important | Relative risk 0.24<br>(CI 95% 0.11 — 0.55)<br>Based on data from 1,057 participants in 1 studies. [5]<br>(Randomized controlled) | **55**<br>per 1000<br>Difference: | **13**<br>per 1000<br>**42 fewer per 1000**<br>( CI 95% 49 fewer — 25 fewer ) | **Low**<br>Due to serious imprecision, Due to serious indirectness [6] | Sotrovimab may decrease hospitalisation [any cause or duration] (36 events). |
| **ICU admission**<br>Within 29 days of treatment<br>6 Important | Relative risk 0.05<br>(CI 95% 0 — 0.81)<br>Based on data from 1,057 participants in 1 studies. [7]<br>(Randomized controlled) | **19**<br>per 1000<br>Difference: | **1**<br>per 1000<br>**18 fewer per 1000**<br>( CI 95% 19 fewer — 4 fewer ) | **Low**<br>Due to serious imprecision, Due to serious indirectness [8] | Sotrovimab may have little impact on ICU admission (10 events). |
| **Invasive mechanical ventilation** | Relative risk 0.11<br>(CI 95% 0.01 — 2.06)<br>Based on data from 1,057 | **8**<br>per 1000 | **1**<br>per 1000 | **Very low**<br>Due to very serious imprecision, Due to | We are uncertain whether sotrovimab impacts invasive mechanical ventilation (4 events). |

| **Outcome**<br>Timeframe | **Study results and measurements** | **Comparator**<br>Placebo | **Intervention**<br>Sotrovimab | **Certainty of the evidence**<br>(Quality of evidence) | **Summary** |
|---|---|---|---|---|---|
| Within 29 days of treatment<br><br>9 Critical | participants in 1 studies. [9]<br>(Randomized controlled) | Difference: | **7 fewer per 1000**<br>( CI 95% 8 fewer — 8 more ) | serious indirectness [10] | |
| **Non-invasive ventilation / HFNO**<br>Within 29 days of treatment<br><br>6 Important | Relative risk 0.05<br>(CI 95% 0 — 0.81)<br>Based on data from 1,057 participants in 1 studies. [11]<br>(Randomized controlled) | **19**<br>per 1000<br><br>Difference: | **1**<br>per 1000<br><br>**18 fewer per 1000**<br>( CI 95% 19 fewer — 4 fewer ) | **Low**<br>Due to serious imprecision, Due to serious indirectness [12] | Sotrovimab may have little impact on non-invasive ventilation / HFNO (10 events). |
| **Adverse events**<br>Within 29 days of treatment<br><br>6 Important | Relative risk 0.93<br>(CI 95% 0.74 — 1.17)<br>Based on data from 1,049 participants in 1 studies. [13]<br>(Randomized controlled) | **234**<br>per 1000<br><br>Difference: | **218**<br>per 1000<br><br>**16 fewer per 1000**<br>( CI 95% 61 fewer — 40 more ) | **Low**<br>Due to serious imprecision, Due to serious indirectness [14] | Sotrovimab may have little impact on adverse events (237 events). |
| **Serious adverse events**<br>Within 29 days of treatment<br><br>6 Important | Relative risk 0.35<br>(CI 95% 0.18 — 0.68)<br>Based on data from 1,049 participants in 1 studies. [15]<br>(Randomized controlled) | **61**<br>per 1000<br><br>Difference: | **21**<br>per 1000<br><br>**40 fewer per 1000**<br>( CI 95% 50 fewer — 20 fewer ) | **Low**<br>Due to serious imprecision, Due to serious indirectness [16] | Sotrovimab may decrease serious adverse events (43 events). |

1, 3, 5, 7, 9, 11. Systematic review [184] with included studies: COMET-ICE final.
2, 6, 8, 12, 14, 16. **Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: serious.** Only data from one study.
4, 10. **Indirectness: serious.** Differences between the population of interest and those studied. **Imprecision: very serious.** Only data from one study, due to few events.
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### 4.2.3 Tixagevimab plus cilgavimab (Evusheld) for children and adolescents

Only in research settings

Do not use tixagevimab plus cilgavimab for the treatment of COVID-19 in children under 12 years of age without risk factors for deterioration who do not require oxygen outside of randomised trials with appropriate ethical approval.

***Additional information***

*Please note: A consensus recommendation for the use of tixagevimab plus cilgavimab in children and adolescents is available in the primary Taskforce guideline.*

*This is a high priority recommendation and will be updated as soon as new evidence becomes available.*

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