

Episode 57 – COVID-19 Treatment March 25, 2022

Treatment of COVID-19

Currently, there are 5 medications authorized in Canada for the treatment of COVID-19. Several more drugs are under review and over 90 clinical trials authorized by Health Canada are underway for the treatment of COVID-19. [1] [2] [3]

COVID-19 treatments authorized in Canada [4] [5] [6] [7] [8] [9]

Product name	Active ingredient(s)	Product type	Administration route	Company	Date of approval
Veklury	Remdesivir	Antiviral	Intravenous	Gilead Sciences Canada Inc.	July 27, 2020
Paxlovid	Nirmatrelvir Ritonavir	Antiviral	Oral	Pfizer Canada ULC	January 17, 2022
Bamlanivimab	Bamlanivimab	Monoclonal antibody	Intravenous	Eli Lilly Canada Inc.	November 20, 2020
Casirivimab & imdevimab	Casirivimab Imdevimab	Monoclonal antibody	Intravenous	Hoffmann-La Roche Limited	June 09, 2021
Sotrovimab	Sotrovimab	Monoclonal antibody	Intravenous	GlaxoSmithKline Inc	July 30, 2021

ANTIVIRAL TREATMENT

Veklury

Veklury is a broad-spectrum antiviral authorized for COVID-19 treatment in individuals ≥12 years (with body weight at least 40 kg) with pneumonia requiring supplemental oxygen. It is not authorized for use in youth <12 years or weighing <40 kg. [10] [11]

Remdesivir, the active ingredient in Veklury, was originally developed to treat hepatitis C and respiratory syncytial virus (RSV), and was subsequently investigated for Ebola virus disease, Middle Eastern respiratory syndrome virus (MERS-CoV), and Marburg virus[1] infections before being studied as a treatment for COVID-19. [12] [13]

Mechanism of action

Remdesivir interrupts production of the virus. Coronaviruses have genomes made up of ribonucleic acid (RNA). Remdesivir is a nucleotide analogue prodrug[2] that mimics

[1] Note these viruses are RNA viruses.

[2] A prodrug is a pharmacologically inactive substance that is converted in the body by metabolic processes (e.g., by enzymatic action) into a pharmacologically active drug. [64]

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adenosine, one of the building blocks of any RNA virus's genome. Drugs that act as nucleotide analogs interfere with the coronavirus's RNA polymerase, an essential enzyme the virus uses to replicate RNA, which prevents the virus from multiplying. [13] [14] [15] [16]

Ingredients
Medicinal ingredients:
- Remdesivir (100 mg/vial, 5 mg/mL when reconstituted)

Non-medicinal ingredients:
- Betadex sulfobutyl ether sodium
- Hydrochloric acid
- Sodium hydroxide [5]

Dosage
Recommended dosage:
- Day 1: single loading dose of 200 mg administered by intravenous (IV) infusion. Each infusion lasts 30 to 120 minutes.
- Day 2 onwards: 100 mg once daily via IV for at least 5 days.
- Treatment may extend up to a total of 10 days.
- No dose adjustment is required in individuals >65 years. [5] [10]

Efficacy
In a randomized, double-blind, placebo-controlled trial, among non-hospitalized individuals at high risk for COVID-19 progression, a 3-day course of remdesivir had an acceptable safety profile and resulted in an 87% lower risk of hospitalization or death than placebo, and an 81% lower risk of COVID-19-related medically attended visits or death than placebo. [17]

In a double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults hospitalized with COVID-19 with evidence of lower respiratory tract infection, those who received remdesivir had a median recovery time of 10 days, as compared with 15 days among those who received placebo. Recovery time was defined as being medically stable enough to be discharged from hospital.

Remdesivir also improved mortality rates for those receiving supplemental oxygen (4% with remdesivir versus 13% with placebo). All-cause mortality among all participants was 11% with remdesivir and 15% with placebo. However, this difference between treatment groups was not large enough to rule out chance.

The study also suggested remdesivir treatment may prevent individuals from progressing to more severe respiratory disease. Those treated with remdesivir were less likely to need high levels of respiratory support. Remdesivir appeared to most benefit individuals who were receiving supplemental oxygen.

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The findings show remdesivir alone was not sufficient treatment for all individuals but did provide some benefit. Studies are underway to evaluate remdesivir in combination with other therapies. [14] [18]

Contraindications

Remdesivir is contraindicated in:

- Individuals with an allergy to the drug or to any ingredient in the formulation, including any non-medicinal ingredient, or its container. [10] [11]

Warnings and precautions

Warnings and precautions with use of remdesivir administration include:

- Individuals with liver conditions. Some individuals develop increased transaminases (liver enzymes) during remdesivir treatment. Transaminase elevations have been observed in healthy volunteers and in individuals with COVID-19 who received remdesivir therapy. Transaminase elevations have been reported as a component of COVID-19, including in individuals receiving placebo in remdesivir clinical trials. Blood tests are performed prior and during treatment to monitor liver enzymes.
- Individuals with renal impairment. Blood tests are performed prior and during treatment to monitor kidney function.
- Remdesivir should be used during pregnancy only if the potential benefit justifies the potential risk for the pregnant individual and the fetus. There is limited data on the use of remdesivir in pregnant individuals.
- Data are not available on the presence of remdesivir in human milk, effects on breastfed infants, or effects on milk production. If a lactating individual potentially would derive benefit from treatment, the risks and benefits of initiating treatment should be discussed with the individual.
- Coadministration with chloroquine or hydroxychloroquine is not recommended due to risk of reduced antiviral activity.
- Remdesivir may affect the way certain medicines (e.g., theophylline, midazolam) work. [10] [19] [20]

Side effects

<u>Very common side effects</u> (may affect more than 1 in 10 individuals):

- Blood tests may show an increase in transaminases [5]

<u>Common side effects</u> (may affect up to 1 in 10 individuals):

- Headache
- Nausea
- Rash [5]

<u>Rare</u> (may affect up to 1 in 1000 individuals)

Symptoms of allergic reactions or reactions following administration may include:

- Hypotension or hypertension
- Tachycardia or bradycardia
- Hypoxia (low blood oxygen)
- Fever

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- Dyspnea, wheezing
- Angioedema (swelling of the face, lips, tongue, or throat)
- Rash
- Nausea
- Vomiting
- Diaphoresis (excessive, abnormal sweating)
- Shivering [5]

Paxlovid

Paxlovid is a SARS-CoV-2 protease inhibitor antiviral therapy. Paxlovid is indicated to treat mild to moderate COVID-19 in adults with a positive COVID-19 test, and high risk of severe disease progression, including hospitalization or death.

Conditions placing individuals at high risk for progression to severe COVID-19 include:
- Older age (≥60 years)
- Overweight (BMI >25)
- Current smoker
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease
- Hypertension
- Chronic lung disease (e.g., chronic obstructive pulmonary disease, moderate-to-severe asthma, interstitial lung disease, cystic fibrosis, pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (e.g., cerebral palsy, Down's syndrome) or other medically complex conditions (e.g., genetic or metabolic syndromes, severe congenital anomalies)
- Active cancer
- Individuals who received less than 3 doses of COVID-19 vaccination[3] [21] [22]

Paxlovid is not authorized:
- To treat individuals requiring hospitalization due to severe or critical COVID-19.
- For pre-exposure or post-exposure prophylaxis to prevent COVID-19.
- For use longer than 5 consecutive days.
- For use in individuals <18 years. Safety and effectiveness have not been established in pediatric individuals. [6] [21] [23]

Paxlovid consists of 2 medications co-packaged together:
- Nirmatrelvir – 150 mg (pink) tablet
- Ritonavir – 100 mg (white) tablet [21]

Both nirmatrelvir and ritonavir are protease inhibitors. Nirmatrelvir is a new drug. Ritonavir is an existing drug that is widely used in combination with other protease

[3] Refer to Episodes 15, 28, 34, 39, 40, 48, & 56 for additional information on COVID-19 vaccines.

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inhibitors in the therapy and prevention of human immunodeficiency virus (HIV) infection. Ritonavir is used as a pharmacokinetic boosting agent to boost the HIV protease inhibitor. In Paxlovid, nirmatrelvir is co-administered with ritonavir to increase nirmatrelvir concentrations to the target therapeutic range. [24] [25]

Mechanism of action

Overview of how protease inhibitors function:

- SARS-CoV-2 is a single strand of RNA wrapped in a protein envelope.
- RNA contains the genetic instructions the virus uses to replicate.
- When the virus invades a human cell, its RNA is translated into a polypeptide, a long protein chain that includes several enzymes necessary to continue replication.
- Before these enzymes can start working, they need to be separated from each other.
- Protease enzymes acts like scissors, cutting (cleaving) the polypeptide into the different enzymes to become functional.
- Protease inhibitor medications interfere with the cleaving step. These medications are designed to tightly bind to the protease enzyme, blocking its ability to cleave. [26]

Nirmatrelvir inhibits the virus from replicating by blocking the activity of the SARS-CoV-2-3CL protease, a critical enzyme the coronavirus needs to replicate. Nirmatrelvir inhibits viral replication at a stage known as proteolysis, which occurs before viral RNA replication. Coadministration with a low dose of ritonavir helps slow the metabolism or breakdown of nirmatrelvir by liver enzymes in order for it to remain active in the body for longer periods of time at higher concentrations to help combat the virus. [27] [28]

Ingredients [21]

Paxlovid	**Nirmatrelvir**	**Ritonavir**
Medicinal	Nirmatrelvir	Ritonavir
Non-medicinal	Colloidal silicon dioxide Croscarmellose sodium Lactose monohydrate Microcrystalline cellulose Sodium stearyl fumarate	Anhydrous dibasic calcium phosphate Colloidal silicon dioxide Copovidone Sodium stearyl fumarate Sorbitan monolaurate
Film-coating	Hydroxy propyl methylcellulose Iron oxide red Polyethylene glycol Titanium dioxide	Colloidal silicon dioxide Hydroxypropyl cellulose Hypromellose Polyethylene glycol Polysorbate 80 Talc Titanium dioxide

Dosage

Recommended dosage for Paxlovid is 300 mg nirmatrelvir (2 x 150 mg tablets) with 100 mg ritonavir (1 x 100 mg tablet). All 3 tablets are taken together orally twice daily for 5 days. Treatment should begin as soon as possible after confirmed COVID-19 diagnosis

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and within 5 days of symptom onset. Tablets can be taken with or without food and should be swallowed whole and not chewed, broken, or crushed. [21]

Efficacy
In a phase 2-3 double-blind, randomized, controlled clinical trial symptomatic, unvaccinated, nonhospitalized adults at high risk for severe disease progression were assigned to receive either 300 mg of nirmatrelvir, plus 100 mg of ritonavir (n=1120) or placebo (n=1126) every 12 hours for 5 days. Treatment of symptomatic COVID-19 with nirmatrelvir plus ritonavir resulted in an 89% reduction in the risk of hospitalization and death than placebo, without evident safety concerns. [29]

The clinical trials for Paxlovid took place before Omicron[4] became predominant. However, Pfizer has stated the drug works against the Omicron variant. To date, several *in vitro* studies show efficacy of Paxlovid is maintained against Omicron. These studies have not yet been published in peer-reviewed medical journals. [30] [31]

Contraindications
Paxlovid is contraindicated in individuals with a history of clinically significant hypersensitivity reactions to its active ingredients (nirmatrelvir or ritonavir) or any other components of the product.

There are over 30 medications (prescription and over-the-counter) that are contraindicated with concomitant use with Paxlovid and may cause serious or life-threatening side effects. Some medications may lead to faster breakdown of Paxlovid significantly reducing plasma concentrations, which may result in loss of its therapeutic effect and possible development of viral resistance. Paxlovid cannot be started immediately after discontinuing some of these medications because their effects remain after discontinuation.[5]

Paxlovid is not recommended in individuals with severe renal or hepatic impairment. [6] [21] [32]

Serious warnings and precautions
Paxlovid has serious warnings and precautions stating individuals with moderate renal impairment should take only 1 tablet of nirmatrelvir with the tablet of ritonavir every 12 hours.

The potential for drug interactions prior to and during Paxlovid therapy must be considered. Review concomitant medications before Paxlovid therapy and monitor for adverse reactions associated with the concomitant medication use during Paxlovid treatment (e.g., increased or decreased medication effects). [21]

Warnings and precautions
Warnings and precautions with the use of Paxlovid include:

[4] Refer to Episode 52 for additional information on the Omicron variant.
[5] Refer to the drug monograph for the full list of contraindicated medications.

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- Caution should be exercised with administration of Paxlovid to individuals with preexisting liver diseases, liver enzyme abnormalities, or hepatitis because clinical hepatitis and jaundice have occurred with receipt of ritonavir.
- Caution should be exercised when administering Paxlovid in individuals with HIV. Paxlovid may lead to HIV becoming resistant to some antiretroviral medications if the individual is living with HIV and is not on antiretroviral medication.
- Use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Effective alternative contraception should be utilized during treatment with Paxlovid.
- Paxlovid should not be used in pregnant individuals unless the potential benefits outweigh the potential risks to the fetus.
- There are no available data on the presence of nirmatrelvir in human or animal milk, or its effects on the breastfed infant or milk production. Limited published data reports ritonavir is present in human milk. There is no information on the effects of ritonavir on the breastfed infant or on milk production. If a lactating individual potentially would derive benefit from treatment, the risks and benefits of initiating treatment should be discussed with the individual. [6] [21] [22] [33]

Side effects
Most common side effects of Paxlovid include:
- Dysgeusia
- Diarrhea
- Myalgia
- Hypertension [6] [25]

MONOCLONAL ANTIBODIES[6]
Bamlanivimab
Bamlanivimab is a neutralizing immunoglobulin G1 (IgG1) monoclonal antibody directed against the SARS-CoV-2 spike protein. It is indicated for the treatment of adults and youth (≥12 years weighing ≥40 kg) with mild to moderate COVID-19, who are at high risk of progressing to severe illness and/or hospitalization. [34] [35]

Conditions placing individuals at high risk for progression to severe COVID-19 and/or hospitalization include:
- Older age (≥60 years)
- Body mass index (BMI) ≥35 for individuals ≥18 years
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or receiving immunosuppressive treatment
- ≥55 years and have:
    - Cardiovascular disease,

[6] Refer to Episode 52 for additional information on monoclonal antibodies.
Monoclonal antibodies are produced by B cells (type of white blood cell) when exposed to an antigen (e.g., virus, bacteria). This is part of humoral or antibody-mediated immunity. Monoclonal antibodies can be laboratory-produced by exposing B cells to a particular viral protein, which is then cloned to mass produce antibodies to target that virus. Refer to Episodes 44 & 45 for additional information on antibodies, antigens, B cells, and humoral immunity.

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    - Hypertension, or
    - Chronic obstructive pulmonary disease or other chronic respiratory disease

- 12 to 17 years and have:
    - BMI ≥85th percentile for their age and gender
    - Sickle cell disease
    - Congenital or acquired heart disease
    - Neurodevelopmental disorders (e.g., cerebral palsy)
    - Medical-related technological dependence (e.g., tracheostomy, gastrostomy, or positive pressure ventilation not related to COVID-19)
    - Asthma, reactive airway, or other chronic respiratory disease requiring daily medication for control [34] [36]

Bamlanivimab is not recommended in individuals hospitalized with severe COVID-19. This recommendation was based on clinical trial data suggesting bamlanivimab was unlikely to help individuals hospitalized with COVID-19 recover from advanced stages of the disease. Bamlanivimab may be associated with worse clinical outcomes when administered to hospitalized individuals with COVID-19 requiring high-flow oxygen or mechanical ventilation. [34] [36] [37]

Mechanism of action
Bamlanivimab is a neutralizing IgG1 monoclonal antibody directed against the spike protein of SARS-CoV-2. The monoclonal antibody blocks the attachment of the spike protein to human angiotensin-converting enzyme 2 (ACE2) receptors preventing subsequent viral entry into human cells and viral replication. [36]

Ingredients
Medicinal ingredients:
- Bamlanivimab

Non-medicinal ingredients:
- L-histidine
- L-histidine hydrochloride monohydrate
- Polysorbate 80
- Sodium chloride
- Sucrose
- Water for injection [7] [34]

Dosage
Bamlanivimab is formulated as a solution for IV infusion (35 mg/mL). The recommended dose is a single infusion of 700 mg administered as soon as possible after a positive COVID-19 test and within 10 days after onset of clinical signs and symptoms of infection. Bamlanivimab is diluted with 0.9% sodium chloride immediately before administration. Infusion takes at least 1 hour. [7] [34] [35]

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Efficacy
A randomized, double-blind, placebo-controlled, single-dose clinical trial was conducted at 41 centres in the United States. Participants (n=452) were aged ≥18 years, non-hospitalized, with positive SARS-CoV-2 test results, and 1 or more mild or moderate symptoms (e.g., fever, cough, sore throat, malaise, headache, myalgia (muscle aches), GI symptoms, shortness of breath with exertion). Participants received 700 mg, 2800 mg, or 7000 mg of bamlanivimab, or placebo within a median of 4 days after symptom onset.

The proportions of participants requiring hospitalization or emergency room visits within 28 days after treatment were approximately:
- 1% for 700 mg
- 2% for 2800 mg
- 2% for 7000 mg
- 6% for placebo

For participants at high-risk for disease progression, the proportions of individuals requiring hospitalization or emergency room visits were approximately:
- 2% for 700 mg
- 2% for 2800 mg
- 4% for 7000 mg
- 10% for placebo

These data suggest reduction in the rate of hospitalizations and emergency room visits observed between placebo and bamlanivimab groups was mainly driven by those at high risk of progressing to severe COVID-19 or hospitalization.

From days 2 to 6, participants who received bamlanivimab had a slightly lower severity of symptoms compared to placebo. The change from baseline symptoms continued to be better in the bamlanivimab group than the placebo group from day 7 to 11, although by these time points most participants in the 2 groups had fully recovered or had only very mild symptoms. The median time for symptom improvement was 6 days for bamlanivimab group, as compared with 8 days for placebo group.

The safety profile of bamlanivimab was similar to that of the placebo group. The data indicated treatment with bamlanivimab was safe. [34] [36] [38]

Contraindications
Bamlanivimab is contraindicated in individuals with hypersensitivities to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. [34]

Warnings and precautions
Warnings and precautions of bamlanivimab treatment include:

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- Certain circulating SARS-CoV-2 viral variants[7] may be associated with resistance to bamlanivimab. Consequently, there is a potential risk for treatment failure. Use of bamlanivimab alone should only be considered if other monoclonal antibodies that retain neutralization activity against prevalent variants are not available.
- Clinical worsening of COVID-19 24 hours after administration has been reported. Signs or symptoms may include fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to bamlanivimab or COVID-19 progression.
- Serious hypersensitivity and/or anaphylactic reactions have occurred with administration of bamlanivimab.
- Infusion-related reactions have been observed with administration of bamlanivimab. These reactions may be severe or life threatening. Signs and symptoms of infusion-related reactions may include urticaria, pruritis, rash, angioedema, and chest discomfort.
- Bamlanivimab should only be used during pregnancy if the potential benefit outweighs the potential risk for the pregnant individual and the fetus. There is insufficient data to evaluate a drug-associated risk to the pregnant individual or the fetus.
- There are no available data on the presence of bamlanivimab in human or animal milk, or its effects on the breastfed infant or milk production. If a lactating individual potentially would derive benefit from treatment, the risks and benefits of initiating treatment should be discussed with the individual.
- The safety and efficacy of bamlanivimab in children have not been established. However, treatment may be considered in adolescents ≥12 years who weigh ≥40 kg and are at high risk of developing severe COVID-19 and/or hospitalization because:
    - The mechanism of action of bamlanivimab is directed against the virus and not the host response to the SARS-CoV-2 infection.
    - Bamlanivimab has an acceptable safety profile in treating adults who weigh at least 40 kg. Close monitoring of adolescents receiving treatment is highly recommended. [34] [39]

Side effects

Possible side effects of bamlanivimab may include:

- Allergic reactions during and after infusion, such as:
    - Fever, chills, nausea, headache, shortness of breath, hypotension, wheezing, angioedema, rash including hives, itching, myalgia, and dizziness.
- New or worsening symptoms after infusion, such as:
    - Fever, difficulty breathing, tachycardia or bradycardia, tiredness, weakness or confusion. If these occur, immediate medical attention should be sought as some of these events have required hospitalization. It is unknown if these events were related to treatment or due to disease progression.

Side effects of receiving any medication intravenously may include:

[7] Refer to Episodes 39 & 52 for additional information on SARS-CoV-2 variants.

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- Brief pain, bleeding, bruising, soreness, swelling, and possible infection at the infusion site.

All possible side effects are unknown because of the population size who have received treatment. Bamlanivimab is still being studied so it is possible all risks are not known at this time.

It is possible bamlanivimab may:
- Interfere with the body's ability to fight off a future SARS-CoV-2 infection.
- Reduce the immune response to a COVID-19 vaccine. [7] [34]

Casirivimab & imdevimab

Casirivimab and imdevimab are monoclonal antibodies against SARS-CoV-2 spike protein.

Casirivimab and imdevimab are administered together to treat mild to moderate COVID-19, confirmed by SARS-CoV-2 testing, in adults and adolescents (≥12 years and weighing at least 40 kg) who are at high risk for hospitalization and/or death.

Casirivimab and imdevimab are not authorized for use in individuals who:
- Are hospitalized due to COVID-19; or
- Require oxygen therapy due to COVID-19; or
- Require increase oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to non-COVID-19-related comorbidity; or
- Are younger than 12 years of age or weighing <40 kg. [40] [41]

Currently, Health Canada and the Ontario COVID-19 Science Table[8] do not recommend the use of casirivimab and imdevimab to treat COVID-19 for any severity of illness due to lack of neutralizing activity against the Omicron variant. [42] [43]

Mechanism of action

Casirivimab and imdevimab are 2 non-competing immunoglobulin G1 (IgG1 variant) monoclonal antibodies that bind to the receptor-binding domain of the spike glycoprotein of SARS-CoV-2. This action neutralizes virus infectivity by blocking the virus from binding to ACE2 receptors. [41]

Ingredients

Medicinal ingredients:
- Casirivimab
- Imdevimab

Non-medicinal ingredients:
- L-histidine

[8] The Ontario COVID-19 Science Advisory Table is a group of scientific experts and health system leaders who evaluate and report on emerging evidence to inform Ontario's response to the COVID-19 pandemic. [65]

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- L-histidine monohydrochloride monohydrate
- Polysorbate 80
- Sucrose
- Water for injection [40]

Dosage
Casirivimab (1200 mg) and imdevimab (1200 mg) are administered together as a single IV infusion. Administration takes a least 1 hour and individuals should be monitored for 1 hour after infusion. Casirivimab and imdevimab is diluted before administration utilizing an infusion bag containing 250 mL 0.9% Sodium Chloride Injection. [8] [40]

Efficacy
A multicenter, double-blind, randomized, placebo-controlled, phase 3 clinical trial evaluated the efficacy of the combination of casirivimab and imdevimab in the treatment of outpatients with COVID-19 infection at risk for progression to severe disease. Participants were assigned to receive either 2400 mg or 1200 mg of treatment or placebo.

For the 2400 mg group versus placebo, there was a 71% reduction in hospitalization or death up to day 29. For the 1200 mg group versus placebo, there was a similar result with a 70% reduction. Resolution of COVID-19 symptoms was 4 days shorter with either dose compared to placebo.

Serious adverse events occurred more frequently in the placebo group (4%) versus the treatment groups (1200 mg [1%] and 2400 mg [1%]). [44]

Contraindications
Casirivimab and imdevimab are contraindicated in individuals with hypersensitivity to these drugs or any ingredient in the formulations, including any non-medicinal ingredients, or component of the container. [40]

Warnings and precautions
Warnings and precautions for casirivimab and imdevimab include:
- Serious hypersensitivity reactions, including anaphylaxis, have been reported with administration of the combination of casirivimab and imdevimab.
- Infusion-related reactions have been reported with IV administration of casirivimab and imdevimab therapy. These reactions may be severe or life-threatening.
- Circulating SARS-CoV-2 variants may be associated with resistance to monoclonal antibodies such as casirivimab and/or imdevimab. Consequently, there is a potential risk for treatment failure.
- There are limited data from the use of casirivimab with imdevimab in pregnant individuals. Casirivimab and imdevimab treatment should only be used during pregnancy if the potential benefit justifies the potential risk for the pregnant individual and fetus.
- There are no available data on the presence of casirivimab and/or imdevimab in human or animal milk, or the effects on the breast-fed infant or on milk production. If

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a lactating individual potentially would derive benefit from treatment, the risks and benefits of initiating treatment should be discussed with the individual.
- Casirivimab and imdevimab treatment is not authorized for use in children <12 years or adolescents weighing <40 kg. [40]

Side effects
Possible side effects of casirivimab and imdevimab may include:
- Allergic reactions or reactions following infusion such as:
  - Fever, chills, stomach pain, nausea, vomiting, headache, altered mental status, difficulty breathing, chest tightness, abdominal pain, decrease or increase in blood pressure, red face or swelling of the face, throat irritation, rash with hives, itching, tachycardia or bradycardia, myalgia, light-headedness, arrhythmia, low oxygen saturation, increased sweating.
- New or worsening symptoms after infusion such as:
  - Fever, difficulty breathing, tachycardia or bradycardia, tiredness, weakness, or confusion. If these occur, immediate medical attention should be sought as some of these events have required hospitalization. It is unknown if these events are related to treatment or due to disease progression.

Side effects of receiving any medication intravenously may include:
- Brief pain, bleeding, bruising, soreness, swelling, and possible infection at the infusion site.

It is possible casirivimab and imdevimab may:
- Interfere with the body's ability to fight off a future SARS-CoV-2 infection.
- Reduce the immune response to a COVID-19 vaccine. [8] [40]

Sotrovimab
Sotrovimab is a monoclonal antibody against the SARS-CoV-2 spike protein. Sotrovimab is authorized to treat mild to moderate COVID-19, confirmed by SARS-CoV-2 testing, in adults and adolescents (≥12 years weighing at least 40 kg) at high risk for progressing to hospitalization and/or death.

Sotrovimab is not authorized for use in individuals who:
- Are hospitalized due to COVID-19, or
- Require oxygen therapy due to COVID-19, or
- Require an increase oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to a non-COVID-19-related comorbidity.
- Are <12 years of age or weigh less than 40 kg.

Sotrovimab treatment has not shown benefit to individuals hospitalized due to COVID-19. Anti-SARS-CoV-2 monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized individuals with COVID-19 requiring high-flow oxygen or mechanical ventilation. [45] [46]

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Mechanism of action
Sotrovimab is a fully human immunoglobulin G (IgG1) monoclonal antibody directed against SARS-CoV-2. It binds to a highly conserved epitope on the receptor-binding domain of the SARS-CoV-2 spike protein, thus blocking viral entry into host cells. [46]

The monoclonal antibody binds to an epitope on SARS-CoV-2 that is shared with SARS-CoV-1 (the virus that causes SARS), indicating the epitope is highly conserved, which may make it more difficult for resistance to develop. [47]

Ingredients
Medicinal ingredients:
- Sotrovimab

Non-medicinal ingredients:
- L-histidine
- L-histidine monohydrochloride
- L-methionine
- Sucrose
- Polysorbate 80
- Water for injection [45]

Dosage
Sotrovimab (500 mg) is administered as a single IV infusion. Administration takes a least 1 hour and individuals should be monitored for 1 hour after infusion. Sotrovimab is diluted prior to administration utilizing a 100 mL infusion bag containing 0.9% Sodium Chloride Injection or 5% dextrose for injection. [9]

Efficacy
In a multicenter, double-blind, phase 3 clinical trial, nonhospitalized individuals with symptomatic COVID-19 (≤5 days after symptom onset) and at least 1 risk factor for disease progression were randomly assigned to receive a single infusion of sotrovimab (500 mg) or placebo. For this interim analysis, participants were recruited on August 27, 2020, and were followed through March 4, 2021, at 37 trial sites in 4 countries (United States, Canada, Brazil, Spain).

For the sotrovimab group, 1% had disease progression leading to hospitalization as compared to 7% in the placebo group. The relative risk reduction in hospitalization (for >24 hours) or death between sotrovimab group and placebo was 85%. Among those who were hospitalized, none of the sotrovimab group were admitted to ICU, as compared with 5 individuals who received placebo, suggesting sotrovimab prevented more severe COVID-19 complications in addition to preventing hospitalization. Overall, no safety signals were identified in this trial. [48]

Contraindications
Sotrovimab is contraindicated in individuals with hypersensitivity to this drug or to any ingredient in the formulation, including any non-medicinal ingredients, or component of the container. [46] [47]

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Warnings and precautions
Warnings and precautions for sotrovimab include:

- Serious hypersensitivity reactions, including anaphylaxis, have been reported with sotrovimab administration.
- Infusion-related reactions have been reported with sotrovimab IV administration. These reactions may be severe or life threatening. Signs and symptoms of infusion-related reactions may include fever, difficulty breathing, reduced oxygen saturation, chills, nausea, arrhythmia (e.g., atrial fibrillation, tachycardia, bradycardia), headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, dizziness, fatigue, and diaphoresis.
- Circulating SARS-CoV-2 variants may be associated with resistance to monoclonal antibodies such as sotrovimab. Consequently, there is a potential risk for treatment failure.
- There are insufficient data to evaluate the effects of sotrovimab in pregnant individuals. Sotrovimab treatment should only be used during pregnancy if the potential benefit justifies the potential risk for the pregnant individual and fetus.
- There are insufficient data on the presence of sotrovimab in human milk, or its effects on the breastfed infant or milk production. If a lactating individual potentially would derive benefit from treatment, the risks and benefits of initiating treatment should be discussed with the individual.
- Sotrovimab is not authorized for use in individuals ≤12 years or weighing less than 40 kg. [45]

Side effects
Possible side effects of sotrovimab may include:

- Diarrhea
- Rare serious reactions following infusion such as:
    - Fever, chills, nausea, headache, difficulty breathing, chest tightness, fall or increase in blood pressure, angioedema, throat irritation, rash with hives, itching or an itchy rash, myalgia, arrhythmia, low oxygen in blood, increased sweating, dizziness or light headedness.

Side effects of receiving any medication intravenously may include:

- Brief pain, bleeding, bruising, soreness, swelling, and possible infection at the infusion site.

All possible side effects of are unknown because of the population size who have received treatment.

It is possible sotrovimab may:

- Interfere with the body's ability to fight off a future SARS-CoV-2 infection.
- Reduce the immune response to a COVID-19 vaccine. [9] [45]

Recommended drugs and biologics in adults with COVID-19
The Ontario COVID-19 Science Advisory Table created a clinical practice guideline summary for the treatment of adults with COVID-19 who are mildly to critically ill:

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- Mildly ill – Individuals who do not require new or additional supplemental oxygen from their baseline status.
- Moderately ill – Individuals newly requiring low-flow supplemental oxygen.
- Critically ill – Individuals requiring ventilatory and/or circulatory support, including high-flow nasal oxygen, non-invasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).[9]

In the current edition of the summary, dated February 23, 2022, several medications (i.e., dexamethasone, tocilizumab, baricitinib, fluvoxamine, budesonide) are listed for the treatment of COVID-19, in addition to medications authorized by Health Canada (i.e., Veklury [remdesivir], sotrovimab, and Paxlovid [nirmatrelvir/ritonavir]). [43]

Dexamethasone is a glucocorticoid (corticosteroid) used to reduce inflammation and decrease immune response. It is used to treat many conditions including arthritis, allergic reactions, cancer, and asthma.

SARS-CoV-2 triggers an overreaction of the immune system in some individuals that can result in severe injury to a number of organs, including the lungs, heart, and kidneys. In a clinical trial, dexamethasone (6 mg daily for up to 10 days) was shown to modulate inflammation-mediated lung injury and thereby reduced the risk of death in hospitalized individuals with COVID-19 who required supplemental oxygen and/or mechanical ventilation. It also reduced the need for future mechanical ventilation in hospitalized individuals with COVID-19 who required supplemental oxygen. It is not recommended in mildly ill individuals. [49] [50]

Tocilizumab is an interleukin (IL-6)[10] receptor antagonist that is used to treat rheumatoid arthritis and other rheumatologic conditions. Tocilizumab reduces the need for mechanical ventilation and the progression to mechanical ventilation or death in hospitalized individuals with COVID-19, with no increase in serious adverse events.

Tocilizumab should be used in hospitalized individuals who are moderately or critically ill with suspected or confirmed COVID-19 who are on recommended doses of dexamethasone (or another dose-equivalent corticosteroid) and are within 14 days of hospital admission or within 14 days of a new COVID-19 diagnosis if acquired in a healthcare setting.

Moderately ill individuals should have additional evidence of systemic inflammation (i.e., C-reactive protein (CRP) of ≥75 mg/L), and have disease progression (i.e., increasing oxygen or ventilatory requirements) while on dexamethasone or another dose-equivalent corticosteroid for COVID-19 treatment. [43] [51]

Baricitinib is a Janus-associated kinase (JAK) inhibitor. Baricitinib works by blocking Janus kinase, a signaling protein involved in the inflammatory response to infections,

[9] In extracorporeal membrane oxygenation (ECMO), blood is pumped outside of the body to a heart-lung machine that removes carbon dioxide and returns the oxygenated blood back to tissues in the body.
[10] Refer to Episodes 44 & 45 for additional information on interleukins and the immune system.

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such as COVID-19. It may also directly inhibit the virus from entering the body's cells. Baricitinib reduces mortality and may reduce progression to mechanical ventilation in individuals with COVID-19, with no increase in serious adverse events.

Baricitinib should be used in moderately ill individuals and critically ill hospitalized individuals with COVID-19 who are on recommended doses of dexamethasone (or another dose-equivalent corticosteroid) or who have a contraindication to corticosteroids. [52]

Fluvoxamine is a selective serotonin reuptake inhibitor (SSRI) used to treat depression and anxiety. Fluvoxamine affects the sigma-1 receptor that controls inflammation and may reduce inflammation in COVID-19. Fluvoxamine should be offered preferentially to individuals at higher risk of severe disease or complications from COVID-19, who are not yet on supplemental oxygen, and who are within 7 days of symptom onset. Fluvoxamine should not replace outpatient therapies with a higher effectiveness, such as sotrovimab and remdesivir. [43] [53] [54]

Budesonide is an inhaled corticosteroid that has been shown to shorten duration of symptoms for high-risk outpatients with COVID-19. It has not been shown to reduce the risk of hospitalization or other serious outcomes. [53]

Treatments not recommended

The following therapies for treatment of COVID-19 are not recommended in individuals with any severity of illness due to lack of benefit, potential harm, and system implications of overuse:

- Antibiotics (azithromycin) [43]
    - Previous evidence has suggested azithromycin has anti-inflammatory and antiviral properties. However, research has found no benefit of using azithromycin for treatment of COVID-19. Antibiotic stewardship is important as inappropriate antibiotic use leads to increased antimicrobial resistance. [55] [56] [57]
- Casirivimab-imdevimab is currently not recommended due to lack of neutralizing activity against the Omicron variant. [43] [42]
- Hydroxychloroquine or chloroquine is not approved by Health Canada or US Food & Drug Administration (FDA) for the treatment of COVID-19. [58] [59]
    - Chloroquine and hydroxychloroquine are approved prescription medications to treat malaria and certain autoimmune diseases, including lupus and rheumatoid arthritis.
    - A systematic review and meta-analysis of blinded, placebo-controlled, randomized clinical trials showed no clinical benefits of hydroxychloroquine for pre-and post-exposure prophylaxis and treatment of non-hospitalized and hospitalized individuals with COVID-19. [60]
- Ivermectin is not approved by Health Canada or FDA for the treatment of COVID-19. [43] [61] [62]
    - Ivermectin (veterinary or human versions) is an antiparasitic agent. Ivermectin approved for human uses can interact with other medications (e.g., blood-thinners) and overdose with ivermectin is possible. Overdose can cause

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nausea, vomiting, diarrhea, hypotension, allergic reactions (itching and hives), dizziness, ataxia, seizures, coma, death. The veterinary version of ivermectin can be dangerous for humans and can cause serious health problems (e.g., vomiting, diarrhea, hypotension, allergic reactions, dizziness, seizures, coma, death). The veterinary version has a higher concentrated dose than ivermectin products for humans and can be highly toxic in humans. [61] [62]

- Lopinavir-ritonavir [43]
    - In a randomized clinical trial, lopinavir-ritonavir did not show any significant benefit for decreasing COVID-19-associated hospitalization or other secondary clinical outcomes. [63]

Additional treatments currently not recommended

As per the Ontario COVID-19 Science Table, there is insufficient evidence to support the use of the following therapies to treat COVID-19 in individuals with any severity of illness outside of clinical trials or where other indications would justify their use:

- Colchicine (used to treat gout)
- Interferon (with or without lopinavir-ritonavir and ribavirin)
- Vitamin D[11] [43]

Take home messages

- Vaccination remains a key part of prevention, even as more COVID-19 treatments become available.
- Circulating SARS-CoV-2 variants may become resistant to monoclonal antibodies leading to treatment failure, further stressing the importance of vaccination and following public health measures.
- It is important for oral health professionals to be aware of COVID-19 treatment and contraindications to be able to educate their clients, act as a resource, and provide optimism.

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