AUSTRALIAN COMMISSION
ON SAFETY AND QUALITY IN HEALTH CARE

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Potential medicines to treat COVID-19

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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. 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 any proposed therapies are considered experimental at this stage. Some are included in clinical trial research.

The emphasis of investigation of potential treatments for COVID-19 has focussed on repurposing existing medicines[1] For example, lopinavir / ritonavir and chloroquine.[2,3]

The SOLIDARITY trial 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.

In Australia, on 30 March 2020 it was announced that the Peter Doherty Institute for Infection and Immunity at the University of Melbourne received funding to work on the ASCOT trial. Specifically, lopinavir-ritonavir and hydroxychloroquine will be assessed in patients with COVID-19, admitted to hospital but not to an ICU in 60 hospitals across Australia over the next 2 months.[4]

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nature of the COVID-19 pandemic, and the number of papers being prepared to share findings, many references have not been peer-reviewed.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 the information presented may be erroneous. This should be acknowledged when considering options for application in clinical practice.

Work is ongoing to fact check and build on the entries for each medicine. To support this work, the Commission will 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 to support the areas described here.

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.

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.

China's National Health Commission in treatment guidelines published online, indicated Actemra may be used to treat coronavirus patients with severe lung damage and high IL-6 levels. Researchers in China are expected to enrol a total of 188 patients with COVID-19 in a clinical trial running through to 10 May 2020.[5,6]

Actemra does not directly kill the novel coronavirus, known as 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 Actmera may have potential against this activity as an inhibitor of the interleukin 6 (IL-6) receptor.

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.

Meplazumab

Australian sponsor	To be determined
Australian status	Not registered
Approach	Treatment

Stage: To evaluate the safety and efficacy of humanized Meplazumab for Injection in patients infected by 2019-nCoA – ClinicalTrials.gov Identifier: NCT04275245

A trial in China in February 2020[7] aimed to assess the efficacy and safety of meplazumab, a humanized anti-CD147 antibody, as add-on therapy in patients with COVID-19 pneumonia. It has been proved that host-cell-expressed CD147 could bind the spike protein of SARS-CoV-2 involved in host cell invasion. Antibody against CD147 could block the infection of SARS-CoV-2. The authors interpreted that meplazumab efficiently improved the recovery of patients with SARS-CoV-2 pneumonia with a favourable safety profile. They support further large-scale investigation of meplazumab as a treatment for COVID-19 pneumonia.

Monoclonal Antibodies unspecified

Australian sponsor	To be determined
International sponsor	Vir Biotechnology
Approach	Treatment
Stage	Preclinical

Vir Biotechnology has isolated antibodies from people who survived Severe Acute Respiratory Syndrome (SARS), a viral relative of the novel coronavirus COVID-19. Vir has identified a number of monoclonal antibodies that bind to SARS-CoV-2, which were isolated from individuals who had survived a SARS infection. Research continues to determine if its antibodies, or additional antibodies that it may be able to identify, can be effective as treatment and/or prophylaxis against SARS-CoV-2.[8]

WuXi Biologics in partnership with Vir is in the early stages of development and has not specified when it expects to have products ready for human testing.[9]

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 al[10] 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 al[11] 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.[12]

Antiretrovirals

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.

In January 2020, AbbVie donated a supply of lopinavir / ritonavir to the Chinese health authorities for use as an experimental treatment option.[13] AbbVie's fixed-dose HIV drug Kaletra, a combination of antivirals 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.[14] 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.[15]

Darunavir / Cobicistat (Prezcobix®)

Australian sponsor	Janssen-Cilag Pty Ltd
Australian status	TGA registered
PBS listing	Yes
Indication	In combination with other antiretroviral agents for the treatment of adult patients with human immunodeficiency virus1 (HIV-1) infection
Prescribing information	TGA

There are several classes of drugs in development, including antivirals, immunotherapies, and vaccines. It is unknown whether a single drug could work or if a combination is needed. Prezcobix used to treat HIV infections is under investigation.[16]

Janssen has donated 300 boxes of its HIV medicine darunavir/cobicistat to the Shanghai Public Health Clinical Center and Zhongnan Hospital of Wuhan University to support research into a solution for the SARS-CoV-2. Another 50 boxes have been provided to the Chinese Centre for Disease Control and Prevention for laboratory-based drug-screening for antiviral properties against SARS-CoV-2.[17] More recently, Johnson & Johnson announced that there have been anecdotal and unsubstantiated reports that darunavir marketed by its company Janssen as Prezista / Prezcobix is being used in treatment. However, there is no evidence of any effect against SARS-CoV-2.[18]

Antivirals

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 is thought to act by disrupting viral entry by inhibiting cellular transmembrane serine protease 2 (TMPRSS2) partially blocking SARS-CoV-2 infection of lung epithelial cells *in vitro.*[19]

Danish researchers plan to enrol 180 patients with COVID-19 in a placebo-controlled trial for 5 days to determine effect in vivo. Results are expected in three months.[20] [21]

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.[22]

In March 2020, an interventional planned Phase IV trial at Xianga 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 200mg and 400mg of umifenovir respectively, alongside control arm of conventional antiviral therapy in the treatment of coronavirus.[23]

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".[24]

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.[25]

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.[26]

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.[27] 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. 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.

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.[28]

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.

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.[29] 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.

On 29 April 2020, a trial of remdesivir adult patients hospitalised with COVID-19 was published in the Lancet. Across 10 hospitals in Hubei, China, 237 patients were recruited in a randomised, double-blind, trial to receive either remdesivir or placebo.[30] Patients were assigned in a 2:1 ratio to receive remdesivir 200 mg on day 1, followed by 100 mg in a single daily infusion or placebo infusion for 10 days. Remdesivir demonstrated a reduction in time to clinical improvement. However, the clinical benefits were not statistically significant. The authors state the numerical reduction in time to clinical improvement in those treated earlier requires confirmation in larger studies. Remdesivir was adequately tolerated; adverse events reported were comparable across the two groups at 66%, remdesivir and 64%, placebo.

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 randomized, 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.[31]

In Japan, favipiravir was developed as an anti-influenza medication by Toyama Chemical Co. Ltd., a division of Fujifilm. Avigan was approved in Japan in March 2014 to treat influenza in patients who do not respond to other therapies. On 22 February 2020, Katsunobu Kato, Japan's Minister of Health, Labor and Welfare, said the country is planning to test Fujifilm's favipiravir against the coronavirus.

Although Avigan has not been approved by the South Korean government, South Korea's Ministry of Food and Drug Safety also said on 25 February 2020 that it is considering fast-track approval to import Avigan for the treatment of COVID-19.[32]

Rintatolimod

Australian sponsor (likely)	AIM ImmunoTech Inc
Australian status	Not registered
PBS listing	No
Indication	Approved for treatment of chronic fatigue syndrome in Argentina.
Prescribing information	Unavailable

Rintatolimod is a class of specifically configured ribonucleic acid (RNA) compounds targeted as potential treatment of diseases with immunologic defects and/or viral causation. It has been used as an experimental immunotherapeutic, for chronic fatigue syndrome (myalgic encephalomyelitis) in Australia and New Zealand.[33]

In vitro, Rintatolimod has been shown to inhibit replication of other human coronaviruses (SARS[34] and MERS) associated with high morbidity.

Rintatolimod is to be tested as a prophylaxis/early-onset agent against COVID-19 in a clinical trial conducted by Japan's National Institute of Infectious Diseases (NIID) and the University of Tokyo.[35]

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.[36]

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

Yao et al[37] found hydroxychloroquine to be more potent than chloroquine to inhibit SARS-CoV-2 in vitro.

Gautret et al[38] published the results in March 2020 of an open-label non-randomised clinical trial using hydroxychloroquine and azithromycin as a treatment for COVID-19. The authors concluded that hydroxychloroquine treatment is significantly associated with viral load reduction / disappearance in COVID-19 patients and its effect is reinforced by azithromycin. This paper attracted much attention – criticism that it was published before a meaningful endpoint was reached and conclusions were drawn on a small sample size. However, there was support for raising awareness of the prospects for hydroxychloroquine.

Considerable media attention on anti-malarial medicines with potential to treat COVID-19 has seen increased demand, especially for chloroquine and hydroxychloroquine. The FDA has not approved these medicines to treat COVID-19.

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.[39]

On 30 March 2020, a group of academic colleges (American Academy of Dermatology, American College of Rheumatology) and associations of disease states (Lupus Foundation of America, Arthritis Foundation) wrote to US Vice President Pence, urging collaboration to ensure the continued availability of chloroquine and hydroxychloroquine for patients with lupus and rheumatoid arthritis who are maintained on them to avoid disability, illness and early death.[40]

On 31 March 2020, a study by Chen et al[41] concluded that among patients with COVID-19, the use of hydroxychloroquine could significantly shorten time to clinical recovery (TTCR) and promote the absorption of pneumonia. Between the control group and the hydroxychloroquine group, the body temperature recovery time and the cough remission time were significantly shortened in the hydroxychloroquine treatment group.

On 14 April 2020, Tang et al[42] reported their assessment of the efficacy and safety of hydroxychloroquine plus standard-of-care (SOC) compared with SOC alone in adult patients with COVID-19. They concluded that the administration of hydroxychloroquine did not result in a higher 28-day negative conversion rate of SARS-CoV-2. However, there was more alleviation of clinical symptoms in patients hospitalised with COVID-19 receiving hydroxychloroquine than SOC alone, possibly through anti-inflammatory effects.

On 18 April 2020, Wang et al[43] reported that a meta-analysis of randomised clinical trials to evaluate the efficacy and safety of chloroquine and hydroxychloroquine in the treatment of viral diseases, revealed that both the plasma viral load and the improvement of clinical symptoms were not different between the intervention and placebo arm.

Following the release in pre-print of a number of retrospective analyses, there is continuing conjecture regarding the lack of evidence for the efficacy of hydroxychloroquine against COVID-19 in vivo. Recommendations highlight the importance of waiting for the results of ongoing, prospective, randomised, controlled studies before hydroxychloroquine is adopted more widely for the treatment of COVID-19.[44] [45]

A number of trials, underway and planned, aim to establish the role of hydroxychloroquine in the treatment of COVID-19. These include:

- The World Health Organization (WHO) **SOLIDARITY trial**[46] of adults recently hospitalised with confirmed COVID-19 randomly allocated to any of the study treatments (local standard of care, OR local standard of care plus one of the treatments – remdesivir, chloroquine or **hydroxychloroquine**, lopinavir/ritonavir, or lopinavir/ritonavir plus interferon beta-1a).
- The UK **PRINCIPLE trial** of primary care patients diagnosed with COVID-19[47] aims to assess the impact of selected treatments (in the first instance, **hydroxychloroquine**) given to older people at higher risk of becoming more ill when they are infected with COVID-19. 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 Australasian **ASCOT trial**[48] to assess the safety and effectiveness of **hydroxychloroquine** and lopinavir/ritonavir at more than 70 Australian hospitals and 11 New Zealand hospitals. Patients sick enough to require hospitalisation but not requiring admission to intensive care will be asked to participate. A quarter of the patients will be given hydroxychloroquine, a quarter will be given lopinavir/ritonavir, a quarter will be given a combination of the two drugs, and a quarter will be given no treatment.

On 23 April 2020, NPS MedicineWise released a summary of emerging evidence and current guidelines about hydroxychloroquine.[49]

Mefloquine hydrochloride (Larium®)

Australian sponsor	Pharmaco (Australia) Ltd
Australian status	TGA registered
PBS listing	No
Indication	For the treatment of acute attacks of malaria due to P. falciparum infection resistant to conventional antimalarial drugs.
Prescribing information	TGA

Mefloquine hydrochloride 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. Further, they comment of the veracity of the model, suggesting the 2019-nCoVr model could play an important role in the development of therapies and vaccines against 2019-nCoV. Moreover, cultured long before the outbreak of 2019-nCoV with high homology to 2019-nCoV, this 2019-nCoVr isolate could be a potential live vaccine candidate and play a significant role in the combat against COVID-19.[50]

Antimicrobials / Antiseptics / Anthelmintics

In March 2020, Poschet et al[51] 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.

- 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 pneumophilia, 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.

Ciprofloxacin

Australian sponsor	Bayer Australia Ltd
Originator brand	Ciproxin®
Australian status	TGA registered
PBS listing	Yes
Indication	Antibacterial
Prescribing information	TGA

The bactericidal action of ciprofloxacin appears to result from interference with the enzyme, DNA gyrase, with activity against a wide range of Gram-negative and Gram-positive organisms.

Teicoplanin (Targocid®)

Australian sponsor	Sanofi-Aventis Australia Pty Ltd
Australian status	TGA registered
PBS listing	No
Indication	Antibacterial
Prescribing information	TGA

Based on its previously shown efficacy to inhibit the first stage of the Middle East respiratory syndrome coronavirus (MERS-CoV) life cycle in human cells, Baron et al[52] report that the glycopeptide antibiotic teicoplanin is a potential treatment for patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Zhang et al[53] tested the efficacy of teicoplanin against 2019-nCoV virus infection and found that teicoplanin potently prevents the entrance of 2019-nCoV-Spike-pseudoviruses into the cytoplasm. Although the inhibitory effect upon the replication of wild-type viruses ex vivo and in vivo remains to be determined, Zhang et al conclude the preliminary result indicates that the potential antiviral activity of teicoplanin could be applied for the treatment of 2019-nCoV virus infection.

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 al[54] 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 cetylpiridium chloride (CPC). In vivo, with subjects in groups of 6 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 3 gargling agents used. The authors concluded that of the 3 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 2013[55], 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.

In 2015, Eggers M et al[56] 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 2018[57], 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.

Povidone iodine topical solution is included in the World Health Organization's list of essential medicines[58]. 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.[59]

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

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.[60] 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 newly discovered antiviral effects of ivermectin against SARS-CoV-2 is established. 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 al[61] 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.

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).[62]

Selamectin

Australian sponsor (likely)	Zoetis Australia Pty Ltd
Australian status	Not registered for human use; registered for use as parasticide on dogs and cats by APVMA
PBS listing	No
Indication	Selamectin is an approved veterinary medicine to control a range of parasites in small domestic animals (dogs and cats)
Prescribing information	Unavailable

Selamectin is a semisynthetic avermectin that is approved for use in dogs to control fleas, heartworms, ear mites, ticks, and sarcoptic mange mites. It is also used in cats to treat fleas, heartworms, ear mites, roundworms, intestinal hookworms and nematodes.

Peripheral vasodilators

A North American leader in continuing medical education, myCME, has developed a COVID-19 resource centre[63]. This includes a section on the management of patients with COVID-19, summarising antivirals, immunotherapy and other drug classes being trialled to treat COVID-19. The resource includes the following medicines originally developed to treat peripheral vascular disease.

Aviptadil

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

Aviptadil is approved in Europe with a history of safety in trials for sarcoidosis, pulmonary fibrosis, bronchospasm, and erectile dysfunction (ED). Aviptadil is an analogue of a vasoactive intestinal polypeptide with potent anti-inflammatory and anti-cytokine activity in the lungs.

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. Symptoms of pulmonary hypertension include shortness of breath, syncope, tiredness, chest pain, swelling of the legs, and an increased heart rate. Symptoms of COVID-19 infected patients may also include shortness of breath, tiredness and chest pain.[64]

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.

Sildenafil (Viagra®/Revatio®)

Australian sponsor (likely)	Pfizer Australia Pty Ltd
Australian status	ARTG registered
PBS listing	Yes – Authority required for erectile dysfunction in Department of Veterans' Affairs patients Yes – Authority required for pulmonary arterial hypertension
Indication	For the treatment of erectile dysfunction in adult males (under the brand Viagra® and others) For the treatment of pulmonary arterial hypertension (under the brand Revatio® and others)
Prescribing information	TGA

Sildenafil is a phosphodiesterase-5 (PDE5) inhibitor approved for the treatment of pulmonary arterial hypertension (PAH) in World Health Organization (WHO) Group 1 patients. The goal of this therapy is to improve exercise ability and delay clinical worsening. Research studies showing the effectiveness of the medication included mostly patients with symptoms that were rated as WHO Functional Class II-III.[65]

A Phase 3 study to observe the efficacy and safety of sildenafil in patients with COVID-19 is underway in China at Tongji Hospital in Wuhan.[66]

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. The company reports that it has finalised the protocol for Phase 2 clinical study of ifenprodil for COVID-19 patients in South Korea. The study will be supported by Algernon and Novotech. Novotech is a contract research organisation (CRO) known for its work in Australia, New Zealand, South Africa and Asia. Algernon also contracted Novotech for a second Phase 2 study of Ifenprodil to treat coronavirus patients in Australia, which the company will sponsor.[67] This Australian study is not yet listed on the Australian New Zealand Clinical Trials Registry.

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.[68]

Others

Convalescent plasma

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.[69]

On April 16, the US Food & Drug Administration (FDA) release a statement[70] 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.[71]

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.

Melatonin (Circadin®)

Australian sponsor	RAD Data Australia Pty Ltd
Distributed by	Aspen Pharmacare Australia Pty Ltd
Australian status	TGA registered
PBS listing	No
Indication	Monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over

Zhang et al[72] propose that excessive inflammation, oxidation, and an exaggerated immune response likely contribute to COVID-19 pathology. This is based on clinical features, pathology and the pathogenesis of acute respiratory disorder induced by coronaviruses or other pathogens. They suggest this leads to a cytokine storm and subsequent progression to acute lung injury (ALI) / acute respiratory distress syndrome (ARDS) and often death. Melatonin, is an anti-inflammatory and anti-oxidative molecule, and the authors suggest it may be protective against ALI / ARDS caused by viral and other pathogens. The authors also note that melatonin is effective in critical care patients by reducing vessel permeability, anxiety, sedation use, and improving sleeping quality.

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).[73] 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 5 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.

BCG vaccination may be considered in the following:

1. Children over 5 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.

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.[74]

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.[75]

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 Melbourne[76] with other hospitals in Victoria and Western Australia to participate.
- Reducing health care workers absenteeism in COVID-19 Pandemic through BCG vaccine in The Netherlands.[77]
- BCG vaccine for health care workers as defence against SARS-COV-2 in the USA.[78]
- 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.[79]

Dayal et al[80] 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.

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 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)-1β and IL6.[81]

In 2019, a report in Biomolecules[82] 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.[83]

Chlorpromazine

Australian sponsor	Sanofi-Aventis Australia Pty Ltd
Originator brand	Largactil®
Australian status	TGA registered
PBS listing	Yes
Indication	Antipsychotic
Prescribing information	TGA

Chlorpromazine is used to treat acute functional psychosis (e.g. schizophrenia, mania or psychotic depression), long-term treatment of schizophrenia, short-term treatment of agitation and severe depression. It is also used in terminal illness management to enhance the effect of analgesics and control nausea, vomiting, and intractable hiccough.

Yang et al[84] reviewed the endocytic pathway and autophagy process in viral infection of several pathogenic coronaviruses including SARS-CoV, MERS-CoV and the new SARS-CoV-2. They discuss the development of therapeutic agents targeting these processes and concluded that the exact role of autophagy is debatable. However, evidence suggests that the endocytic pathway plays a role in mediating viral entry for many coronaviruses, including SARS-CoVs, and possibly SARS-CoV-2. As a result, several inhibitors targeting the endocytic pathway appear to have the therapeutic potential in treatment of COVID-19, including a lysosomotropic agent, chloroquine and a clathrin-mediated endocytosis inhibitor, chlorpromazine. The authors call for clinical trials either as a single therapy or in combination with other anti-viral drugs as the medicines are already FDA approved.

Further resources and treatment summaries

The Australian Department of Health off-label medicines advice for treatment and prophylaxis of COVID-19[85]

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-19[86]

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

International Union of Basic and Clinical Pharmacology (IUPHAR) / British Pharmacological Society (BPS) Guide to Pharmacology

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

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