

Potential medicines to treat COVID-19

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Potential medicines to treat COVID-19

SARS-CoV-2 is a novel coronavirus that causes the illness COVID-19. There are no approved medicines to treat COVID-19 and no vaccine is available. Most treatments focus on symptom relief. Oxygen therapy represents the major treatment intervention for patients with severe infection. Mechanical ventilation may be necessary in cases of respiratory failure refractory to oxygen therapy. Hemodynamic support is essential for managing septic shock.

The following sections summarise medicines being investigated to treat COVID-19. The emphasis of investigation of potential treatments for COVID-19 has focussed on repurposing existing medicines.¹ For example, dexamethasone and remdesivir.^{2,3} Medicines where there is emerging evidence against COVID-19 are described. There is a lack of robust evidence on specific treatment options for COVID-19 and proposed therapies are considered experimental at this stage. Some treatments have demonstrated efficacy such as remdesivir and dexamethasone. For detailed analysis of these agents together with a consulted recommendation on use refer to the [National COVID-19 Clinical Evidence Taskforce Guidance](#).

Due to the rapidly evolving nature of the COVID-19 pandemic, and the number of papers being prepared to share findings, many references have not been peer-reviewed. Their purpose is to allow other scientists to see, discuss, and comment on the findings immediately. Such preprints are yet to be evaluated by the medical community and this should be acknowledged when considering potential for application in clinical practice.

The first section draws together some of these larger trials which in many cases are conducted globally.

A further consideration in the drive to establish treatment options is resourcing both in terms of medicines and the research capacity. The number of studies which are too small to generate meaningful data are potentially depleting supplies of potential treatments without first establishing in collaborative larger studies the profile of efficacy in prevention and treatment of COVID-19. Glasziou, Sanders and Hoffmann review the potential for waste in COVID-19 research in a paper published 12 May 2020.⁴

To support this work, the Commission seek expert opinion from within Australia, for example in pharmacology, epidemiology and virology. The Commission is supported across programs by an extensive network of experts and stakeholders, including peak bodies and universities. Specifically, for medication safety this includes the Health Services Medication Expert Advisory Group that meets quarterly and includes members from all States and Territories. The Commission expects to consult with these organisations to assist with development of resources.

Managing medicines in patients with COVID-19, outside of investigating experimental treatments is considered in a set of position statements under consultation and reviewed regularly at [Medicines management COVID-19](#).

On 17 May 2020, Australia's Chief Scientist, Dr Alan Finkel, wrote to Ministers Hunt and Andrews with a report by a Rapid Research Information Forum on the most promising COVID-19 therapeutics in development globally and nationally. The [report](#) was updated 6 July 2020. In addition to the potential treatments described in this document, the report references other experimental treatments including nelfinavir, tenofovir and emtricitabine (Truvada), ribonucleoside analogue beta-D-N4-hydroxycytidine, small interfering RNAs, broadly neutralising antibodies (bNAbs) and CSL anti-cytokine antibody products.

Large trials for COVID-19 treatments

Early in the pandemic, Misra S, et al⁵ conducted systematic review and meta-analysis of the effect of various treatments on COVID-19. Eighty-one studies involving 44 in vitro and 37 clinical studies including 8,662 COVID-19 patients were included in the review. Lopinavir/ritonavir compared to controls was significantly associated with shorter mean time to clinical improvement and remdesivir compared to placebo was significantly associated with better overall clinical improvement. Hydroxychloroquine was associated with less overall clinical improvement and longer time to clinical improvement but with a risk of higher mortality and adverse events. The authors concluded results from upcoming large clinical trials must be awaited to draw any profound conclusions.

SOLIDARITY

The [SOLIDARITY trial](#)⁶ was launched by the World Health Organization on 20 March 2020. It is an international clinical trial of four treatment options assessing effectiveness against COVID-19. The trial aims to reduce clinical trial investigation time by 80% by recruiting many countries in a single study of scale to generate data in a short time. [At 1 July 2020, nearly 5,500 patients were recruited in 21 countries.](#)

RECOVERY

Over 11,500 patients from 175 NHS hospitals in the UK were enrolled in the Randomised Evaluation of COVID-19 thERapY trial ([RECOVERY trial](#)), making it the largest randomised controlled trial of potential COVID-19 treatments in the world. Adult patients who have been admitted to hospital with COVID-19 are being invited to take part. The trial is supported by a grant to the University of Oxford from UK Research and Innovation/National Institute for Health Research. Data from the trial are regularly reviewed so that any effective treatment can be identified quickly and made available to all patients, and any ineffective treatment can be removed from the trial.

The RECOVERY trial began by testing some of these suggested treatments:

- lopinavir/ritonavir
- low-dose dexamethasone
- hydroxychloroquine
- azithromycin
- tocilizumab
- convalescent plasma.

On 5 June, the investigators concluded⁷ that [there was no beneficial effect of hydroxychloroquine](#) in patients hospitalised with COVID-19. Enrolment of participants to the hydroxychloroquine arm of the RECOVERY Trial was ceased with immediate effect.⁸

On 25 June, the trial Steering Committee concluded that [there is no beneficial effect of lopinavir/ritonavir](#) in patients hospitalised with COVID-19 and closed randomisation to that treatment arm.⁹

On 16 June, the RECOVERY trial reported [improved outcomes with dexamethasone](#). The trial demonstrated a reduction in death by a third in ventilated patients and a fifth in patients receiving oxygen therapy with no benefit in patients not requiring respiratory support randomised to receive dexamethasone.¹⁰

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The RECOVERY Trial is currently testing some of these suggested treatments:

- Low-dose Dexamethasone (now only recruiting children)
- Azithromycin (a commonly used antibiotic)
- Tocilizumab (an anti-inflammatory treatment given by injection)
- Convalescent plasma (collected from donors who have recovered from COVID-19 and contains antibodies against the SARS-CoV-2 virus).

The RECOVERY trial was designed to add investigational medicines as they became available. On 14 September, the RECOVERY trial announced [the inclusion of REGN-COV2](#). This is the first antiviral, antibody combination specifically designed to treat SARS-CoV-2 infection to be studied in a largescale randomised trial.

REMAP-CAP

Randomised, Embedded, Multifactorial, Adaptive Platform trial for Community-Acquired Pneumonia ([REMAP-CAP](#)) is designed to determine and continuously update the optimal set of treatments for community-acquired pneumonia. At the outset of the COVID-19 response, participants with COVID-19 were allocated to two domains:

- Evaluation of prolonged macrolide therapy, as a modulator of immune function
- Evaluation of alternative corticosteroid strategies (no corticosteroids, low-dose hydrocortisone for seven days, or hydrocortisone while the patient is in septic shock). This domain was suspended on release of the RECOVERY trial report on dexamethasone.

Five new domains have since been granted ethical approval:

- Antiviral therapy: lopinavir/ritonavir (Kaletra), hydroxychloroquine, and the combination of hydroxychloroquine and lopinavir/ritonavir
- Immune Modulation therapy: Interferon-beta-1a, interleukin-1 receptor antagonist (Anakinra), tocilizumab and sarilumab
- Antibody therapy: evaluating the use of convalescent plasma for COVID-19
- Therapeutic anticoagulation: evaluating the use of low molecular-weight heparin or unfractionated heparin compared to standard pharmacologic thromboprophylaxis
- Vitamin C: evaluating the use of high-dose vitamin C for patients with severe CAP including CAP caused by COVID-19.

PRINCIPLE

The UK Platform Randomised trial of INterventions against COVID-19 in older peopLE (PRINCIPLE trial) of primary care patients diagnosed with COVID-19¹¹ aims to assess the impact of selected treatments given to older people at higher risk of becoming more ill when they are infected with COVID-19. The trial will compare with the best available care a number of treatments including a seven-day course of hydroxychloroquine or the antibiotic azithromycin. Specifically, the study will focus on the need for hospitalisation, the length of stay (if required) and if treatment may help people recover quicker and with fewer complications. The trial is funded by the Medical Research Council with the National Institute for Health Research and led by a team at Oxford University. The trial is aimed at over-50s, Patients presenting to GPs with a new, continuous cough or high temperature are being recruited.

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CATALYST

The [CATALYST trial](#) is a randomised multi-stage trial with proof of principle (phase II) guiding selection of interventions for phase III trials in hospitalised patients with COVID-19. The monoclonal antibodies, infliximab, namlumab and gemtuzumab ozogamicin are under investigation for their ability to manage inflammation in COVID-19. In this [collaboration by Universities of Birmingham and Oxford, UK](#), single doses of each drug given to a total of 40 patients in each trial arm will measure efficacy according to disease severity indicators including blood oxygen levels.

TACTIC-R

Ravulizumab and baricitinib are being investigated in the multi-Arm Therapeutic Study in Pre-ICU Patients Admitted With COVID-19 – Repurposed Drugs ([TACTIC-R](#)) study at Cambridge University Hospital. The trial uses a platform design with interim decisions to against efficacy and futility as appropriate and is estimated to enrol 1,167 patients.

Monoclonal antibodies

Tocilizumab (Actemra®)

Australian sponsor	Roche Products Pty Ltd
Australian status	TGA registered
PBS listing	Yes
Sponsor information	Roche, Actemra
Prescribing information	TGA
	Guildlink
	Complications

Tocilizumab (Actemra) is a biologic medicine indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients with poor prognostic factors in combination with methotrexate (MTX) or other non-biological disease-modifying anti-rheumatic drugs (DMARDs).

In 2010, Actemra secured approval from the US Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis (RA). The drug is capable of inhibiting high interleukin-6 (IL-6) protein levels. This is a pro-inflammatory cytokine implicated in some inflammatory diseases.

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Actemra does not directly kill SARS-CoV-2. In the disease COVID-19, the body may respond to the pathogen by overproducing immune cells and their signalling molecules in a dangerous phenomenon called a cytokine storm. Similar lung inflammation happened in SARS patients during the 2003 outbreak, mainly in China. It is hypothesised that Actemra may have potential against cytokine release in COVID-19 as an inhibitor of the interleukin-6 (IL-6) receptor.

Numerous trials are investigating safety and efficacy of tocilizumab in COVID-19. These include the REMAP-CAP and RECOVERY trials. A multicentre randomised controlled study across North America and Europe recruited 450 patients hospitalised with COVID-19 to receive either tocilizumab (8 mg/kg up to a maximum of 800 mg) or placebo. The phase III [COVACTA trial](#) demonstrated a positive trend in time to hospital discharge. However, the primary endpoint of improved clinical status was not reached and there was no impact on patient mortality after four weeks.

On 14 August 2020, Biran et al¹² reported a multicentre observational study of tocilizumab in patients in intensive care with COVID-19. They report patients with baseline C-reactive protein levels of 15 mg/dL or higher were most likely to show an associated improved survival with tocilizumab, whereas no association was seen in patients with lower levels of C-reactive protein. An editorial in the same journal¹³ issue offers a comparison with COVACTA trial suggesting that at the reduced dose in a targeting a population with inflammation may be the most appropriate use of treatments interfering with the interleukin-6 blockade in COVID-19, such as tocilizumab.

Sarilumab (Kevzara®)

Australian sponsor	Sanofi-Aventis Australia Pty Ltd
Australian status	TGA registered
PBS listing	No (Public summary document 1 March 2019)
Prescribing information	TGA
	Injection
	Locations

Sarilumab (Kevzara) is an IL-6 inhibitor that in combination with non-biological Disease-Modifying Anti-Rheumatic Drugs (DMARDs) or as monotherapy is indicated for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have had an inadequate response or intolerance to one or more DMARDs.

Kevzara was approved by the FDA in 2017. Sanofi-Aventis development partner, Regeneron is planning a clinical trial in severe/critical COVID-19 patients to evaluate Sarilumab. The trial is based on findings from China with another IL-6 inhibitor that showed a benefit in reducing fever and increasing lung capacity in severe and critical hospitalised patients with COVID-19.

Regeneron is also pursuing further clinical tests of an antibody, potentially finding a use as a prophylaxis in first responders and healthcare workers as a stand-alone treatment or as a combo with Kevzara.

Namilumab

Australian sponsor (likely)	Amgen
Australian status	Not registered
PBS listing	No
Indication	Phase II trials for ankylosing spondylitis and rheumatoid arthritis
Prescribing information	Unavailable

Namilumab is a human immunoglobulin G1 monoclonal antibody under license with Izana, Amgen and Takeda. It is under investigation for the management of inflammation in COVID-19, including the CATALYST Trial. Namilumab is active against granulocyte-macrophage colony stimulating factor (GM-CSF) which is a pro-inflammatory cytokine implicated in lung inflammation and immunological disease. Therapeutic benefits of the moderation of GM-CSF is being investigated in patients with COVID-19 according to University of Melbourne researchers¹⁴ and one such agent is namilumab.

Ravulizumab (Ultomiris®)

Australian sponsor	Alexion Pharmaceuticals Australasia Pty Ltd
Australian status	TGA registered
PBS listing	No
Indication	Paroxysmal nocturnal haemoglobinuria (PNH)
Prescribing information	TGA

Ravulizumab is a recombinant monoclonal antibody. It is a long-acting complement (C5) inhibitor used in blood diseases where complement activation destroys red blood cells. Ravulizumab is being studied within the TACTIC-R trial alongside baricitinib.

Leronlimab (PRO 140)

Sponsor	CytoDyn Inc. (USA)
Australian status	No
PBS listing	No
Indication	Phase III trial (leronlimab in combination with standard antiretroviral therapies in HIV-infected treatment-experienced patients) Phase Ib/II trial in metastatic breast cancer

Leronlimab is a humanised IgG4 monoclonal antibody that antagonises CCR5 on T-cells and prevents viral entry. The CCR5 is important in HIV infection and cancer metastases. In March 2020, [leronlimab was studied in a small trial](#) of patients with severe COVID-19 on the basis of its ability to disrupt CCR5, reduce viral load and inflammation.¹⁵

Leronlimab is being supplied under the FDA’s emergency Investigational New Drug (eIND) program for investigation in patients with severe COVID-19. A randomised, double blind, placebo controlled, adaptive design multicenter phase III trial is underway to evaluate the safety and efficacy of leronlimab in patients with severe COVID-19. Patients are randomised to receive weekly doses of 700 mg leronlimab or placebo, administered via weekly subcutaneous injection for two weeks. The requisite number of enrolled patients (190) in the [Phase III trial for COVID-19 patients with severe-to-critical symptoms](#) was surpassed following the first 28-day screening phase of the trial.

CD10 is a randomised, double-blind, placebo-controlled, phase III study to evaluate the efficacy and safety of [leronlimab in patients with mild-to-moderate symptoms](#) of COVID-19. Leronlimab demonstrated improvement in total clinical symptom score at day 3 in patients with mild-to-moderate symptoms of COVID-19. Among patients who received leronlimab in the study, 90% had an improvement in total clinical symptom score versus 71% in the placebo group.

REGN-COV2

REGN-COV2 combines one Regeneron-made antibody and a second antibody isolated from humans who recovered from COVID-19. Multiple antibodies have been investigated by Regeneron for the development of resistance against antibodies to the spike protein that potently neutralize SARS-CoV-2. Two antibodies in particular appear to provide a safeguard against virus mutation that leads to resistance in SARS-CoV-2, REGN10933 and REGN10987.¹⁶ These antibodies remain effective against spike variants that have arisen in the human population and are combined in REGN-COV2.

Regeneron commenced the first clinical trial of REGN-COV2 on 12 June 2020 and went on to [phase 2 treatment trials across 150 sites](#) in the US, Brazil, Mexico and Chile. These involved 1,850 hospitalised and 1,050 non-hospitalised patients.

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On 14 September 2020, the [RECOVERY trial announced the inclusion of REGN-COV2](#). The trial was designed to add investigational medicines as they became available. The open-label RECOVERY trial will assess the impact of adding REGN-COV2 to the usual standard-of-care on all-cause mortality 28 days after randomisation. Other endpoints include the impact on hospital stay and the need for ventilation. It is anticipated that at least 2,000 patients will be randomly allocated to receive REGN-COV2 plus usual standard-of-care, and results will be compared with at least 2,000 patients who receive standard-of-care on its own.

Regeneron and Roche have announced they will [collaborate in developing and manufacturing REGN-COV2](#). This will boost overall capacity for REGN-COV2 by at least three and a half times.

Other immunosuppressants

Baricitinib (Olumiant®)

Australian sponsor	Eli Lilly Australia Pty. Ltd
Australian status	TGA registered
PBS listing	Yes – Authority required
Indication	For the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately, or who are intolerant, to one or more Disease-modifying anti-rheumatic drugs (DMARDs)
Prescribing information	TGA

In February 2020, Stebbing et al¹⁷ identified a group of approved drugs that could inhibit clathrin-mediated endocytosis and thereby inhibit viral infection of cells. Baricitinib, fedratinib, and ruxolitinib are potent and selective inhibitors of Janus kinase-mediated (JAK) cytokine release, and are approved for indications such as rheumatoid arthritis and myelofibrosis. Although the three candidates have similar JAK inhibitor potencies, a high affinity for AAK1 suggests baricitinib is the best of the group, especially given its once-daily oral dosing and acceptable side-effect profile.

Favalli et al¹⁸ responded with caution to the Stebbing et al report that JAK-STAT signal blocking by baricitinib (a selective JAK1 and JAK2 inhibitor) produces an impairment of interferon-mediated antiviral response, with a potential facilitating effect on the evolution of SARS-CoV-2 infection. This mechanism is thought to be involved in an increased risk of herpes zoster and simplex infection. Viral infections (including herpes zoster and herpes simplex) in intensive care units can account for up to 10% of community-acquired and up to 5% of ventilator-associated pneumonia, the incidence of which might be expected to be higher in immuno-compromised patients given JAK inhibitors.

Debate continues over the risks with baricitinib therapy for COVID-19, with acknowledgement that the results of investigator-led and other prospective studies (for example, [NCT04320277](#) and [NCT04321993](#)) with numerous treatments, including baricitinib, in individuals with COVID-19 are awaited.¹⁹

Antivirals

Remdesivir

Australian sponsor (likely)	Gilead Sciences Pty Ltd
Australian status	TGA – not registered

Remdesivir is an investigational nucleotide analogue originally developed for Ebola. It is not approved anywhere globally and has not been demonstrated to be safe or effective for any use.²⁰

Remdesivir has demonstrated broad-spectrum antiviral activity both in vitro and in animal models against multiple emerging viral pathogens including Marburg, MERS, SARS, and more recently Ebola. The viral pathogens MERS and SARS are also coronaviruses and are structurally similar to the SARS-CoV-2 that causes COVID-19. The limited preclinical data for remdesivir in MERS and SARS indicates that the medicine may have potential activity against SARS-CoV-2.

In March 2020, Gilead commenced a phase 3 studies of remdesivir in adults diagnosed with COVID-19 to evaluate the safety and efficacy. These randomised, open-label, multicentre studies aim to enrol approximately 1,000 patients at medical centres primarily across Asian countries, as well as other countries globally with high numbers of diagnosed cases. The trial aims to determine whether multiple doses of remdesivir can reverse the infection. The primary goals are reducing fever and helping patients discharge from hospital within two weeks. Gilead's remdesivir, an intravenous treatment, has been used to treat one infected patient in the US.²¹

These studies complement those being undertaken by the National Institute of Allergy and Infectious Diseases (NIAID) in the US, and others being conducted in China led by the China-Japan Friendship Hospital.²² Reports from these studies became available on 29 April 2020 and are summarised below.

On 27 March 2020, the WHO announced that in Norway and Spain, the first patients will be enrolled in the SOLIDARITY trial.⁶ SOLIDARITY will compare the safety and effectiveness of four different medicines or medicine combinations against COVID-19: remdesivir; chloroquine and hydroxychloroquine; lopinavir plus ritonavir; and lopinavir plus ritonavir and interferon-beta.⁶

More than 90 countries are contributing to the trial, and more have expressed interest. The high numbers are expected to dramatically cut the time needed to generate robust evidence about what drugs are effective.²³

On 1 April 2020, Gilead Sciences announced the initiation of two phase 3 randomised studies to evaluate the safety and efficacy of its investigational treatment remdesivir in patients with moderate to severe COVID-19. The two studies which have been given urgent public health research (UPHR) status by the Chief Medical Office will initially involve 15 centres in the UK.

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On 29 April 2020, the National Institutes of Health in the US, released the findings of preliminary data analysis of the Adaptive COVID-19 Treatment Trial.²⁴ In this randomised, controlled trial, hospitalised patients with advanced COVID-19 and lung involvement who received remdesivir appear to have recovered faster than similar patients who received placebo. Preliminary results indicate that patients who received remdesivir had a 31% faster time to recovery than those who received placebo ($p < 0.001$). Specifically, the median time to recovery was 11 days for patients treated with remdesivir compared with 15 days for those who received placebo. Results also suggested a survival benefit, with a mortality rate of 8.0% for the group receiving remdesivir versus 11.6% for the placebo group ($p = 0.059$). More detailed information about the trial results, including more comprehensive data, will be available in a forthcoming report.

A study from China was also published online on 29 April 2020 in *The Lancet*²⁵ in which 237 patients were enrolled and randomly assigned to a treatment group (158 to remdesivir and 79 to placebo). Remdesivir use was not associated with a difference in time to clinical improvement (hazard ratio 1.23 [95% CI 0.87–1.75]). Although not statistically significant, patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo among patients with symptom duration of 10 days or less (hazard ratio 1.52 [0.95–2.43]). The authors concluded that the numerical reduction in time to clinical improvement in those treated earlier requires confirmation in larger studies.

A comment published online on 29 April 2020 in *The Lancet*²⁶ highlights the challenges of underpowered studies, reminding the reader that an absence of statistical significance in an underpowered trial means that the findings are inclusive.

On 2 May 2020, the US FDA issued an Emergency Use Authorization (EUA)²⁷ to permit the emergency use of the unapproved product remdesivir for treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in adults and children hospitalised with severe disease. Severe disease is defined as patients with an oxygen saturation (SpO_2) $\leq 94\%$ on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).

Beigel et al reported the Adaptive COVID-19 Treatment Trial (ACTT-1) in the *New England Journal of Medicine* (22 May 2020) Remdesivir was found to be superior to placebo in shortening recovery time in adults hospitalised with COVID-19.

In a pre-print published on 27 May 2020, Piscoya A et al²⁸ evaluated the efficacy and safety of remdesivir for the treatment of COVID-19. Two placebo-controlled RCTs ($n = 1300$) and two case series ($n = 88$) were included – one of which is the Wang et al study (Ref 31). All studies used remdesivir 200mg IV the first day and 100mg IV for nine more days, and followed up until 28 days. They concluded that there is paucity of adequately powered and fully reported RCTs evaluating effects of remdesivir in adult, hospitalised COVID-19 patients. Remdesivir should not be recommended for the treatment of severe COVID-19.

On 1 July 2020, Gilead Sciences Pty Ltd, the Australian subsidiary of US pharmaceutical company Gilead Sciences, Inc announced it has donated a supply of the antiviral medication remdesivir to Australia's national medical stockpile.

An international expert panel reported in the [BMJ \(30 July 2020\)](#) that 'remdesivir may be effective in reducing recovery time of patients with severe COVID-19, although the certainty of the evidence is low'. A [clinical practice guideline](#) for remdesivir in severe COVID-19 was published at the same time.

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The National COVID-19 Clinical Evidence Taskforce provided an updated recommendation on the use of remdesivir in adults on 3 July 2020 – Whenever possible remdesivir should be administered in the context of a randomised trial with appropriate ethical approval. Use of remdesivir for adults with moderate, severe or critical COVID-19 outside of a trial setting may be considered. They also recommend that the use of remdesivir for pregnant women, children or adolescents with COVID-19 outside of a trial setting should not be considered routinely.

On 10 July, the Therapeutic Goods Administration announced it granted provisional approval to remdesivir (Veklury[®], Gilead Sciences Pty Ltd) for COVID-19.²⁹ It has received provisional approval for use in adults and adolescent patients with severe COVID-19 symptoms who have been hospitalised. Remdesivir will not be available to Australians unless they are severely unwell, requiring oxygen or high-level support to breathe, and in hospital care. It is important to emphasise that the product has not been shown to prevent coronavirus infection or relieve milder cases of infection. Provisional approval, which is limited to a maximum of six years, was made on the basis of preliminary clinical data, as there is the potential for substantial benefit to Australian patients.

Lopinavir/ritonavir (Kaletra[®])

Australian sponsor	AbbVie Pty Ltd
Australian status	TGA – combination registered
PBS listing	Yes
Indication	For the treatment of HIV-1 infection, in combination with other antiretroviral agents in adults and children aged 2 years and older
Prescribing information	TGA

Lopinavir and ritonavir inhibit protease, an enzyme that HIV and coronaviruses use to replicate.

Lopinavir and ritonavir, was trialled in January 2020 in Wuhan with the published results concluding no improvement in clinical symptoms, extension of lifespan or cutting viral shedding in patients hospitalised with severe COVID-19.³⁰ In further analysis a mortality benefit was reported for patients who received Kaletra earlier. The death rate in Kaletra patients was 15.0% at day 28, versus 27.1% among placebo patients, provided therapy started within 12 days of showing symptoms.³¹

In late June 2020, the lopinavir/ritonavir arm of the RECOVERY trial has ceased enrolling patients. There was no significant difference in the primary endpoint of 28-day mortality (22.1% lopinavir/ritonavir versus 21.3% usual care; relative risk 1.04 [95% confidence interval 0.91–1.18]; p=0.58) and the results were consistent in different subgroups of patients. There was also [no evidence of beneficial effects on the risk of progression](#) to mechanical ventilation or length of hospital stay. The trial Steering Committee stated that these data convincingly rule out any meaningful mortality benefit of lopinavir/ritonavir in the hospitalised COVID-19 patients studied.

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On 4 July 2020, WHO accepted the recommendation from the Solidarity Trial's International Steering Committee to discontinue the trial's lopinavir/ritonavir arm. The interim trial results show that lopinavir/ritonavir produces little or no reduction in the mortality of hospitalised COVID-19 patients when compared to standard of care.⁶

The National COVID-19 Clinical Evidence Taskforce recommends that for people with COVID-19, lopinavir/ritonavir is only administered in the context of randomised trials with appropriate ethical approval.

Umifenovir (Arbidol®)

Australian sponsor	Not identified
Australian status	TGA – not registered

Arbidol is the trade name for umifenovir, a non-nucleoside antiviral and immunomodulating drug. The influenza remedy Arbidol (umifenovir) is not approved in Western countries but has been approved for use in China.

Umifenovir was first developed in the Russian Research Chemical-Pharmaceutical Institute in the late 1980s. In 2006, Arbidol was approved for the treatment of upper respiratory tract infections caused by influenza virus A and B in adults by the China Food and Drug Administration.³²

In March 2020, an interventional planned Phase IV trial at Xiang Hospital of central South University in Hunan province in China, aimed to recruit 500 patients to investigate the use of umifenovir as an add-on to antiviral combination therapy. The trial is split into three arms. The two experimental arms study the administration of 200 mg and 400 mg of umifenovir respectively, alongside control arm of conventional antiviral therapy in the treatment of coronavirus.³³

In Russia and China, umifenovir is widely used as a prophylactic against and treatment for colds with hundreds of millions of doses sold per year. While there is evidence that it has antiviral properties, its effectiveness has been disputed in some trials, and it is not approved for use in the EU or the US.

The UK Medicines and Healthcare Regulatory Agency (MHRA) confirmed that the Arbidol being sold on eBay UK and other websites 'is not licensed for sale in UK'. The MHRA note that while some drugs can be legally sold online by registered pharmacists, 'many websites are operating illegally, there are no qualified healthcare providers involved in the supply and the medicines supplied may not be the authorised product'.³⁴

Favipiravir (Avigan®)

Australian sponsor (likely)	FUJIFILM Toyama Chemical Co. Ltd
Australian status	TGA – not registered

Favipiravir is a broad-spectrum antiviral originally developed for influenza and also tested against Ebola virus disease. After oral absorption, it is converted into a bioactive nucleoside triphosphate compound that shares a similar structure with purine and competes with purine to inhibit RNA polymerase and block virus replication.

China now has six clinical trials investigating favipiravir. Sihuan Pharmaceutical Holdings Group Ltd. said it has initiated clinical trials of broad-spectrum antiviral favipiravir to treat COVID-19. According to the Chinese Clinical Trial Registry, it is a randomised, open-label, controlled trial to investigate the efficacy and safety of favipiravir. Low, middle and high dosage groups will each see 20 patients receive favipiravir twice a day at 1,600 mg, 1,800 mg and 2,400 mg, respectively, for 10 days. The clinical trial was registered on 20 February 2020.³⁵

A number of small studies have been initiated with favipiravir. India started [Phase III clinical trials of favipiravir](#) as a potential treatment for patients suffering from COVID-19. In Egypt, the [efficacy and safety of favipiravir are being studied](#)³⁶ versus oseltamivir and hydroxychloroquine as the national standard of care therapy.

In China, [a randomised controlled, open-label multicenter trial](#)³⁷ enrolling 240 adult patients with COVID-19 compared treatment with either favipiravir or arbidol and found no significant difference in recovery rate.

The Alfred Health in Melbourne are conducting an Adaptive randomised placebo Controlled Phase II Trial of favipiravir for COVID-19 Infection ([VIRCO trial](#)). Participants with COVID-19 may be at home or in hospital. Those assigned to the treatment arm receive 1,800 mg Favipiravir twice daily on day 1 followed by 800 mg Favipiravir twice daily for the next 13 days. Participants swab of the back of their throat every two days to assess viral activity. The trial is estimated to complete in November 2020.

The National COVID-19 Clinical Evidence Taskforce recommends that for people with COVID-19, favipiravir is only administered in the context of randomised trials with appropriate ethical approval.

Interferons

Interferons are a family of naturally occurring small cytokine proteins that are made and secreted by cells of the immune system. For example, white blood cells, natural killer cells, fibroblasts, and epithelial cells. The interferons are known to cause flu-like symptoms. When interferons ramp up the immune system, COVID-19's flu-like symptoms are likely to become worse before they get better. For a ventilated patient when symptoms are about to overwhelm them, giving them an interferon-based medicine could be catastrophic. For this reason, interferon therapies for viral infections are typically considered as a last resort.³⁸ However, the interferons are being studied and on 22 September 2020, [95 studies of interferons in COVID -19 were registered](#).

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Interferon beta-1a (Avonex[®], Rebif[®])

Australian sponsor (likely)	Biogen Australia Pty Ltd Merck Healthcare Pty Ltd
Australian status	TGA registered
PBS listing	Yes
Indication	Multiple sclerosis (MS) and in patients who have experienced a single demyelinating event and are at risk of developing clinically definite MS.
Prescribing information	TGA TGA

Interferon beta (IFN- β) is an antiviral protein made in the lungs during viral lung infections. Many viruses inhibit IFN- β as part of their effort to evade the immune system. It has been shown that older people and people with some chronic diseases have an IFN- β deficiency. In vitro, IFN- β protects cells against the Middle East Respiratory Syndrome (MERS) and (SARS) coronaviruses.

A UK trial of an [inhaled formulation of IFN- \$\beta\$ 1a \(SNG001\)](#) in patients confirmed with COVID-19 is in progress at the University of Southampton, UK to determine if this could help prevent worsening or accelerate recovery of severe lower respiratory tract illness in COVID-19 patients.³⁹ Encouraging early results were [published on 20 July 2020](#) and demonstrated development of severe disease reduced significantly by 79% compared to patients who received placebo over a 16-day treatment period.

Interferon β -1a along with lopinavir/ritonavir is also one of the medicine combination trialled in COVID-19 patients as part of the WHO SOLIDARITY trial.⁶ The SNG001 trial was the template for the UK ACCORD⁴⁰ clinical trial program to accelerate experimental treatments of COVID-19.

The National COVID-19 Clinical Evidence Taskforce recommends that for people with COVID-19, interferon β -1a is only administered in the context of randomised trials with appropriate ethical approval.

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Interferon alpha-2b

Australian sponsor (likely)	Roche Products Pty Ltd
Australian status	Not registered
PBS listing	No
Indication	Used to treat hairy cell leukemia, malignant melanoma, follicular lymphoma, Kaposi's sarcoma caused by AIDS, and certain types of genital warts. Also used to treat chronic hepatitis B or C in adults, and to treat chronic hepatitis B in children who are at least one year old.
Prescribing information	N/A

Pre-print reports from a study in China found that treatment with nebulised IFN- α 2b with or without arbidol significantly reduced the duration of detectable virus in the upper respiratory tract and in parallel reduced duration of elevated blood levels for the inflammatory markers IL-6 and CRP.⁴¹

Interferon alpha-1b

Australian sponsor (likely)	Merck Sharpe & Dohme Australia Pty Ltd TEVA Pharmaceuticals Australia Pty Ltd
Australian status	Not registered
PBS listing	No
Indication	Used to treat hairy cell leukemia, malignant melanoma, follicular lymphoma, venereal or genital warts, AIDS-related Kaposi's Sarcoma, chronic hepatitis C, chronic hepatitis B (adults and children).
Prescribing information	N/A

A pre-print report of a study in China that investigated the efficacy and safety of recombinant human interferon alpha1b (rhIFN- α 1b) nasal drops in healthy medical staff to prevent COVID-19 has delivered promising results. The authors observed that in this investigator-initiated open-label study of nearly 3,000 subjects, rhIFN- α 1b nasal drops can effectively prevent COVID-19 in treated medical personnel. The results suggest that rhIFN- α 1b nasal drops may have potential for protecting susceptible healthy people during the coronavirus pandemic.⁴²

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Pegylated interferon lambda (Lambda®)

Australian sponsor (likely)	Eiger BioPharmaceuticals, Inc.
Australian status	Not registered
PBS listing	No
Indication	Used to treat inflammatory diseases, infections, and cancers.
Prescribing information	N/A

Pegylated interferon lambda (peg-IFN- λ 1) (Lambda) is the only interferon lambda (IFN- λ) available as a therapeutic agent. In vitro, treatment with IFN- λ showed potency against a variety of viruses, including SARS-CoV and MERS-CoV. The main function of IFN- λ is to prevent viral infection by establishing an antiviral state and, if infected, to slow viral replication and dissemination. IFN- λ targets type III IFN receptors which are distinct from the type I IFN receptors.⁴³

The absence of pro-inflammatory effects in the lungs is one of the most important arguments for the specific advantage of IFN- λ over type I IFNs (IFN alpha, beta) as a treatment option for COVID-19. However, it is very important to establish if immune cells are responsive to IFN- λ in COVID-19, as their activation exacerbates inflammation. It also remains to be seen whether IFN- λ shares the known antiproliferative effect of type I IFNs and whether this could impede repair processes during recovery or sensitize epithelial cells to virus-induced cell death.⁴¹

In 2017, the US FDA granted Fast Track designation for peg-IFN- λ 1 as a potential treatment for chronic hepatitis delta virus infection. On 30 April 2020, it was announced that the first patients had been dosed in a Phase 2 study of peg-IFN- λ 1 (Lambda) in outpatients with mild COVID-19 at the Stanford University School of Medicine. The study will investigate the hypothesis that Lambda may be effective in patients who have confirmed infection with mild symptoms to reduce duration and severity of COVID-19.⁴⁴

There are a number of other trials of pegylated interferon lambda proposed in the US for the treatment of COVID-19 – ClinicalTrials.gov Identifier: NCT04343976; ClinicalTrials.gov Identifier: NCT04354259; ClinicalTrials.gov Identifier: NCT04344600.⁴⁵

Camostat mesylate

Australian sponsor (likely)	Unknown
Australian status	Not registered
PBS listing	No
Indication	Approved for treatment of pancreatic inflammation in Japan and South Korea
Prescribing information	Unavailable

Camostat mesylate acts by disrupting viral entry by inhibiting cellular transmembrane serine protease 2 (TMPRSS2) partially blocking SARS-CoV-2 infection of lung epithelial cells *in vitro*.⁴⁶ The research by Hoffman et al⁴⁷ showed that concentrations of the active metabolite GBPA after a clinically approved dose will result in antiviral activity.

Danish researchers plan to enrol 180 patients with COVID-19 in a placebo-controlled trial for five days to determine effect *in vivo*. Results are expected in three months.^{48,49}

A phase III randomised, multi-centre, prospective, open label, clinical trial ([SPIKE1](#)) is underway with Cancer Research UK. The trial aims to recruit patients who test positive for COVID-19 but who have mild disease and can treat their symptoms in the community. The aim of SPIKE1 is to determine if the drug could help control COVID-19 symptoms and prevent patient hospitalisation.

Antimalarials

Chloroquine (Chlorquin™)

Australian sponsor	Aspen Pharmacare Australia Pty Ltd
Australian status	TGA registered
PBS listing	No
Indication	Treatment of malaria

Chloroquine blocks viral infection by increasing endosomal pH required for virus/cell fusion, as well as interfering with the glycosylation of cellular receptors of SARS-CoV.⁵⁰

Hydroxychloroquine (Plaquenil®)

Australian sponsor	Sanofi-Aventis Australia Pty Ltd
Australian status	TGA registered
PBS listing	Yes
Indication	Rheumatoid arthritis; mild systemic and discoid lupus erythematosus; the suppression and treatment of malaria
Prescribing information	TGA

On 4 July 2020, WHO accepted the recommendation from the SOLIDARITY Trial's International Steering Committee to discontinue the trial's hydroxychloroquine arm. On 15 June 2020, the US Food and Drug Administration (FDA) revoked the emergency use authorisation (EUA) that allowed for chloroquine phosphate and hydroxychloroquine sulfate donated to the Strategic National Stockpile to be used to treat certain hospitalised patients with COVID-19 outside of a clinical trial. The FDA determined that chloroquine and hydroxychloroquine are unlikely to be effective in treating COVID-19 for the authorised uses in the EUA.⁵¹

Earlier in the pandemic, hydroxychloroquine and chloroquine were considered as potential medicines for the treatment of COVID19 and were included in several clinical trials. Early results from some of the non-randomised studies such as Gautret et al⁵², Chen et al⁵³ were encouraging and led to considerable media attention for chloroquine and hydroxychloroquine. However, data from more rigorous trials such as the SOLIDARITY trial (including the French Discovery trial data), RECOVERY trial and a Cochrane review of hydroxychloroquine reported that hydroxychloroquine does not reduce mortality of hospitalised COVID-19 patients when compared with standard of care⁴.

In the RECOVERY trial, a total of 1,542 patients were randomised to hydroxychloroquine and compared with 3,132 patients randomised to usual care alone. There was no significant difference in the primary endpoint of 28-day mortality (25.7% hydroxychloroquine versus 23.5% usual care. There was no evidence of beneficial effects on hospital stay duration or other outcomes.¹⁰

A meta-analysis⁵⁴ of randomised clinical trials to evaluate the efficacy and safety of chloroquine and hydroxychloroquine in the treatment of viral diseases was reported in April. It revealed no difference between intervention and placebo for plasma viral load or improvement of clinical symptoms.

Results from an observational, multinational study also reported no benefit on outcomes associated with hydroxychloroquine or chloroquine.⁵⁵ Patients hospitalised with COVID-19 over a four-month period across 671 hospitals in six continents received one of the study treatments within 48 hours of diagnosis. There were four treatment groups (chloroquine alone, chloroquine with a macrolide, hydroxychloroquine alone, or hydroxychloroquine with a macrolide). Patients who received none of these treatments formed the control group. Across 14,888 patients in the treatment groups, there was no benefit on outcomes associated with hydroxychloroquine or chloroquine, when used alone or with a macrolide. Each of these drug regimens was associated with decreased in-hospital survival and an increased frequency of de-novo ventricular arrhythmias when used for treatment of COVID-19.

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Results from another observation study published by Geleris et al in the New England Journal of Medicine also could not prove either benefit or harm of hydroxychloroquine treatment. In this study, 1,376 patients received hydroxychloroquine (600 mg twice on day 1, then 400 mg daily for a median of five days) during a median follow-up of 22.5 days.⁵⁶

On 11 May 2020, a study in patients hospitalised in metropolitan New York with COVID-19, concluded treatment with hydroxychloroquine, azithromycin, or both, compared with neither treatment, was not significantly associated with differences in in-hospital mortality. However, there was a significant increase in the risk of cardiac arrest with the combination of hydroxychloroquine and azithromycin compared to the other groups.

In response to off-label use in Australia, the Therapeutic Goods Administration (TGA) on 24 March 2020 introduced new restrictions on who can initiate therapy with hydroxychloroquine in unapproved indications. Only the following medical specialties will be able to prescribe: dermatology, intensive care medicine, paediatrics and child health, physician, and emergency medicine.⁵⁷

In Australia, the National COVID-19 Clinical Evidence Taskforce guidelines⁵⁸ for the clinical care of people with COVID-19, hydroxychloroquine is not recommended. It should only be administered in the context of randomised trials with appropriate ethical approval for people with COVID-19.

Antimicrobials / Antiseptics / Anthelmintics

In March 2020, Poschet et al⁵⁹ reported that azithromycin and ciprofloxacin have a chloroquine-like effect on respiratory epithelial cells. They report that azithromycin and ciprofloxacin (as has been previously demonstrated for chloroquine) alter the pH within the intracellular organelles in respiratory epithelial cells. This correction results in a normalisation of the cell-autonomous immune functions of respiratory epithelia in CF. There is a suggestion that the actions of azithromycin and ciprofloxacin's action may overlap with chloroquine's mode of action and propose clinical trials with patients at risk of developing severe COVID-19.

Azithromycin (Zithromax®)

Australian sponsor	Pfizer Australia Pty Ltd
Australian status	TGA registered
PBS listing	Yes
Indication	Antibacterial
Prescribing information	TGA

Azithromycin is indicated for use in adults for the treatment of the following infections of mild to moderate severity, and is used for lower respiratory infections such as:

- Acute bacterial bronchitis due to *Streptococcus pneumoniae*, *Haemophilus influenzae* or *Moraxella catarrhalis*

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- Community acquired pneumonia due to *Streptococcus pneumoniae* or *Haemophilus influenzae* in patients suitable for outpatient oral treatment
- Community acquired pneumonia caused by susceptible organisms in patients who require initial intravenous therapy.

In clinical studies efficacy has been demonstrated against *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Legionella pneumophila*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, *Staphylococcus aureus* and *Streptococcus pneumoniae*.

Azithromycin is also used for upper respiratory infections such as acute sinusitis due to *Streptococcus pneumoniae* or *Haemophilus influenzae* and acute Streptococcal pharyngitis.

The azithromycin arm of the RECOVERY Trial is continuing.⁶⁰

Povidone-iodine

Australian sponsor	Sanofi-Aventis Australia Pty Ltd
Originator brand	Betadine®
Australian status	TGA registered
PBS listing	Betadine Ready to Use Sore Throat Gargle: No Betadine Antiseptic Topical Solution: Yes – Repeat only
Indication	Antiseptic/disinfectant
Prescribing information	TGA

The use of povidone-iodine gargle is well established. In 2002, Shiraishi T et al⁶¹ published results of a study to compare the bactericidal activities of a povidone-iodine (PVP-1) gargle with those of other commercially available gargles containing chlorhexidine gluconate (CHG) and cetylpyridium chloride (CPC). In vivo, with subjects in groups of six each, the reduction rate in the oral bacterial count after gargling as compared to the baseline count before gargling was determined and compared among the three gargling agents used. The authors concluded that of the three gargles tested, PVP-I showed the highest bactericidal rate and the highest reduction rate in oral bacterial count. They also investigated whether the encouragement to use the PVP-I gargle had an effect on the absence rate from middle school due to common cold and influenza. They concluded that encouraging the use of the PVP-I gargle contributed to the decrease in absence rates due to common cold and influenza.

In 2013⁶², a study on *in vitro* bactericidal and virucidal efficacy of povidone-iodine (PVP-I) 7% gargle/mouthwash at defined dilution (equivalent to a concentration of 0.23% PVP-I) against oral and respiratory tract pathogens showed effective bactericidal activity against *Klebsiella pneumoniae* and *Streptococcus pneumoniae*. It also rapidly inactivated SARS-CoV, MERS-CoV, influenza virus A (H1N1) and rotavirus after 15 seconds of exposure. The authors concluded that povidone-iodine gargle/mouthwash may provide a protective oropharyngeal hygiene measure for individuals at high risk of exposure to oral and respiratory pathogens.

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In 2015, Eggers M et al⁶³ published results of the virucidal activity of povidone-iodine against Middle East Respiratory Syndrome Coronavirus (MERS-CoV). The authors concluded that povidone-iodine gargle/mouthwash for reduction of viral load in the oral cavity and the oropharynx may help to support hygiene measures to prevent transmission of MERS-CoV.

In a study published in 2018⁶⁴, the authors concluded that a povidone-iodine 7% gargle/mouthwash showed rapid bactericidal activity and virucidal efficacy in vitro at a concentration of 0.23% PVP-I and may provide a protective oropharyngeal hygiene measure for individuals at high risk of exposure to oral and respiratory pathogens.

A planned Australian clinical trial, *Virucidal pilot study of Nasodine® Antiseptic Nasal Spray (povidone-iodine 0.5%) in people with COVID-19 and confirmed nasal shedding of SARS-CoV-2 virus*, has been prospectively registered on the Australian & New Zealand Clinical Trial register (ACTRN12620000470998p), and is awaiting approval from Sir Charles Gairdner and Osborne Park Health Care Group Human Research Ethics Committee in Western Australia.⁶⁵

Povidone iodine topical solution is included in the World Health Organization's list of essential medicines⁶⁶. The high potency of povidone-iodine for virucidal activity has been observed against viruses including hepatitis A and influenza, as well as MERS-CoV and SARS-CoV coronaviruses.⁶⁷

Pelletier et al⁶⁸ report the first US studies of povidone-iodine (PVP-I) against SARS-CoV-2 in a virucidal assay. They also report the first and only anti-SARS-CoV-2 evaluation of nasal and oral antiseptics containing PVP-I preparations developed for safe, routine intranasal and intraoral use. The authors conclude the data reported demonstrate the in vitro efficacy of PVP-I nasal and oral preparations specifically developed for use in the nasal passages, nasopharynx and oral cavities. Further, they conclude the antiseptics studied are rapidly virucidal at concentrations suitable for safe administration to the nasal and oral mucosa.

Pelletier⁶⁹ goes on to propose preparing patients for surgical procedures or in any other setting that may create aerosols. Also, to consider routinely using PVP-I iodine nasal and oral preparations to decrease asymptomatic viral shedding, and to mitigate further disease spread.

Ivermectin

Australian sponsor	Merck Sharp & Dohme Pty Ltd
Originator brand	Stromectol®
Australian status	TGA registered
PBS listing	Yes
Indication	Onchocerciasis, Strongyloidiasis, crusted scabies, human sarcoptic scabies (Authority required)
Prescribing information	TGA

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A collaborative study published on 3 April 2020 has shown that the anti-parasitic drug, ivermectin stopped the SARS-CoV-2 virus growing in cell culture within 48 hours.⁷⁰ The study is led by the [Monash Biomedicine Discovery Institute \(BDI\)](#) with the Peter Doherty Institute of Infection and Immunity (Doherty Institute), a joint venture of the University of Melbourne and Royal Melbourne Hospital. While ivermectin is widely used with a well-documented safety profile, investigators cautioned that they need to establish if the dosage that can be used safely in humans will be effective to treat those with COVID-19.

The academic, virological and pharmacological impact of the antiviral effects of ivermectin against SARS-CoV-2 is established. Indeed, studies on RNA and DNA viruses are reviewed by Heidary and Gharebaghi in *The Journal of Antibiotics*⁷¹ (June 2020). However, the possible clinical translation and repurposing with intense media coverage, needs to be carefully considered with reference to the pharmacokinetics of ivermectin. Momekov et al⁷² analysed the in vitro antiviral activity end-points from the pharmacokinetic perspective. They concluded the available pharmacokinetic data from clinically relevant and excessive dosing studies indicate that the SARS-CoV-2 inhibitory concentrations are not likely to be attainable in humans.

The Centre for Digestive Disease (CDD) Medical Director Professor Thomas Borody has suggested [triple therapy with ivermectin](#) in combination with zinc and doxycycline could be used as a preventative treatment for high-risk individuals or by those testing positive to COVID-19 to minimise need for hospitalisation. There is no published data on this combination to date in COVID-19.

Ivermectin improved the nutrition, general health and wellbeing of billions of people worldwide ever since it was first used to treat onchocerciasis in humans in 1988. It is highly effective, has a broad spectrum of activity, is well tolerated and could be easily administered via a single, annual oral dose. It is used to treat a variety of internal nematode infections including onchocerciasis, strongyloidiasis, ascariasis, cutaneous larva migrans, filariases, gnathostomiasis and trichuriasis. It is also used as oral treatment of ectoparasitic infections, such as pediculosis (lice infestation) and scabies (mite infestation).⁷³

Peripheral vasodilators

Aviptadil (RLF-100)

Australian sponsor (likely)	Biogen Australia Pty Ltd
Australian status	Not registered.
PBS listing	No
Indication	For the treatment of pulmonary hypertension, a condition of increased blood pressure within the arteries of the lungs
Prescribing information	Unavailable

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Aviptadil is approved in Europe with a history of safety in trials for sarcoidosis, pulmonary fibrosis, bronchospasm, and erectile dysfunction (ED). Aviptadil is a synthetic analogue of a vasoactive intestinal polypeptide (VIP) with potent anti-inflammatory and anti-cytokine activity in the lungs. VIP is effective in protecting the cell that is attacked by the SARS-CoV-2 virus that causes COVID-19.

Relief Therapeutics, based in Geneva, previously partnered with US multinational biotech firm Biogen to develop Aviptadil for the treatment of pulmonary hypertension, a condition of increased blood pressure within the arteries of the lungs.⁷⁴ Relief have now combined forces with NeuroRx to develop RLF-100, a patented formulation of aviptadil.

[Intravenous aviptadil is being studied](#) in patients critically ill with COVID-19. Patients are randomised to receive escalating doses of aviptadil from 50–150 pmol/kg/hr over 12 hours. At 26 August 2020, 60 patients had been enrolled with a target of 144 patients. The intention is to [study RLF-100 in less severe disease](#) to establish if there is an impact on disease progression.

Aviptadil, a synthetic form of Human Vasoactive Intestinal Polypeptide (VIP) has been awarded FDA Orphan Drug Designation for the treatment of ARDS and admitted to the FDA CoronaVirus Technology Accelerator Program.

Ifenprodil

Australian sponsor (likely)	Unknown
Australian status	Not registered
PBS listing	No
Indication	Approved in some countries in Asia to treat peripheral vascular disease In Japan: approved for treatment of the dizziness caused by cerebral infarction sequela or cerebral haemorrhage sequela, where it is claimed the medicine improves cerebral blood flow by relaxing vascular smooth muscle and blocking sympathetic α receptor
Prescribing information	Unavailable

Ifenprodil, also known as NP-120, is an N-methyl-D-aspartate (NMDA) receptor antagonist specifically targeting the NMDA-type subunit 2B (Glu2NB). Ifenprodil prevents glutamate signalling. The NMDA receptor is found on many tissues including lung cells and T-cells, neutrophils.

Algernon Pharmaceuticals Inc, based in Vancouver, is a drug repurposing company that investigates approved drugs for new disease applications. The company has filed new intellectual property rights around the world for ifenprodil for the treatment of respiratory diseases and is working to develop a proprietary injectable, slow-release formulation.

Algernon has finalised the protocol for Phase 2 clinical study of ifenprodil for COVID-19 patients in South Korea and reports it is about to start a randomised open label [phase 2b/3 study of safety and efficacy of ifenprodil](#) in 150 patients hospitalised with COVID-19. The study will be supported by Algernon and Novotech (Australia).

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The Company believes ifenprodil can reduce the infiltration of neutrophils and T-cells into the lungs where they can release glutamate and cytokines respectively. The latter can result in the highly problematic cytokine storm that contributes to the loss of lung function and ultimately death as has been reported in COVID-19 infected patients.⁷⁵

Glucocorticoids

Glucocorticoids reduce inflammation by acting in the same way as steroids produced by the body. The relative potencies of corticosteroids are dependent on their relative glucocorticoid activity versus their mineral corticosteroid activity.

At the start of the coronavirus pandemic robust data on efficacy in severe infections was limited.⁷⁶ Research has grown and by 24 July 2020, 55 studies of corticosteroids for the treatment of COVID-19 were registered on ClinicalTrials.gov. To manage the generated data a World Health Organization (WHO) working group⁷⁷ developed a protocol for a prospective meta-analysis⁶ of ongoing randomised clinical trials. While the review was in development, the preliminary findings for dexamethasone within the RECOVERY trial were reported (See below). Overall, dexamethasone resulted in an absolute reduction in mortality of 2.8% (22.9% versus 25.7% for usual care; age-adjusted rate ratio, 0.83 [95% CI, 0.75–0.93]). This announcement led to the suspension of treatment in most ongoing trials of corticosteroids. The WHO prospective meta-analysis was completed and concluded that in critically ill patients with COVID-19, administration of systemic corticosteroids, compared with usual care or placebo, was associated with lower 28-day all-cause mortality.

A single-centre retrospective controlled cohort study conducted in Spain by Fernandex-Cruz A et al⁷⁸, reviewed the impact of steroid use in COVID-19 pneumonia in-hospital mortality. Among 463 hospitalised patients with COVID-19 pneumonia who fulfilled inclusion criteria, 396 (46.7%) consecutive patients were treated with steroids and 67 patients were assigned to the control cohort. In-hospital mortality was lower in patients treated with steroids than in controls (13.9% [55/396] versus 23.9% [16/67], OR 0.51 [0.27 to 0.96], p=0.044). Global mortality was 15.1%. They concluded survival of patients with SARS-CoV-2 pneumonia is higher in patients treated with glucocorticoids than in those not treated and support the use of glucocorticoids in SARS-CoV-2 infection.

Dexamethasone

Australian sponsor	Multiple sponsors, see TGA website
Brand	Multiple brands available, see TGA website
Australian status	TGA registered
PBS listing	Yes
Indication	Used in a wide range of conditions for anti-inflammatory and immunosuppressant effects
Prescribing information	TGA

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Dexamethasone has a long duration of action and a lack of mineralocorticoid activity. It is routinely used in acute care for suppression of inflammatory and allergic disorders.

In a statement released on 16 June 2020, the chief investigators of the UK [RECOVERY](#) trial reported that [dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19](#).⁷⁹ In this trial, a total of 2,104 patients were randomised to receive dexamethasone 6 mg once per day (either by mouth or by intravenous injection) for 10 days and were compared with 4,321 patients randomised to usual care alone.

Overall, dexamethasone reduced the 28-day mortality rate by 17% (0.83 [0.74–0.92]; $P=0.0007$) with a highly significant trend showing the greatest benefit among those patients requiring ventilation (test for trend $p<0.001$). Dexamethasone reduced deaths by one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48–0.88]; $p=0.0003$) and by one fifth in other patients receiving oxygen only (0.80 [0.67–0.96]; $p=0.0021$). The investigators found no evidence of benefit for patients who did not require respiratory support (1.22 [0.86–1.75]; $p=0.14$). These preliminary results were peer reviewed and reported in *The New England Journal of Medicine* on 15 July 2020.¹⁰

The WHO clinical guidance⁸⁰ on the use of dexamethasone in COVID-19 was updated on 2 September 2020. WHO recommends systemic corticosteroids for treatment of patients with severe and critical COVID-19. This is based on the RECOVERY trial in a [meta-analysis with seven other trials](#) of systemic corticosteroids for COVID-19.

In the US⁸¹, Keller et al (July 2020) demonstrated early use of glucocorticoids was not associated with mortality or mechanical ventilation. However, in patients with initial C-reactive protein (CRP) ≥ 20 mg/dL glucocorticoid treatment was associated with significantly reduced risk of mortality or mechanical ventilation. Researchers recommend further study to understand the role of CRP in guiding glucocorticoid use in randomised controlled trials.

Hydrocortisone

Hydrocortisone is a corticosteroid with relatively high mineralocorticoid activity making it unsuitable for disease suppression on a long-term basis. However, it is used for the emergency management of some conditions. Hydrocortisone has been used to manage septic shock in patients with COVID-19.

Hydrocortisone was studied within the REMAP-CAP trial.⁸² Within the randomised trial 403 patients with severe COVID-19 were treated with a seven-day fixed-dose course of hydrocortisone or shock-dependent dosing of hydrocortisone, compared with no hydrocortisone. The active treatment resulted in 93% and 80% probabilities of superiority, respectively, with regard to the odds of improvement in organ support-free days within 21 days. However, follow up ended after the results of another trial were released.¹⁰ The authors concluded whilst hydrocortisone appeared beneficial 'no treatment strategy met prespecified criteria for statistical superiority, precluding definitive conclusions'.

Others

Convalescent plasma

[Convalescent plasma](#) is the liquid part of blood that contains antibodies. When someone recovers from COVID-19, the virus antibodies stay in their plasma. It can be directly transfused into patients, or used to make a potential treatment, COVID-19 Immunoglobulin.

The Lancet April 2020 edition commented that evidence shows that convalescent plasma from patients who have recovered from viral infections can be used as a treatment without the occurrence of severe adverse events. Therefore, it might be worthwhile to test the safety and efficacy of convalescent plasma transfusion in SARS-CoV-2-infected patients.⁸³

On 16 April, the US Food and Drug Administration (FDA) release a statement⁸⁴ encouraging recovered patients to donate plasma for development of blood-related therapies. Known as 'convalescent plasma' it is an antibody-rich product made from blood donated by people who have recovered from the disease caused by the coronavirus. Prior experience with respiratory viruses and limited data that have emerged from China suggest that convalescent plasma has the potential to lessen the severity or shorten the length of illness caused by COVID-19.⁸⁵

More than 1,040 sites and 950 physician investigators nationwide have signed on to participate in the expanded access protocol in the US led by the Mayo Clinic www.uscovidplasma.org. A number of clinical trials are taking place to evaluate the safety and efficacy of convalescent plasma and the FDA has granted numerous single patient emergency investigational new drug (eIND) applications.

On 30 April, Rubin published a review commentary on convalescent plasma in COVID-19 in *JAMA*.⁸⁶ The article raises issues around establishing control groups and the use of convalescent plasma for other infections including influenza and Ebola. The author comments that for patients with COVID-19, convalescent plasma seems more effective given earlier in the course of the disease. Indeed, Stanford University researchers will [soon begin testing convalescent plasma](#)⁸⁷ in emergency department patients with COVID-19 respiratory symptoms who do not require hospitalisation. Columbia University is [recruiting for patients](#)⁸⁸ testing positive to SARS-CoV-2 but asymptomatic or with mild symptoms of COVID-19.

The FDA advises antibody titres are measured on blood collection before convalescent plasma is infused. If not measured a sample of donor blood should be saved so that future testing may investigate if higher titres correlate with [better outcomes](#).⁸⁹

The Mayo Clinic study was reported in August 2020⁹⁰ and revealed possible efficacy of convalescent plasma for hospitalised patients with COVID-19. A relationship between earlier transfusion time (three days versus four days) and higher IgG antibody levels was suggested. On 23 August 2020, [FDA released an authorisation for emergency use \(EUA\)](#) of investigational convalescent plasma in patients hospitalised with COVID-19. Convalescent plasma is not approved by the FDA but the EUA includes recommendations on use, collection, recording and compliance with an [accompanying fact sheet](#).

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The [WHO acknowledges](#) that evidence is low-quality to date and treatment is difficult to standardise as donors produce different levels of antibodies. Therefore, WHO recommends that convalescent plasma should continue to be validated in well-designed randomised controlled trials.

In Australia, the Australian Red Cross Lifeblood began to collect convalescent plasma in May 2020. The plasma collected from people who have recovered from COVID-19 will be used in clinical trials, both as a form of direct treatment and as COVID-19 Immunoglobulin, which may provide passive immunity. Convalescent plasma [can only be donated](#) by someone with a confirmed laboratory diagnosis of COVID-19, who has fully recovered from the virus and been symptom-free for at least 28 days.

COVID-19 Immunoglobulin will be developed by CSL Behring in Australia. Firstly, a small batch of COVID-19 Immunoglobulin will be produced to develop tests that detect the presence of the antibodies that fight the SARS-CoV-2 virus. The second phase will involve a larger batch of COVID-19 Immunoglobulin for use in clinical trials in Australia. CSL Behring are part of the global [CoVig-19 Plasma Alliance](#).

A Cochrane review⁹¹ acknowledged 98 ongoing studies evaluating convalescent plasma and hyperimmune immunoglobulin, of which 50 are randomised controlled trials. The authors concluded available evidence on the safety and effectiveness of convalescent plasma and hyperimmune immunoglobulin for treatment of people hospitalised with COVID-19 is of very low certainty.

The National COVID-19 Clinical Evidence Taskforce provided an updated provision recommendation on the use of convalescent plasma on 3 July 2020 – For people with COVID-19, only administer convalescent plasma in the context of randomised trials with appropriate ethical approval.

Bacillus Calmette-Guérin (BCG) vaccination (ImmuCyst®)

Australian sponsor	Sanofi-Aventis Australia Pty Ltd
Australian status	TGA registered
PBS listing	No
NIPS listing	No
Indication	Active immunisation against tuberculosis
Prescribing information	TGA

Bacillus Calmette-Guérin (BCG) vaccination is not recommended for general use in the Australian population or for most health care workers (HCWs).⁹² BCG vaccination is contraindicated in HIV infected persons. BCG vaccination is recommended for:

1. Aboriginal and Torres Strait Islander neonates in communities with a high incidence of tuberculosis (TB)
2. Neonates and children five years of age and under who will be travelling to or living in countries or areas with a high prevalence of TB for extended periods
3. Neonates born to parents with leprosy or a family history of leprosy.

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BCG vaccination may be considered in the following:

1. Children over five years of age who will be travelling to or living in countries or areas with a high prevalence of TB for extended periods
2. HCWs who may be at high risk of exposure to drug resistant TB.

BCG (as OncoTICE[®]) is also used for the treatment of primary or recurrent carcinoma in situ (CIS) of the urinary bladder. Manufactured by Merck Sharp & Dohme (Australia) Pty Limited, this contains the BCG Tice strain.

It has been proposed that the incidence of COVID-19 cases in countries where the BCG vaccine is used is less compared with countries where it is not used and observed that countries routinely vaccinating neonates had less reported cases of COVID-19 to date. In the absence of evidence, the World Health Organization (WHO) does not recommend BCG vaccination for the prevention of COVID-19.⁹³

BCG was developed as a vaccine against tuberculosis, but studies have shown its ability to induce potent protection against other infectious diseases. A favourable in vitro or in vivo effect has been observed in studies for distinct viral pathogens, including respiratory syncytial virus, yellow fever, herpes simplex virus; human papilloma virus.⁹⁴

A number of studies are underway testing the hypothesis that BCG vaccination reduces the incidence and severity of COVID-19 amongst health workers during the 2020 pandemic:

- BCG Vaccination to Protect Healthcare Workers Against COVID-19 (BRACE) in the Royal Children's Hospital Melbourne⁹⁵ with other hospitals in Victoria and Western Australia to participate. BRACE uses BCG Danish strain 1331. The BRACE trial investigators have provided a statement regarding BCG outside of a [clinical trial](#).
- Reducing health care workers absenteeism in COVID-19 Pandemic through BCG vaccine in The Netherlands.⁹⁶
- BCG vaccine for health care workers as defence against SARS-CoV-2 in the USA.⁹⁷
- German researchers from the Max Planck Institute for Infection Biology in Berlin will soon begin testing a potential COVID-19 vaccine based on an old tuberculosis vaccine. This trial will include high-risk patients, such as older patients and healthcare workers.⁹⁸
- [In the Netherlands, a study aiming to recruit at least 5,200 vulnerable elderly patients](#) began in September. This adaptive, multi-centre, double blind randomised placebo-controlled trial aims to determine the impact of BCG vaccination on the incidence of clinically relevant respiratory infections or COVID-19 in vulnerable elderly patients.

Dayal et al⁹⁹ compared the impact of COVID-19 in terms of case fatality rates between countries with high disease burden and those with BCG revaccination policies, presuming that revaccination practices would have provided added protection to the population against severe COVID-19. They concluded that their data supports the view that universal BCG vaccination has a protective effect on the course of COVID-19 probably preventing progression to severe disease and death and called for clinical trials of BCG vaccine to establish its beneficial role in COVID-19.

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On 13 May, Hamiel et al¹⁰⁰ published a study in JAMA concluding that does not support the hypothesis that BCG vaccination in childhood has a protective effect against COVID-19 in adulthood. The BCG vaccine was routinely administered to all newborns in Israel as part of the national immunisation program between 1955 and 1982, with acceptance rate greater than 90%. Since 1982, the vaccine has been administered only to immigrants from countries with high prevalence of tuberculosis. This change allowed comparison of infection rates and proportions with severe COVID-19 disease in two similar populations with differing BCG status.

A review published in *Nature Reviews Immunology*, 11 May¹⁰¹ considers the induction of trained immunity by BCG as protection against COVID-19, noting the need for rigorous randomised clinical trials. The authors suggest inducing trained immunity for protection against COVID-19 could be extended to other vaccines including the recombinant BCG-based vaccine VPM1002.

To address the controversial issue of correlation between BCG vaccination at population level and mortality rates across different countries, Italian investigators performed a strict epidemiological study¹⁰² collecting data available on a global scale, considering additional variables such as cultural-political factors and adherence to other vaccination coverages. Relying on a very large dataset and a wide array of control variables, the authors conclude in the preprint published 26 May 2020 that there is a strong and robust association between COVID-19 diffusion and mortality with BCG vaccination and a set of socio-economic factors.

Whilst studies have focussed on the protective effects of BCG alone, researchers from [University of Sydney are investigating BCG](#) used as a vehicle to deliver distinctive proteins that originate from the SARS-CoV-2 virus. Ongoing studies aim to determine how long the immune response lasts after vaccination in animal models.

Cepharanthine

Australian sponsor (likely)	Unknown
Australian status	Not registered
PBS listing	No
Indication	Cepharanthine is approved in Japan, where it has been used for over 40 years to treat a range of health issues, including inflammatory diseases, septic shock, alopecia and various types of cancer. Cepharanthine has also been shown to be effective against other viruses such as HIV and herpes.
Prescribing information	Unavailable

Cepharanthine (CEP) is a naturally occurring alkaloid extracted from the plant *Stephania cepharantha Hayata*. It has been widely used in Japan for more than 40 years to treat a wide variety of acute and chronic diseases. It has also been shown to scavenge free radicals and to have a protective effect against some of the responses mediated by pro-inflammatory cytokines such as TNF- α , interleukin (IL)-1 β and IL6.¹⁰³

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In 2019, a report in *Biomolecules*¹⁰⁴ identified CEP as a potential natural antiviral agent for the prevention and treatment of HCoV-OC43 infection.

In 2020, CEP was one of three drugs identified by Chinese researchers as exhibiting complete inhibition of cytopathic effects in cell culture (in vitro) against pangolin coronavirus GX_P2V in a workable model.¹⁰⁵

A summary¹⁰⁶ of in vitro and early in vivo testing of cepharanthine implies clear antiviral and anti-inflammatory activity in Sars-CoV-2. There are potential accentuated effects when used in combination with the antiviral nelfinavir, mefloquine or selamectin. However, further research is necessary to substantiate these claims.

Tranexamic acid

Australian sponsor	Pfizer Australia Pty Ltd
Australian status	TGA registered
PBS listing	Oral: Yes IV: No
Indication	Oral: For the treatment of hereditary angioneurotic oedema, short-term use in the treatment of hyphaemia and in patients with established coagulopathies who are undergoing minor surgery, and menorrhagia. IV: <ul style="list-style-type: none"> Adults: For the reduction of peri- and post-operative blood loss and the need for blood transfusion in patients undergoing cardiac surgery or total knee arthroplasty or total hip arthroplasty. Paediatrics: For the reduction of peri- and post-operative blood loss and the need for blood transfusion in patients undergoing cardiac surgery.
Prescribing information	TGA

A clinical trial sponsored by the University of Alabama, Birmingham¹⁰⁷ will examine the use of tranexamic acid to inhibit the conversion of plasminogen to plasmin in COVID-19 patients. The hypothesis is that COVID-19 patients with comorbidities such as hypotension, diabetes, coronary artery disease, cerebrovascular illness, lung disease and kidney dysfunction commonly have elevated levels of plasmin/plasminogen. Due to recent reviews proposing endogenous protease plasmin acts on COVID-19 virus resulting in increased infectivity and virulence, the activity of tranexamic acid reducing conversion of plasminogen to plasmin may reduce the infectivity and virulence of the virus in COVID-19 positive patients with these comorbidities.

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Thrombosis UK has produced guidelines for the prevention of thrombosis and management of coagulopathy and disseminated intravascular coagulation of patients infected with COVID-19.¹⁰⁸ Recommendation 7 advises tranexamic acid **not to be used** in COVID-associated disseminated intravascular coagulation.

The results of the University of Alabama trial are awaited. Further consultation and advice on the use of tranexamic acid in patients with COVID-19 is required.

Isotretinoin

Australian sponsor*	Roche Products Pty Ltd
Originator brand	Roaccutane®
Australian status	TGA registered
PBS listing	Yes – Authority required (Streamlined)
Indication	Severe cystic acne unresponsive to other therapy
Prescribing information	TGA

*For information on other sponsors and brands, refer [TGA website](#).

Isotretinoin could affect inflammation and viral entry in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection via modulating and reducing cytokine storm factors and via blocking viral entry by inhibiting androgenic factors.¹⁰⁹

Isotretinoin is reported as a strong down-regulator of the angiotensin-converting enzyme 2 (ACE2) receptor.^{110,111} ACE2-expressing cells are found in the lungs, oral mucosa, intestine, heart, kidney, endothelium, and skin. ACE2-expressing cells can act as home cells and are prone to SARS-CoV-2 infection as the ACE2 receptor facilitates cellular viral entry and replication in SARS-CoV-2 infection.^{110,111} Isotretinoin is a potential papain-like protease (PLpro) inhibitor, which is a protein encoded by SARS-CoV-2 genes.^{111,112} Isotretinoin is also reported to increase cluster of differentiation 4 (CD4) counts and markedly decrease viremia in HIV positive patients suffering from acne vulgaris.¹¹¹

A review of isotretinoin potential in COVID-19 was published in May 2020.¹¹³ Research from the contributing authors is awaited. Tanta University in Egypt has registered a randomised comparative phase III clinical trial in adult patients with confirmed COVID-19 to evaluate the safety and efficacy of isotretinoin.¹¹¹ The primary outcome measure of the trial is the difference in time to resolution of clinical signs and symptoms of COVID-19 in patients treated with isotretinoin, standard therapy, or isotretinoin plus standard therapy.

The Kafrelsheikh University in Egypt has also registered for a randomised comparative clinical trial assessing the outcome of oral isotretinoin plus standard therapy and aerosolised isotretinoin plus standard therapy against standard therapy in COVID-19 patients.¹⁰⁹

In both Tanta University and Kafrelsheikh University trials, the same combination of medicines is used for COVID-19 standard therapy and includes paracetamol, hydroxychloroquine, oseltamivir, azithromycin or clarithromycin, ascorbic acid, and cyanocobalamin plus lopinavir 400 mg / ritonavir in severe cases.

Famotidine

Australian sponsor	Multiple sponsors, see TGA website
Brand	Multiple brands available, see TGA website
Australian status	TGA registered
PBS listing	Yes
Indication	Duodenal ulcer, benign gastric ulcer, Zollinger-Ellison syndrome, gastroesophageal reflux disease.
Prescribing information	TGA

Computational screening of drug libraries against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) proteins identified famotidine as one of the drugs with the potential to bind viral proteases (3-chymotrypsin-like protease and papain-like protease) essential for viral replication.^{112,114,115}

Anecdotal observations from a retrospective review of COVID-19 patient records in Wuhan noted that many COVID-19 survivors were on famotidine for chronic heartburn.^{115,116} The mortality rate of COVID-19 patients on famotidine appeared to be 14% compared with 27% for those not on famotidine.¹¹⁵ However, the data analysis was crude and the results were not statistically significant.

Freedberg et al.¹¹⁷ conducted a retrospective cohort study in a United States hospital to assess whether famotidine use is associated with improved clinical outcomes in hospitalised COVID-19 patients. The study reported that famotidine use is associated with reduced risk of clinical deterioration leading to intubation or death in hospitalised COVID-19 patients.¹¹⁷ The results were specific for famotidine and proton pump inhibitors, which also suppress gastric acid, were not associated with reduced risk for death or intubation.¹¹⁷ The findings of this study are observational and further randomised controlled trials are required to establish the effect of famotidine in COVID-19 patients.

A retrospective, observational study of famotidine¹¹⁸ was conducted in 83 patients receiving famotidine. The study published in the American Journal of Gastroenterology indicates famotidine was associated with a lower risk of mortality and intubation. However, the patients were a younger cohort in numbers too small to draw conclusions.

A multi-site randomised double-blind clinical trial is currently underway in Northwell Health, New York, United States to evaluate the clinical efficacy of famotidine in hospitalised COVID-19 patients. The trial will compare the clinical outcomes associated with hydroxychloroquine plus high-dose intravascular famotidine against hydroxychloroquine and the control arm (historical data from Northwell patients received 'standard care' earlier in the outbreak).¹¹⁹

A pre-print research article by Malone RW et al¹²⁰ follows up on the suggestion that clinical data for famotidine may mitigate COVID-19 disease, but highlights that both the mechanism of action and the rationale for dose selection remain obscure. The paper proposes that the principal famotidine mechanism of action for COVID-19 involves on-target histamine receptor H2 activity, and that the development of clinical COVID-19 involves dysfunctional mast cell activation and histamine release.

Further resources and treatment summaries

[The Australian Department of Health off-label medicines advice for treatment and prophylaxis of COVID-19¹²¹](#)

[UK guidelines for the use of medicines in COVID-19 \(D20-8578\)](#)

[American Society of Hospital Pharmacists: Assessment of Evidence for COVID-19-Related Treatments](#)

[The Council of Australian Therapeutic Advisory Groups \(CATAG\) position on Antiviral treatment of COVID-19¹²²](#)

[The Centre for Communicable Diseases in the US drug treatment guidelines](#)

[National Institutes of Health – COVID-19 latest research information](#)

[Elsevier COVID-19 Drug Therapy](#)

[Medscape Coronavirus Disease 2019 \(COVID-19\) Treatment & Management](#)

[Drug Virus information](#)

[National COVID-19 Clinical Evidence Taskforce](#)

[COVID-19 Pharmacology Resource Center](#)

[Australian Medical Association \(AMA\) COVID-19 Pharmacologic Treatment](#)

[The International Union of Basic Pharmacology \(IUPHAR\) and the British Pharmacological Society \(BPS\) Guide to Pharmacology](#)

[Clinical trials for the prevention and treatment of coronavirus disease 2019 \(COVID-19\): The current state of play. Medical Journal of Australia April 2020¹²³](#)

[COVID-19 Biocentury Resource Center](#)

[Drug treatments for covid-19: living systematic review and network meta-analysis. BMJ 30 July 2020 online](#)

[Rapid Evidence Review: Clinical evidence for the use of antivirals in the treatment of COVID-19. 2 September 2020 Prepared for Ireland's Health Services](#)

[Everything you need to know about the COVID-19 therapy trials. The Pharmaceutical Journal, PJ 2 September 2020 online](#)

[Rapid Research Information Forum, Australian Academy of Science. Update: The most promising therapeutics for COVID-19. 6 July 2020](#)

[Cochrane Special Collections – Coronavirus \(COVID-19\): evidence relevant to critical care 2 September 2020](#)

[myCME: COVID-19 Learning Centre](#)

[COVID-19: Clinical Information and Treatment Guidelines: International Pharmaceutical Federation \(FIP\) July 2020](#)

References

- ¹ Understanding SARS-CoV-2 and the drugs that might lessen its power. The Economist (2020); March 12, 2020. Available from www.economist.com/briefing/2020/03/12/understanding-sars-cov-2-and-the-drugs-that-might-lessen-its-power [Accessed 17 March 2020]
- ² Repurposed drugs may help scientists fight new coronavirus. Science News (2020: March 10, 2020). Available from www.sciencenews.org/article/coronavirus-covid19-repurposed-treatments-drugs [Accessed 17 March 2020]
- ³ Smith T, Prosser T. COVID-19 Drug Therapy – Potential Options. Elsevier (March 2020). Available from www.elsevier.com/_data/assets/pdf_file/0007/988648/COVID-19-Drug-Therapy_Mar-2020.pdf [Accessed 17 March 2020]
- ⁴ Glasziou P, Sanders S and Hoffmann T. Waste in COVID-19 research. BMJ 2020;369:m1847 Available from www.bmj.com/content/369/bmj.m1847 [Accessed 6 October 2020]
- ⁵ Misra S, Nath M, Hadda V, Vibha D. Effect of various treatment modalities on the novel coronavirus (nCoV-2019) infection in humans: a systematic review & meta-analysis. medRxiv preprint, posted 26 May 2020. Available from www.medrxiv.org/content/10.1101/2020.05.24.20111799v1 [Accessed 28 May 2020]
- ⁶ ‘Solidarity’ clinical trial for COVID-19 treatments. WHO 2020. Available from www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments [Accessed 23 April 2020 and 9 July 2020]
- ⁷ RECOVERY Collaborative Group. Effect of hydroxychloroquine in hospitalized patients with COVID-19: Preliminary results from a multi-centre, randomized, controlled trial. MedRxiv preprint 15 July 2020. Available from www.medrxiv.org/content/10.1101/2020.07.15.20151852v1.full.pdf [Accessed 6 October 2020]
- ⁸ RECOVERY Trial. [No clinical benefit from use of hydroxychloroquine in hospitalised patients with COVID-19](http://www.recovery-trial.org/press-releases/no-clinical-benefit-from-use-of-hydroxychloroquine-in-hospitalised-patients-with-covid-19). [Accessed 11 June 2020]
- ⁹ RECOVERY Trial. [No clinical benefit from use of lopinavir-ritonavir in hospitalised COVID-19 patients studied in RECOVERY](http://www.recovery-trial.org/press-releases/no-clinical-benefit-from-use-of-lopinavir-ritonavir-in-hospitalised-covid-19-patients-studied-in-recovery) [Accessed 9 July 2020]
- ¹⁰ RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19 – Preliminary report. NEJM 17 July 2020. Available from www.nejm.org/doi/10.1056/NEJMoa2021436 [Accessed 6 October 2020]
- ¹¹ Platform Randomised trial of INterventions against COVID-19 In older peoPLE [PRINCIPLE]. Available from www.hra.nhs.uk/covid-19-research/approved-covid-19-research/281958/ [Accessed 27 April 2020]
- ¹² Biran N, Ip A, Ahn J, et al. Tocilizumab among patients with COVID-19 in the intensive care unit: a multicentre observational study. The Lancet Rheumatology. 14 August 2020. Available from [doi.org/10.1016/S2665-9913\(20\)30277-0](https://doi.org/10.1016/S2665-9913(20)30277-0) [Accessed 6 October 2020]
- ¹³ Campochiaro C and Dana L. The conundrum of interleukin-6 blockade in COVID-19. The Lancet Rheumatology. 14 August 2020. Available from [doi.org/10.1016/S2665-9913\(20\)30287-3](https://doi.org/10.1016/S2665-9913(20)30287-3) [Accessed 6 October 2020]
- ¹⁴ Lang FM, Lee KM, Tejjaro JR, et al. GM-CSF-based treatments in COVID-19: reconciling opposing therapeutic approaches. Nat Rev Immunol 20: 507–514 (2020). Available from doi.org/10.1038/s41577-020-0357-7 [Accessed 6 October 2020]
- ¹⁵ Disruption of the CCL5/RANTES-CCR5 Pathway Restores Immune Homeostasis and Reduces Plasma Viral Load in Critical COVID-19 Patterson BK, Seethamraju H, Dhody K, medRxiv. 5 May 2020. Available from doi.org/10.1101/2020.05.02.20084673 [Accessed 6 October 2020]

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- ¹⁶ Baum A, Fulton BO, Wloga E, et al. [Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies](#) Science 21 August 2020, Vol. 369, Issue 6506: 1014–1018 DOI: 10.1126/science.abd0831 [Accessed 6 October 2020]
- ¹⁷ Stebbing J, et al. COVID-19: combining antiviral and anti-inflammatory treatments. The Lancet 20 April 2020: 400–402. Available from [www.thelancet.com/journals/laninf/article/PIIS1473-3099\(20\)30132-8/fulltext](#) [Accessed 20 April 2020]
- ¹⁸ Favalli EG, et al. Baricitib for COVID-19: a suitable treatment? The Lancet on-line 3 April 2020. Available from [www.thelancet.com/journals/laninf/article/PIIS1473-3099\(20\)30262-0/fulltext](#) [Accessed 20 April 2020]
- ¹⁹ Richardson PJ, et al. Baricitib for COVID-19: a suitable treatment? Author's reply. The Lancet on-line 3 April 2020. Available from [www.thelancet.com/journals/laninf/article/PIIS1473-3099\(20\)30270-X/fulltext](#) [Accessed 20 April 2020]
- ²⁰ Press release from Gilead Sciences, UK & Ireland. Available from [www.pharmiweb.com/press-release/2020-04-01/gilead-sciences-announces-two-phase-3-randomised-studies-to-evaluate-the-safety-and-antiviral-activity-of-remdesivir-gs-5734-in-participants-with-m](#) [Accessed 2 April 2020]
- ²¹ Available from [www.fiercepharma.com/pharma/gilead-s-remdesivir-holds-promise-against-novel-coronavirus-experts-say-and-don-t-expect](#) [Accessed 6 October 2020]
- ²² Press release from Gilead Sciences, USA. Available from [www.gilead.com/news-and-press/press-room/press-releases/2020/2/gilead-sciences-initiates-two-phase-3-studies-of-investigational-antiviral-remdesivir-for-the-treatment-of-covid-19](#) [Accessed 6 October 2020]
- ²³ WHO Director-General's opening remarks at the media briefing on COVID-19 – 27 March 2020. Available from [www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---27-march-2020](#) [Accessed 31 March 2020]
- ²⁴ NIH clinical trial shows Remdesivir accelerates recovery from advanced COVID-19. National Institutes of Health, News release, 29 April 2020. Available from [www.nih.gov/news-events/news-releases/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19](#) [Accessed 30 April 2020]
- ²⁵ Wang Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. The Lancet, Published 29 April 2020. Available from [www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)31022-9/fulltext](#) [Accessed 1 May 2020]
- ²⁶ Norrie JD. Remdesivir for COVID-19: challenges of underpowered studies. The Lancet, Published 29 April 2020. Available from [marlin-prod.literatumonline.com/pb-assets/Lancet/pdfs/S0140673620310230.pdf](#) [Accessed 1 May 2020]
- ²⁷ Fact sheet for health care providers Emergency Use Authorization (EUA) of remdesivir (GS-5734TM). Available from [www.fda.gov/media/137566/download](#) [Accessed 6 October 2020]
- ²⁸ Piscoya A, Ng-Seng LF, Parra del Riego A, Cerna-Viacava R, et al. Efficacy and harms of remdesivir for the treatment of COVID-19: a systematic review and meta-analysis. bioRxiv preprint, posted 27 May 2020. Available from [www.medrxiv.org/content/10.1101/2020.05.26.20109595v1](#) [Accessed 28 May 2020]
- ²⁹ Australia's first COVID treatment approved. Media release, Therapeutic Goods Administration 10 July 2020. Available from [www.tga.gov.au/media-release/australias-first-covid-treatment-approved](#) [Accessed 13 July 2020]
- ³⁰ Bib Cao, et al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe COVID-19. NEJM (2020). DOI: 10.1056/NEJMoa2001282. Available from [www.nejm.org/doi/full/10.1056/NEJMoa2001282?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dpubmed](#) [Accessed 1 April 2020]
- ³¹ Available from [www.fiercepharma.com/pharma-asia/does-abbvie-s-hiv-drug-kaletra-also-works-covid-19-maybe-not-nejm-study-finds](#) [Accessed 6 October 2020]

- ³² Huang L, Zhang L, Liu Y, Luo R, Zeng L, Telegina I, Vlassov VV. Arbidol for preventing and treating influenza in adults and children. Cochrane Database of Systematic Reviews 2015, Issue 1. Art. No.: CD011489. DOI: 10.1002/14651858.CD011489. Available from www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011489/full/es [Accessed 19 March 2020]
- ³³ Largest COVID-19 trial studying Umifenovir or traditional Chinese medicine. Global Data Healthcare. Available from www.clinicaltrialsarena.com/comment/covid-19-clinical-trials/ [Accessed 16 March 2020]
- ³⁴ How coronavirus is worsening the UK's problem with unlicensed drugs. The New Statesman 6 March 2020. Available from www.newstatesman.com/science-tech/coronavirus/2020/03/what-arbidol-russian-coronavirus-cure-being-sold-ebay [Accessed 16 March 2020]
- ³⁵ Sihuan starts clinical trial of Ebola drug favipiravir for COVID-19. BioWorld: 4 March 2020. Available from www.bioworld.com/articles/433502-sihuan-starts-clinical-trial-of-ebola-drug-favipiravir-for-covid-19 [Accessed 17 March 2020]
- ³⁶ Efficacy and Safety of Favipiravir in Management of COVID-19 (FAV-001). Ain Shams University, Egypt. Available from clinicaltrials.gov/ct2/show/NCT04349241 [Accessed 3 June 2020]
- ³⁷ Chen C, Zhang Y, Yin J. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. medRxiv preprint, posted 15 April 2020. Available from www.medrxiv.org/content/10.1101/2020.03.17.20037432v4 [Accessed 3 June 2020]
- ³⁸ Williams E. Interferon: Potential COVID-19 treatment. MedicineNet. Available from www.medicinenet.com/interferon/article.htm [Accessed 6 May 2020]
- ³⁹ Wilkinson T. A randomised double-blind placebo-controlled trial to determine the safety and efficacy of inhaled SNG001. Available from www.hra.nhs.uk/covid-19-research/approved-covid-19-research/281317/ [Accessed 1 May 2020]
- ⁴⁰ Wilkinson T, Dixon R, Page C, et al. ACCORD: A Multicentre, Seamless, Phase 2 Adaptive Randomisation Platform Study to Assess the Efficacy and Safety of Multiple Candidate Agents for the Treatment of COVID-19 in Hospitalised Patients: A structured summary of a study protocol for a randomised controlled trial. *Trials* 21, 691 (2020). Available from doi.org/10.1186/s13063-020-04584-9 [Accessed 6 October 2020]
- ⁴¹ Zhou Q, et al. Interferon-12b treatment for COVID-19. medRxiv 10 April 2020. Available from www.medrxiv.org/content/10.1101/2020.04.06.20042580v1 [Accessed 1 May 2020]
- ⁴² Meng Z, et al. An experimental trial of recombinant human interferon alpha nasal drops to prevent coronavirus disease 2019 in medical staff in an epidemic area. medRxiv 17 April 2020. Available from www.medrxiv.org/content/10.1101/2020.04.11.20061473v1 [Accessed 5 May 2020]
- ⁴³ Prokunina-Olsson L, et al. COVID-19 and emerging viral infections: The case for interferon lambda. *J Experimental Medicine* 2020; 217(5): e20200653. Available from www.ncbi.nlm.nih.gov/pmc/articles/PMC7155807/ [Accessed 6 May 2020]
- ⁴⁴ Eiger BioPharmaceuticals Announces First COVID-19 Patients Dosed with Peginterferon Lambda. Available from <https://pipelinereview.com/index.php/2020043074502/Proteins-and-Peptides/Eiger-BioPharmaceuticals-Announces-First-COVID-19-Patients-Dosed-with-Peginterferon-Lambda.html> [Accessed 6 October 2020]
- ⁴⁵ Interferon and COVID-19 on US National Library of Medicine ClinicalTrials.gov. Available from clinicaltrials.gov/ct2/results?cond=COVID-19&term=interferon&cntry=US&state=&city=&dist=&Search=Search [Accessed 6 October 2020]
- ⁴⁶ Hoffman M, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS1 and is blocked by a clinically proven protease inhibitor. 5 March 2020. Available from [www.cell.com/cell/fulltext/S0092-8674\(20\)30229-4?rss=yes](http://www.cell.com/cell/fulltext/S0092-8674(20)30229-4?rss=yes) [Accessed 27 April 2020]

- ⁴⁷ Hoffmann M, Hofmann-Winkler H, Smith JC, et al. Camostat mesylate inhibits SARS-CoV-2 activation by TMPRSS2-related proteases and its metabolite GBPA exerts antiviral activity. Preprint. bioRxiv. 2020;2020.08.05.237651. Published 5 August 2020. DOI: [10.1101/2020.08.05.237651](https://doi.org/10.1101/2020.08.05.237651) [Accessed 6 October 2020]
- ⁴⁸ These drugs don't target the coronavirus – they target us. Science 2 April 2020. Available from www.sciencemag.org/news/2020/04/these-drugs-don-t-target-coronavirus-they-target-us [Accessed 6 October 2020]
- ⁴⁹ The Impact of Camostat mesilate on COVID-19 infection (CamoCo-19). University of Aarhus, Denmark. Available from clinicaltrials.gov/ct2/show/NCT04321096 [Accessed 6 October 2020]
- ⁵⁰ Vincent MJ, Bergeron E., Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J 2, 69 (2005). Available from doi.org/10.1186/1743-422X-2-69 [Accessed 19 March 2020]
- ⁵¹ Press announcement, US Food and Drug Administration Available from www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-daily-roundup-june-15-2020 [Accessed 6 October 2020]
- ⁵² Gautret, et al. Hydroxychloroquin and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J Antimicrobial Agents – In press 17 March 2020. DOI: 10-1016/j.ijantimicag.2020.105949. Available from www.mediterranee-infection.com/hydroxychloroquine-and-azithromycin-as-a-treatment-of-covid-19/ [Accessed 27 March 2020]
- ⁵³ Chen Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv 31 March 2020. Available from www.medrxiv.org/content/10.1101/2020.03.22.20040758v2 [Accessed 1 April 2020]
- ⁵⁴ Wang J, et al. Benefits and Risks of Chloroquine and Hydroxychloroquine in The Treatment of Viral Diseases: A Meta-Analysis of Placebo Randomized Controlled Trials. medRxiv Posted 18 April 2020. Available from www.medrxiv.org/content/10.1101/2020.04.13.20064295v1 [Accessed 23 April 2020]
- ⁵⁵ Mehra M, Desai S, Ruschitzka F, et al. Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis. The Lancet Online. 22 May 2020. Available from [doi.org/10.1016/S0140-6736\(20\)31180-6](https://doi.org/10.1016/S0140-6736(20)31180-6) [Accessed 6 October 2020]
- ⁵⁶ Geleris J, Sun Y, Platt J. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. New England Journal of Medicine. 7 May 2020. Available from www.nejm.org/doi/full/10.1056/NEJMoa2012410 [Accessed 3 June 2020]
- ⁵⁷ New restrictions for prescribing hydroxychloroquine in COVID-19. Therapeutic Goods Administration. Available from tga.gov.au/alert/new-restrictions-prescribing-hydroxychloroquine-covid-19 [Accessed 6 October 2020]
- ⁵⁸ Caring for people with COVID-19. Weekly Communique from the National Steering Committee of the National COVID-19 Clinical Evidence Taskforce. Available from covid19evidence.net.au/ [Accessed 6 October 2020]
- ⁵⁹ Poschet JF, Perrett EA, Timmins GS, Deretic V. Azithromycin and ciprofloxacin have a chloroquine-like effect on respiratory epithelial cells. bioRxiv preprint (202). DOI: Available from www.biorxiv.org/content/10.1101/2020.03.29.008631v1 [Accessed 2 April 2020]
- ⁶⁰ Randomised Evaluation of COVID-19 Therapy (RECOVERY) Home Page. Available from www.recoverytrial.net/ [Accessed 6 October 2020]
- ⁶¹ Shiraishi T, Nakagawa Y. Evaluation of the bactericidal activity of povidone-iodine and commercially available gargle preparations. Dermatology (2002); 204 (suppl1): 37–41.

- ⁶² Yung D, Tang M. Press release: 10 years after SARS – improper hand washing in the majority of HK people coupled with a 25% drop in cold & flu sick leave for reducing risk of spreading of germs doctor urges to regain strict personal hygiene habits. Hong Kong University Public Opinion Programme. 2013. Available from www.hkupop.hku.hk/english/report/postSARS/content/resources/pr.pdf [Accessed 6 April 2020]
- ⁶³ Eggers M, Eickmann M, Zorn J. Rapid and effective virucidal activity of povidone-iodine products against Middle East Respiratory Syndrome Coronavirus (MERS-CoV) and Modified Vaccinia Virus Ankara (MVA). *Infect Dis Ther* (2015); 4(4): 491–501. Available from www.ncbi.nlm.nih.gov/pubmed/26416214 [Accessed 31 March 2020]
- ⁶⁴ Eggers M, Koburger-Janssen T, Eickmann M, Zorn J. In Vitro Bactericidal and Virucidal Efficacy of Povidone-Iodine Gargle/Mouthwash Against Respiratory and Oral Tract Pathogens. *Infect Dis Ther* (2018) 7:249–259.
- ⁶⁵ Virucidal pilot study of Nasodine® Antiseptic Nasal Spray (povidone-iodine 0.5%) in people with COVID-19 and confirmed nasal shedding of SARS-CoV-2 virus. Australian & New Zealand Clinical Trial Register, submitted 9 April 2020. Available from www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=379590&isReview=true [Accessed 4 May 2020]
- ⁶⁶ World Health Organization. Model List of Essential Medicines 21st List 2019. Available from apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?ua=1 [Accessed 6 October 2020].
- ⁶⁷ Eggers M. Infectious Disease Management and Control with Povidone Iodine. *Infect Dis Ther* (2019) 8:581–593.
- ⁶⁸ Pelletier JS, Tessema B, Westover J, Frank S, et al. Efficacy of Povidone-Iodine Nasal And Oral Antiseptic Preparations Against Severe Acute Respiratory Syndrome-Coronavirus 2 (SARS-CoV-2). medRxiv preprint, posted 26 May 2020. Available from www.medrxiv.org/content/10.1101/2020.05.25.20110239v1 [Accessed 28 May 2020]
- ⁶⁹ Pelletier J. Expanding the Role of Povidone-iodine in a COVID-19 Era. Published Online: 21 August 2020 *US Ophthalmic Review*. 2020;16(2): Online ahead of journal publication. Available from www.touchophthalmology.com/covid-19/journal-articles/expanding-the-role-of-povidone-iodine-in-a-covid-19-era/ [Accessed 6 October 2020]
- ⁷⁰ Lab experiments show anti-parasitic drug, Ivermectin, eliminates SARS-CoV-2 in cells in 48 hours. Monash Biomedicine Discovery Institute, Monash University. 3 April 2020. Available from www.monash.edu/discovery-institute/news-and-events/news/2020-articles/Lab-experiments-show-anti-parasitic-drug.-Ivermectin.-eliminates-SARS-CoV-2-in-cells-in-48-hours [Accessed 6 April 2020]
- ⁷¹ Heidary F, Gharebaghi R. Ivermectin: a systematic review from antiviral effects to COVID-19 complementary regimen. *J Antibiot* 73, 593–602 (2020). Available from doi.org/10.1038/s41429-020-0336-z [Accessed 6 October 2020]
- ⁷² Momekov G, Momekova D. Ivermectin as a potential COVID-19 treatment from the pharmacokinetic point of view. medRxiv 11 April 2020. DOI: doi.org/10.1101/2020.04.11.20061804. Available from www.medrxiv.org/content/10.1101/2020.04.11.20061804v1 [Accessed 20 April 2020]
- ⁷³ Crump A, Omura S. Ivermectin, ‘Wonder drug’ from Japan: the human use perspective. *Proc Jpn Acad, Ser B* 87 (2011) Available from www.istage.jst.go.jp/article/pjab/87/2/87_2_13/article [Accessed 6 April 2020]
- ⁷⁴ US-Israeli Pharma Firm NeuroRx, Relief Therapeutics get FDA nod for COVID-19 trial. No Camels 30 March 2020. Available from nocamels.com/2020/03/us-israel-neurorx-pharmaceutical-drug-development-coronavirus-relief-therapeutics/ [Accessed 23 April 2020]

⁷⁵ Algernon Pharmaceuticals asks Health Canada for multinational clinical trial using ifenprodil as coronavirus therapy. Proactive 22 April 2020. Available from www.proactiveinvestors.com.au/companies/news/917862/algernon-pharmaceuticals-asks-health-canada-for-multinational-clinical-trial-using-ifenprodil-as-coronavirus-therapy-917862.html [Accessed 27 April 2020]

⁷⁶ Prescott HC, Rice TW. Corticosteroids in COVID-19 ARDS: Evidence and Hope During the Pandemic. JAMA. Published online 2 September 2020. DOI: [10.1001/jama.2020.16747](https://doi.org/10.1001/jama.2020.16747) [Accessed 6 October 2020]

⁷⁷ The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA. Published online 2 September 2020. DOI: [10.1001/jama.2020.17023](https://doi.org/10.1001/jama.2020.17023) [Accessed 6 October 2020]

⁷⁸ Fernandex-Cruz A, Ruiz-Antoran B, Munoz-Gomez A, Sancho-Lopez A, et al. Impact of Glucocorticoid Treatment In SARS-CoV-2 Infection Mortality: A Retrospective Controlled Cohort Study. medRxiv preprint, posted 26 May 2020. Available from www.medrxiv.org/content/10.1101/2020.05.22.20110544v1 [Accessed 28 May 2020]

⁷⁹ University of Oxford. Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19. Statement from the Chief Investigators of the RECOVERY trial on dexamethasone, 16 June 2020. Available from www.recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-to-one-third-in-hospitalised-patients-with-severe-respiratory-complications-of-covid-19 [Accessed 17 June 2020]

⁸⁰ World Health Organization Corticosteroids for COVID-19: Living guidance 2 September 2020 Geneva, Switzerland. Available from www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1 [Accessed 6 October 2020]

⁸¹ Keller MJ, Kitsis EA, Arora S, et al. Effect of Systemic Glucocorticoids on Mortality or Mechanical Ventilation in Patients With COVID-19. J. Hosp. Med 2020;8:489–493. 10.12788/jhm.3497 Available from www.journalofhospitalmedicine.com/jhospmed/article/225402/hospital-medicine/effect-systemic-glucocorticoids-mortality-or-mechanical [Accessed 6 October 2020]

⁸² The Writing Committee for the REMAP-CAP Investigators. Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. JAMA. Published online 2 September 2020. DOI: [10.1001/jama.2020.17022](https://doi.org/10.1001/jama.2020.17022) [Accessed 6 October 2020]

⁸³ Chen L, et al. Convalescent plasma as a potential therapy for COVID-19. The Lancet 20 April 2020: 398–399. Available from www.thelancet.com/action/showPdf?pii=S1473-3099%2820%2930141-9 [Accessed 17 April 2020]

⁸⁴ Press announcement, US Food and Drug Administration Available from www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-encourages-recovered-patients-donate-plasma-development-blood [Accessed 6 October 2020]

⁸⁵ Duan K, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proceedings of the National Academy of Sciences of the USA. 6 April 2020. Available from doi.org/10.1073/pnas.2004168117 [Accessed 20 April 2020]

⁸⁶ Rubin R. Testing an Old Therapy Against a New Disease: Convalescent Plasma for COVID-19. Journal of the American Medical Association. April 30, 2020; E1–E4. Available from www.fmda.org/COVID/Published-Peer-Reviewed-Journal-Articles/jama_rubin_2020_mn_200025.pdf [Accessed 6 October 2020]

⁸⁷ Convalescent Plasma in Outpatients With COVID-19. Stanford University, USA. Available from clinicaltrials.gov/ct2/show/NCT04355767 [Accessed 6 October 2020]

⁸⁸ Convalescent Plasma for COVID-19 Close Contacts. Columbia University, USA. Available from clinicaltrials.gov/ct2/show/NCT04390503?term=convalescent+plasma&cond=COVID-19&cntry=US&draw=6&rank=6 [Accessed 3 June 2020]

- ⁸⁹ Recommendations for Investigational COVID-19 Convalescent Plasma. US Food and Drug Administration. 1 May 2020. Available from www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma [Accessed 3 June 2020]
- ⁹⁰ Joyner MJ, Senefeld JW, Klassen SA, et al. Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience edRxiv 2020.08.12.20169359 Preprint. DOI: doi.org/10.1101/2020.08.12.20169359 [Accessed 6 October 2020]
- ⁹¹ Piechotta V, Chai KL, Valk SJ, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database of Systematic Reviews 2020, Issue 7. Art. No.: CD013600. DOI: [10.1002/14651858.CD013600.pub2](https://doi.org/10.1002/14651858.CD013600.pub2) [Accessed 6 October 2020]
- ⁹² The BCG vaccine: information and recommendations for use in Australia. Australian Government Department of Health. Last updated 20 May 2013. Available from www1.health.gov.au/internet/main/publishing.nsf/Content/cda-cdi3701h.htm [Accessed 20 April 2020]
- ⁹³ Bacille Calmette-Guérin (BCG) vaccination and COVID-19. WHO Scientific Brief 12 April 2020. Available from [www.who.int/news-room/commentaries/detail/bacille-calmette-gu%C3%A9rin-\(bcg\)-vaccination-and-covid-19](http://www.who.int/news-room/commentaries/detail/bacille-calmette-gu%C3%A9rin-(bcg)-vaccination-and-covid-19) [Accessed 20 April 2020]
- ⁹⁴ Bonten MJM. Reducing health care workers absenteeism in COVID-19 Pandemic through BCG vaccine. UMC Utrecht. ClinicalTrials.gov 31 March 2020. Available from clinicaltrials.gov/ct2/show/NCT04328441?term=BCG&cond=COVID-19&draw=2&rank=1 [Accessed 20 April 2020]
- ⁹⁵ BCG Vaccination to Protect Healthcare Workers Against COVID-19 (BRACE). ClinicalTrials.gov 31 March 2020. Available from clinicaltrials.gov/ct2/show/NCT04327206 [Accessed 20 April 2020]
- ⁹⁶ Reducing health care workers absenteeism in COVID-19 Pandemic through BCG vaccine. ClinicalTrials.gov 31 March 2020. Available from clinicaltrials.gov/ct2/show/NCT04328441?term=BCG&cond=COVID-19&draw=2&rank=1 [Accessed 20 April 2020]
- ⁹⁷ BCG vaccine for health care workers as defense against SARS-CoV2. ClinicalTrials.gov 16 April 2020. Available from clinicaltrials.gov/ct2/show/NCT04348370?term=BCG&cond=COVID-19&draw=2&rank=5 [Accessed 20 April 2020]
- ⁹⁸ FDA News. Germany tries out tuberculosis vaccine against COVID-19. Available from www.fda.gov/news-events/press-announcements/germany-tries-out-tuberculosis-vaccine-against-covid-19 [Accessed 20 April 2020]
- ⁹⁹ Dayal D, Gupta S. Connecting BCG Vaccination and COVID-19: Additional Data. medRxiv 7 April 2020. Available from www.medrxiv.org/content/10.1101/2020.04.07.20053272v2 [Accessed 20 April 2020]
- ¹⁰⁰ Hamiel U, Kozer E, Youngster I. SARS-CoV-2 Rates in BCG-Vaccinated and Unvaccinated Young Adults. JAMA 13 May 2020. Available from www.ncbi.nlm.nih.gov/pmc/articles/PMC7221856/ [Accessed 6 October 2020]
- ¹⁰¹ O'Neill LAJ, Netea MG. BCG-induced trained immunity: can it offer protection against COVID-19? Nat Rev Immunol (2020). Available from doi.org/10.1038/s41577-020-0337-y [Accessed 6 October 2020]
- ¹⁰² Ventura L, Vitali M, Spica VR. BCG vaccination and socioeconomic variables versus COVID-19 global features; clearing up a controversial issue. medRxiv preprint, posted 26 May 2020. Available from www.medrxiv.org/content/10.1101/2020.05.20.20107755v1 [Accessed 28 May 2020]
- ¹⁰³ Rogosnitsky M, Danks R. Therapeutic potential of the biscochlorine alkaloid, cepharanthine, for a range of clinical conditions. Pharmacol rep (2011); 63(2):337–47.

- ¹⁰⁴ Kim DE, et al. Natural Bis-Benzylisoquinoline Alkaloids-Tetrandrine, Fangchinoline, and Cepharanthine, Inhibit Human Coronavirus OC43 Infection of MRC-5 Human Lung Cells. *Biomolecules* 2019 Nov;9911: 696. Available from www.ncbi.nlm.nih.gov/pmc/articles/PMC6921063/pdf/biomolecules-09-00696.pdf [Accessed 24 April 2020]
- ¹⁰⁵ Fan HH, Wang LQ, Liu WL, et al. Repurposing of clinically approved drugs for treatment of coronavirus disease 2019 in a 2019-novel coronavirus-related coronavirus model. Available from *Chinese Medical Journal*. 2020 May;133(9):1051–1056. DOI: [10.1097/cm9.0000000000000797](https://doi.org/10.1097/cm9.0000000000000797) [Accessed 6 October 2020]
- ¹⁰⁶ Rogosnitzky M, Okediji P, Koman I. Cepharanthine: a review of the antiviral potential of a Japanese-approved alopecia drug in COVID-19. *Pharmacol. Rep* (2020). Available from doi.org/10.1007/s43440-020-00132-z [Accessed 6 October 2020]
- ¹⁰⁷ Tranexamic Acid (TXA) and Corona Virus 2019 (COVID19) in Inpatients. *ClinicalTrials.gov*. Available from clinicaltrials.gov/ct2/show/NCT04338126 [Accessed 22 April 2020]
- ¹⁰⁸ Hunt B, Retter A, McClintock C. Practical guidance for the prevention of thrombosis and management of coagulopathy and disseminated intravascular coagulation of patients infected with COVID-19. *Thrombosis UK* 25 March 2020. Available from thrombosisuk.org/covid-19-thrombosis.php [Accessed 23 April 2020]
- ¹⁰⁹ Kafrelsheikh University. [Assessment the Activity Value of 13- Cis-Retinoic Acid \(Isotretinoin\) in the Treatment of COVID-19 \(Randomized\)](https://clinicaltrials.gov/ct2/show/study/NCT04353180). *ClinicalTrials.gov* Identifier: NCT04353180. [Accessed 25 May 2020]
- ¹¹⁰ Sinha S, Cheng K, Aldape K, et al. Systematic Cell Line-Based Identification of Drugs Modifying ACE2 Expression. *Preprints* 2020, 2020030446. DOI: [10.20944/preprints202003.0446.v1](https://doi.org/10.20944/preprints202003.0446.v1). Available from www.preprints.org/manuscript/202003.0446/v1 [Accessed 6 October 2020]
- ¹¹¹ Tanta University. [Isotretinoin in Treatment of COVID-19 \(Randomized\)](https://clinicaltrials.gov/ct2/show/study/NCT04361422). *ClinicalTrials.gov* Identifier: NCT04361422. [Accessed 25 May 2020]
- ¹¹² Wu C, Liu Y, Yang Y, Zhang P, et al. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. *Acta Pharmaceutica Sinica B*. 27 February 2020.
- ¹¹³ Abdelmaksoud A, Vestita M, El-Amawy HS, et al. Systemic isotretinoin therapy in the era of COVID-19 [published online ahead of print, 1 May 2020]. *Dermatol Ther*. 2020;e13482. DOI: [10.1111/dth.13482](https://doi.org/10.1111/dth.13482) [Accessed 6 October 2020]
- ¹¹⁴ *Nature Medicine*. 15 drugs being tested to treat COVID-19 and how they would work. *Nature*. 15 May 2020 [Accessed 6 October 2020]
- ¹¹⁵ Borrell B. [New York clinical trial quietly tests heartburn remedy against coronavirus](https://www.sciencemag.org/news/2020/04/new-york-clinical-trial-quietly-tests-heartburn-remedy-against-coronavirus). *Science*. 26 April 2020 [Accessed 6 October 2020]
- ¹¹⁶ American Society of Health-System Pharmacists. [Assessment of Evidence for COVID-19-Related Treatments](https://www.ahjournals.com/doi/10.1093/ajhp/2020.05.053). 21 May 2020.
- ¹¹⁷ Freedberg DE, Conigliaro J, Wang TC, et al. [Famotidine Use is Associated with Improved Clinical Outcomes in Hospitalized COVID-19 Patients: A Propensity Score Matched Retrospective Cohort Study](https://doi.org/10.1053/j.gastro.2020.05.053). *Gastroenterology* 1 September 2020. Available from <https://doi.org/10.1053/j.gastro.2020.05.053> [Accessed 6 October 2020]
- ¹¹⁸ Mather JF, Seip RL, McKay RG. Impact of Famotidine Use on Clinical Outcomes of Hospitalized Patients With COVID-19 *The American Journal of Gastroenterology*: October 2020; Volume 115; Issue 10:1617–1623. DOI: [10.14309/ajg.0000000000000832](https://doi.org/10.14309/ajg.0000000000000832) [Accessed 6 October 2020]
- ¹¹⁹ Northwell Health. [Multi-site Adaptive Trials Using Hydroxychloroquine for COVID-19 \(MATCH\)](https://clinicaltrials.gov/ct2/show/study/NCT04370262). *ClinicalTrials.gov* Identifier: NCT04370262. [Accessed 25 May 2020]

¹²⁰ Malone RW, Tisdall P, Fremont-Smith P, Liu Y, et al. COVID-19: Famotidine, histamine, mast cells and mechanisms. Drug Discovery Design & Development pre-print 23 May 2020. Available from www.researchsquare.com/article/rs-30934/v1 [Accessed 29 May 2020]

¹²¹ Australian Health Protection Principal Committee (AHPPC) coronavirus (COVID-19) statements 7th April 2020. Available from www.health.gov.au/news/australian-health-protection-principal-committee-ahppc-coronavirus-covid-19-statements-on-7-april-2020 [Accessed 6 October 2020]

¹²² CATAG Communique Antiviral treatment of COVID-19. Council of Australian Therapeutic Advisory Groups, 23 March 2020. Available from www.catag.org.au/wp-content/uploads/2012/08/23rd-March-Communique-final.pdf [Accessed 6 April 2020]

¹²³ Davis JS, Ferreira D, Denholm JT, Tong SYC. Clinical trials for the prevention and treatment of coronavirus disease 2019 (COVID-19): The current state of play. Med J Aust 2020; www.mja.com.au/journal/2020/clinical-trials-prevention-and-treatment-coronavirus-disease-2019-covid-19-current [Preprint 27 April 2020].