

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

P^rSotrovimab for injection

Solution for infusion, 500 mg/8 mL (62.5 mg/mL) single use vial

ATC Classification: Specific Immunoglobulin
(Anti-SARS-CoV-2 spike protein monoclonal antibody)

HEALTH CANADA HAS AUTHORIZED THE SALE OF THIS COVID-19 DRUG BASED ON LIMITED CLINICAL TESTING IN HUMANS AND/OR QUALITY INFORMATION

Sotrovimab is indicated for the treatment of mild to moderate coronavirus disease 2019 (COVID-19), confirmed by direct SARS-CoV-2 viral testing, in adults and adolescents (12 years of age and older weighing at least 40 kg) who are at high risk for progressing to hospitalization and/or death.

The use of sotrovimab is permitted under an interim authorization delivered in accordance with section 5 of the COVID-19 Interim order (IO)*, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. The interim authorization is associated with Terms and Conditions that need to be met by the sponsor to ascertain the continued quality, safety and efficacy of the product. For further information on authorization under this pathway, please refer to Health Canada's IO Respecting the Importation, Sale and Advertising of Drugs for Use in Relation to COVID-19.

* <https://www.canada.ca/en/health-canada/services/drugs-health-products/covid19-industry/drugsvaccines-treatments/interim-order-import-sale-advertising-drugs.html#a2.8>

Circulating SARS-CoV-2 viral variants may be associated with resistance to monoclonal antibodies. Health professionals should routinely review the Antiviral Resistance information in Section 15 MICROBIOLOGY, in conjunction with literature, for details regarding specific variants and resistance.

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RECENT MAJOR LABEL CHANGES

None.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Sotrovimab is indicated for the treatment of mild to moderate coronavirus disease 2019 (COVID-19), confirmed by direct SARS-CoV-2 viral testing, in adults and adolescents (12 years of age and older weighing at least 40 kg) who are at high risk for progressing to hospitalization and/or death.

Sotrovimab is not authorized for use in patients:

- who are hospitalized due to COVID-19, OR
- who require oxygen therapy due to COVID-19, OR
- who require an increase in baseline oxygen flow rate due to COVID-19 (in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity).

Treatment with sotrovimab has not been shown to benefit patients hospitalized due to COVID-19. SARS CoV-2 monoclonal antibodies may be associated with worse clinical outcomes when administered to hospitalized patients with COVID-19 requiring high flow oxygen or mechanical ventilation.

Circulating SARS-CoV-2 viral variants may be associated with resistance to monoclonal antibodies. Health professionals should routinely review the Antiviral Resistance information in Section [15 MICROBIOLOGY](#), in conjunction with literature, for details regarding specific variants and resistance, which may be updated regularly.

1.1 Pediatrics (12 years of age and older weighing at least 40 kg)

Sotrovimab is not authorized for use in patients younger than 12 years of age or adolescents weighing less than 40 kg. The safety and efficacy (effectiveness) of sotrovimab have not been assessed in pediatric patients (< 18 years of age). The recommended dosing regimen in patients 12-17 years of age, weighing at least 40 kg, is expected to result in comparable serum exposures of sotrovimab as those observed in adults based on an allometric scaling approach (which accounted for the effect of body weight changes associated with age on clearance and volume of distribution). Close monitoring in this patient population is highly recommended.

1.2 Geriatrics

No dosage adjustment is required in patients over 65 years of age (see [10.3 Pharmacokinetics – Special Populations and Conditions](#)).

2 CONTRAINDICATIONS

Sotrovimab is contraindicated in those who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see [6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING](#).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing considerations

Sotrovimab must be diluted prior to administration. For instructions on dilution of the medicinal product before administration, see [4.3 Reconstitution](#). Sotrovimab should be prepared and administered by a qualified healthcare professional.

Sotrovimab is administered as a single intravenous (IV) infusion and must not be administered as an intravenous push or bolus.

Sotrovimab should only be administered in settings in which health care providers have immediate access to medications to treat a severe reaction, such as severe infusion reaction or anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary. Patients should be monitored during and for at least 1 hour after administration of sotrovimab.

Sotrovimab should be administered to patients with mild/moderate COVID-19 as soon as possible after the onset of symptoms and confirmation of disease by a positive result obtained using a direct SARS-CoV-2 validated testing method.

Patient Selection

Sotrovimab is authorized for the treatment of patients with mild to moderate COVID-19 infection at high risk of hospitalization and/or death. To aid in determining the risk of hospitalization or death, prescribers should consider national or international guidelines. For example, the Public Health Agency of Canada, at:

<https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/guidance-documents/signs-symptoms-severity.html>

In the pivotal trial of sotrovimab in ambulatory patients with mild to moderate COVID-19, high risk was defined as any patient who met at least one of the following criteria:

- Advanced age (55 years of age or older), irrespective of comorbidities.
- 18 years of age or older AND presence of one or more of the following comorbidities:
 - diabetes (requiring medication)
 - obesity (BMI > 30 kg/m²)
 - chronic kidney disease (i.e., eGFR < 60 by MDRD)
 - congestive heart failure (NYHA class II or more)
 - chronic obstructive pulmonary disease (history of chronic bronchitis, chronic obstructive lung disease, or emphysema with dyspnea on physical exertion)
 - moderate to severe asthma (participant requires an inhaled steroid to control symptoms or has been prescribed a course of oral steroids in the past year)

4.2 Recommended Dose and Dosage Adjustment

The recommended dose is 500 mg sotrovimab administered as a single intravenous infusion.

Pediatrics (12 years of age and older, weighing at least 40 kg)

No dosage adjustment is required in pediatric patients who are 12 years of age or older and weigh at least 40 kg. Sotrovimab is not recommended for pediatric patients who are younger than 12 years of age or who weigh less than 40 kg (see [10.3 Pharmacokinetics – Special Populations and Conditions](#)).

Geriatrics

The pharmacokinetics of sotrovimab have not been quantified in patients aged 65 years or older. However, a dosage adjustment is not expected to be necessary based on experience with other monoclonal antibodies. In clinical trials, no dosage adjustment was made for patients 65 years of age or older (see [10.3 Pharmacokinetics – Special Populations and Conditions](#)).

Pregnant or breast-feeding women

No dosage adjustment is recommended in pregnant or breast-feeding women (see [7.1.1 Pregnant Women](#) and [7.1.2 Breast-feeding](#)).

Renal impairment

No dose adjustment is required in patients with renal impairment (see [10.3 Pharmacokinetics – Special Populations and Conditions](#)).

Hepatic impairment

The effects of hepatic impairment on the pharmacokinetics (PK) of sotrovimab have not been evaluated. It is unknown whether hepatic impairment affects the PK of sotrovimab (see [10.3 Pharmacokinetics – Special Populations and Conditions](#)).

4.3 Reconstitution

No reconstitution of sotrovimab is required. A diluted infusion solution must be prepared using aseptic technique:

Instructions for Preparation

- 1) Gather the materials for preparation:
 - Polyvinyl chloride (PVC) or polyolefin (PO), sterile prefilled 100 mL infusion bag containing 0.9% Sodium Chloride Injection or 5% dextrose for injection.
 - One vial of sotrovimab (500 mg/8 mL).
- 2) Remove one vial of sotrovimab from refrigerated storage and allow to equilibrate to room temperature, protected from light, for at least 15 minutes.
- 3) Visually inspect the vial to ensure it is free from particulate matter and that there is no visible damage to the vial. Should either be observed, the solution must be discarded, and fresh solution prepared. Sotrovimab is a clear, colourless or yellow to brown solution.
- 4) Gently swirl the vial several times before use without creating air bubbles. Do not shake or vigorously agitate the vial.

- 5) Withdraw 8 mL from an infusion bag containing 100 mL of sodium chloride 9 mg/mL (0.9%) solution for injection or 5% dextrose for injection.
- 6) Withdraw 8 mL from the vial of sotrovimab.
- 7) Inject the 8 mL of sotrovimab into the infusion bag via the septum.
- 8) Discard any unused portion left in the vial as the product contains no preservative. The vial is single use only and should only be used for one patient.
- 9) Prior to the infusion, gently rock the infusion bag back and forth 3 to 5 times. Do not invert the infusion bag. Avoid forming air bubbles.
- 10) This product contains no preservative; and therefore, the diluted infusion solution should be administered immediately. If immediate administration is not possible, store the diluted solution of sotrovimab up to 6 hours at room temperature (up to 25°C) or refrigerated up to 24 hours (2°C to 8°C).

4.4 Administration

Sotrovimab is only to be administered as a single intravenous (IV) infusion. Sotrovimab must be administered by a qualified health professional using aseptic technique.

- Gather the recommended materials for infusion:
 - Polyvinyl chloride (PVC) or polyolefin (PO) infusion set;
 - A 0.2 micron polyethersulfone (PES) filter is recommended.
- Attach the infusion set to the IV bag using standard bore tubing.
- Prime the infusion set.
- Administer as an IV infusion over 60 minutes at room temperature. Do not administer as an IV push or bolus.
- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of sotrovimab with IV solutions and medications other than 0.9% sodium chloride solution and 5% dextrose for injection is not known.
- Administer the entire infusion solution, at a rate of 100 mL/hr, in the bag via pump or gravity through an intravenous line containing a sterile, in-line or add-on 0.2-micron polyethersulfone (PES) filter. Due to potential overfill of prefilled bags, the entire infusion solution in the bag should be administered to avoid underdosage.
- The infusion rate should be slowed or stopped if the patient develops an infusion reaction, and appropriate supportive care provided (see 2 Contraindications, and 7 Warnings and Precautions, Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions).
- The patient should be clinically monitored during drug administration and for 1 hour after infusion of sotrovimab is completed. (see 7 Warnings and Precautions, Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions).
- There may be unforeseen scenarios that may lead to an infusion being paused, other than for an infusion related reaction (IRR) or other drug-related adverse event (AE). Examples may include local infusion site extravasation or IV-line blockade which may be caused by patient upper limb movements, improper IV access or malfunctioning of IV hardware. Based on the knowledge that sotrovimab is not anticipated to cause local irritation based on its chemical properties, it is recommended that healthcare professionals follow local guidelines and medical judgment in the event of a slow-down or pause in the administration of sotrovimab for reasons other than IRRs or other drug-related adverse events. The infusion may be resumed based on the medical judgement

of the healthcare provider, keeping in mind that diluted solutions of sotrovimab may be stored at room temperature up to 6 hours, and following the other instructions in the Product Monograph.

5 OVERDOSAGE

There is no specific antidote for an overdose with sotrovimab. If overdose occurs, the patient should be treated supportively with appropriate monitoring as necessary.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognize the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 1. Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	Solution for intravenous infusion after dilution / 500 mg/8 mL (62.5 mg/mL)	• L-histidine • L-histidine monohydrochloride • L-methionine • polysorbate 80 • sucrose • water for injection

Sotrovimab is supplied in a single-use glass vial with a rubber stopper (not made with natural rubber latex) and flip-off aluminium over-seal. Each carton contains one vial.

7 WARNINGS AND PRECAUTIONS

General

There are limited clinical data available for sotrovimab. Serious and unexpected adverse events may occur that have not been previously reported with sotrovimab use.

Immune

Hypersensitivity and Anaphylaxis

Serious hypersensitivity reactions, including anaphylaxis, have been reported with administration of sotrovimab (see 8 ADVERSE REACTIONS). If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur during infusion, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-Related Reactions

Infusion-related reactions (IRR) have been observed with IV administration of sotrovimab. These reactions may be severe or life threatening (see [8 ADVERSE REACTIONS](#)). Signs and symptoms of infusion-related reactions include, but are not limited to the following: 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. If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care.

Sensitivity/Resistance

Potential Risk of Treatment Failure due to Antiviral Resistance

Circulating SARS-CoV-2 viral variants may be associated with resistance to monoclonal antibodies such as sotrovimab. Health care professionals should routinely review the Antiviral Resistance information in section [15 MICROBIOLOGY](#), in conjunction with literature, for details regarding specific variants and resistance as it may be updated regularly.

7.1 Special Populations

7.1.1 Pregnant Women

There are insufficient data to evaluate the effects of sotrovimab on human pregnancy, such as the drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Sotrovimab should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the foetus.

No animal reproductive and developmental studies have been conducted with sotrovimab. In a cross-reactive binding assay using a protein array enriched for human embryofetal proteins, no off-target binding was detected. Since sotrovimab is an Fc-engineered human immunoglobulin G (IgG), it has the potential for placental transfer from the mother to the developing fetus. The potential treatment benefit or risk of placental transfer of sotrovimab to the developing fetus is not known.

7.1.2 Breast-feeding

There are insufficient data on the presence of sotrovimab in human milk, the effects on the breastfed infant, or the effects on milk production. There are no data in lactating animals. The developmental and health benefits of breast-feeding should be considered along with the mother's clinical need for sotrovimab and any potential adverse effects on the breastfed child from sotrovimab or from the underlying maternal condition. Individuals with COVID-19 who are breastfeeding should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

7.1.3 Pediatrics

Sotrovimab is not authorized for use in patients younger than 12 years of age or adolescents weighing less than 40 kg.

The safety and efficacy of sotrovimab have not been assessed in pediatric patients (17 years of age and younger). As per above (see [1.1 Pediatrics \(12 years of age and older weighing at least 40 kg\)](#)) it is reasonable to consider a single intravenous dose of sotrovimab in adolescents 12 years of age or older who weigh ≥ 40 kg and who are at high risk of developing severe COVID-19 symptoms requiring hospitalization.

7.1.4 Geriatrics

The pharmacokinetics of sotrovimab have not been quantified in patients aged 65 years or older. Of the 430 patients receiving sotrovimab in COMET-ICE, 20% were aged 65 years and older and 10% were over 70 years of age. In clinical trials, no dosage adjustment was made for patients aged 65 years or older (see [14.1 Trial Design and Study Demographics](#)).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of sotrovimab in the pivotal trial for the indicated population is based on an interim analysis from 868 non-hospitalized patients with COVID-19 in the ongoing, double-blind, placebo-controlled randomized COMET-ICE trial. In this trial, patients received a single intravenous infusion of 500 mg sotrovimab (n=430), or placebo (n=438). Adverse events of diarrhea were more common in those receiving sotrovimab (1.4%) than placebo (0.7%). All other adverse events with a frequency of $\geq 1\%$ occurred in the group receiving placebo, as shown in Table 2. Two patients experienced treatment interruptions due to infusion site extravasation, but infusion was completed. No events consistent with antibody dependent enhancement (ADE) were observed.

In COMET-ICE, hospitalizations due to progression of COVID-19 were included as serious adverse events (SAEs). SAEs were reported in 7/430 (2%) in the group receiving sotrovimab and in 26/438 (6%) in the group receiving placebo.

More broadly across the development program, one case of anaphylaxis was reported following infusion of sotrovimab in a study in hospitalized patients; the patient received epinephrine and the event resolved (see [7 WARNINGS AND PRECAUTIONS](#) and [8.2 Clinical Trial Adverse Reactions, Hypersensitivity including Anaphylaxis and Infusion-related Reactions](#)).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Table 2 shows adverse reactions reported in the COMET-ICE trial at an incidence of $\geq 1\%$ at the interim analysis.

Table 2. Incidence of Adverse Events as Reported in at Least 1% of Subjects in Either Treatment Group in COMET-ICE Trial

MedDRA System Organ Class Preferred Term	Sotrovimab 500 mg (n = 430) n (%)	Placebo (n = 438) n (%)
Gastrointestinal disorders		
Nausea	4 (<1%)	5 (1%)
Diarrhea	6 (1%)	3 (<1%)
Infections and infestations		
COVID-19 pneumonia ^a	4 (<1%)	14 (3%)
Pneumonia	0	7 (2%)
Metabolism and nutrition disorders		
Dehydration	0	5 (1%)
Nervous system disorders		
Headache	3 (<1%)	9 (2%)
Respiratory, thoracic and mediastinal disorders		
Dyspnea	2 (<1%)	5 (1%)

^a As recorded by the investigator

SAEs of acute diverticulitis was reported in 2 subjects (onset on Day 50 and Day 90 after treatment, respectively) in the group receiving sotrovimab; each patient with a prior history of diverticulitis. SAEs of COVID-19 pneumonia, pneumonia, and/or dehydration were reported in 2 or more subjects in the placebo arm. In the group receiving sotrovimab, single reports of the following SAEs included: COVID-19 pneumonia, COVID-19, non-small cell lung cancer, small intestinal obstruction, hyperglycemia, and diabetes mellitus. In the group receiving placebo, single reports of the following SAEs included: hypovolemia, acute respiratory failure, dyspnea, hypoxia, pulmonary embolism, respiratory distress, obstructive pancreatitis, oxygen saturation decreased, and acute kidney injury.

Description of selected adverse reactions

Hypersensitivity Including Anaphylaxis and Infusion-related Reactions

One case of anaphylaxis was reported following infusion of sotrovimab in a study in hospitalized patients; the patient received epinephrine and the event resolved.

Immediate, non-serious, hypersensitivity events were noted for 1% of subjects treated with sotrovimab and 1% of subjects treated with placebo in COMET-ICE. Reported events that started within 24 hours of study treatment included: pyrexia, chills, dizziness, dyspnea, pruritus, rash, and infusion-related

reactions. All events were considered Grade 1 (mild) or Grade 2 (moderate). As of the data cut-off, half of the events in the group receiving sotrovimab were noted to have been resolved, 2 events were noted to be not resolved, and 1 event was noted to be resolved with sequelae (see [7 WARNINGS AND PRECAUTIONS](#), Sensitivity/Resistance).

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

The COMET-ICE trial did not include patients < 18 years of age; therefore, no safety data is available in the pediatric population.

8.3 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

This information is not available for this drug product.

8.4 Post-Market Adverse Reactions

This information is not available for this drug product.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No formal drug interaction studies have been performed with sotrovimab. Sotrovimab is not renally excreted or metabolized by cytochrome P450 (CYP) enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely.

An interaction with COVID-19 vaccinations has not been studied and can therefore not be excluded.

9.3 Drug-Behavioural Interactions

Interactions with behaviour have not been established.

9.4 Drug-Drug Interactions

No formal drug interaction studies have been performed with sotrovimab. Sotrovimab is not renally excreted or metabolized by cytochrome P450 (CYP) enzymes; therefore, interactions with concomitant medications that are renally excreted or that are substrates, inducers, or inhibitors of CYP enzymes are unlikely.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Sotrovimab is a recombinant, human IgG1 monoclonal antibody that binds to a highly conserved epitope on the spike (S) protein receptor binding domain (RBD) of SARS-CoV-2 with high affinity (dissociation constant $K_d = 0.21$ nM), but does not compete with human angiotensin-converting enzyme 2 (ACE2) receptor binding. The Fc domain of sotrovimab includes M428L and N434S amino acid substitutions (LS modification) that are expected to extend antibody half-life, but do not impact wild-type Fc-mediated effector functions as assessed in cell culture.

10.3 Pharmacokinetics

Sotrovimab is an Fc-engineered IgG monoclonal antibody that is expected to have a longer half-life than an unmodified IgG monoclonal antibody; however, the half-life of sotrovimab has not been determined.

Partial sparse sampling of sotrovimab serum concentrations through Day 29 demonstrated that a 500 mg dose administered by IV infusion over 1 hr was associated with a geometric mean C_{max} (at the end of a 1 hr IV infusion) of 137 $\mu\text{g/mL}$ (N=129, CV% 40) and a geometric mean Day 29 serum concentration of 34 $\mu\text{g/mL}$ (N = 78, CV% 23).

Metabolism

Sotrovimab is an engineered human IgG1 monoclonal antibody degraded by proteolytic enzymes which are widely distributed in the body and not restricted to hepatic tissue.

Special Populations and Conditions

Pediatrics: The pharmacokinetics of sotrovimab in pediatric patients have not been evaluated. Based on an allometric scaling approach which accounted for effect of body weight changes associated with age on clearance and volume of distribution, the recommended dosing regimen in patients aged 12 years and older weighing at least 40 kg is expected to result in comparable serum exposures of sotrovimab as those observed in adults (see [4.2 Recommended Dose and Dosage Adjustment](#) and [7.1.3 Pediatrics](#)).

Geriatrics: Of the 430 patients receiving sotrovimab in COMET-ICE, 20% were 65 years of age and older and 10% were over 70 years of age. The effect of age on the pharmacokinetics of sotrovimab has not been established.

Hepatic Insufficiency: No clinical trials have been conducted to evaluate the effects of hepatic impairment on the pharmacokinetics of sotrovimab. The effect of hepatic insufficiency on the pharmacokinetics of sotrovimab has not been established.

Renal Insufficiency: No clinical trials have been conducted to evaluate the effects of renal impairment on the pharmacokinetics of sotrovimab. Renal impairment is not expected to impact the PK of sotrovimab since mAbs with molecular weight >69 kDa do not undergo renal elimination. Similarly, dialysis is not expected to impact the PK of sotrovimab.

The effect of other covariates (e.g., sex, race, body weight, disease severity) on the PK of sotrovimab is

unknown.

11 STORAGE, STABILITY AND DISPOSAL

Store vials refrigerated at 2°C to 8°C in original carton to protect from light. Do not freeze.

The solution of sotrovimab in the vial requires dilution prior to administration. The diluted solution of sotrovimab is intended to be used immediately. If immediate administration is not possible, the diluted solution may be stored for up to 6 hours at room temperature (up to 25°C) or refrigerated up to 24 hours (2°C to 8°C). If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 15 minutes prior to administration (see [4.3 Reconstitution](#)).

Sotrovimab is preservative-free. Discard any unused portion of the single-use vial.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

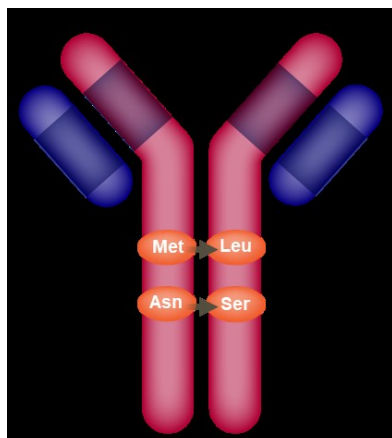
Drug Substance

Proper name: sotrovimab for injection

Chemical name: sotrovimab

Molecular formula and molecular mass: $C_{6492}H_{10092}N_{1744}O_{2038}S_{40}$ approximately 149 kDa

Structural formula (image):



Product Characteristics:

Sotrovimab is an engineered immunoglobulin G (IgG1) monoclonal antibody, produced in a Chinese hamster ovary (CHO) cell line by recombinant DNA technology. It consists of two heavy chain polypeptides and two light chain polypeptides, with a two amino acid “LS” modification in the Fc domain.

Sotrovimab for injection is a sterile, preservative-free, clear, colourless or yellow to brown solution supplied in a single-use glass vial (500 mg / 8 mL). The solution has a pH of 6.0. Each mL contains 62.5 mg sotrovimab in solution with L-histidine, L-histidine monohydrochloride, sucrose, L-methionine, polysorbate 80, and water for injection.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Mild to Moderate COVID-19

The efficacy of sotrovimab is based on the first interim analysis of the phase III portion of the COMET-ICE seamless trial. The pre-specified first interim analysis occurred after 583 randomized subjects had the opportunity to complete at least Day 29 of the COMET-ICE trial.

COMET-ICE is an ongoing, randomized, double-blind, placebo-controlled trial studying sotrovimab for the treatment of adult subjects with mild or moderate COVID-19 (subjects with COVID-19 symptoms who were not hospitalized but were at risk for disease progression).

Eligible subjects were 18 years of age or older and must have had at least one of the following risk factors for severe COVID-19: diabetes, obesity (BMI>30), chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, moderate to severe asthma; or subjects aged 55 years and older regardless of other comorbidities. The study included symptomatic patients with SARS-CoV-2 infection as confirmed by local laboratory tests and/or point of care tests and symptom onset within 5 days of enrollment. Subjects with severe COVID-19 requiring supplemental oxygen or hospitalization were excluded from the trial. Subjects were treated with a single 500 mg intravenous infusion of sotrovimab or placebo over 1 hour.

The primary endpoint was the proportion of patients who had progression of COVID-19 at Day 29; defined as hospitalization >24 hours for acute management of illness or death from any cause. Key secondary endpoints included progression to develop severe and/or critical respiratory COVID-19 at Day 29, and all-cause mortality up to Day 29.

Table 3. Summary of Patient Demographics: COMET-ICE Trial in Mild to Moderate COVID-19, Interim Analysis^a

Study #	Study design	Dosage, route of administration and duration	Study subjects (n) ITT Population	Median age (Range)
COMET-ICE 214367 / (VIR-7831-5001)	Randomized, double blind, placebo-controlled, trial in adult patients with mild or moderate COVID-19 and risk factors for progression to severe COVID-19.	Single dose, intravenous infusion: 500 mg sotrovimab vs. placebo.	N= 583	53 (18-96)

^a Interim analysis data cut-off: 4 March 2021

At baseline, the median age was 53 years (range: 18-96); 22% of subjects were aged 65 years or older and 11% were over 70 years of age. Overall, baseline demographic and disease characteristics were well balanced between the treatment arms (see Table 4).

Table 4. Baseline Characteristics: COMET-ICE Trial in Mild to Moderate COVID-19 (ITT Population)

Characteristic ^a	Sotrovimab 500 mg (n=291)	Placebo (n=292)
Median Age, (min, max) ^b	53.0 (18, 96)	52.5 (18, 88)
Age ≥ 65 years	63 (22%)	65 (22%)
Age > 70 years	33 (11%)	32 (11%)
Male sex	135 (46%)	131 (45%)
Female sex	156 (54%)	161 (55%)

Characteristic ^a	Sotrovimab 500 mg (n=291)	Placebo (n=292)
Race		
White	254 (88%)	252 (87%)
Black or African American	16 (6%)	22 (8%)
Asian	17 (6%)	17 (6%)
Hispanic or Latino Ethnicity	190 (65%)	178 (61%)
Most common conditions as risk factors for COVID-19 progression ^{c, d}		
Obesity (BMI > 30 kg / m ²)	182 (63%)	187 (64%)
Age ≥ 55 years	135 (46%)	141 (48%)
Diabetes requiring medication	66 (23%)	66 (23%)
Moderate to severe asthma	46 (16%)	46 (16%)
Number of conditions met		
≤ 2	261 (89%)	256 (88%)
3 or more	30 (10%)	36 (12%)

^a N (%) except if otherwise indicated

^b Age is imputed from year of birth. The calculation uses 30 June as the day and month and calculates age relative to Screening date.

^c Most common conditions are defined as those with incidence > 10%

^d Medical Conditions present as risk factors at Screening for progression include: diabetes (requiring medication), obesity (BMI was amended under protocol amendment 1 from >30 to >35. Participants are only summarized in the BMI threshold under which they were screened), chronic kidney disease (i.e., eGFR <60 by MDRD), congestive heart failure (NYHA class II or more), chronic obstructive pulmonary disease (history of chronic bronchitis, chronic obstructive lung disease, or emphysema with dyspnea on physical exertion), and moderate to severe asthma (participant requires an inhaled steroid to control symptoms or has been prescribed a course of oral steroids in the past year)

14.2 Study Results

Mild to Moderate COVID-19

In the COMET-ICE study, there were 21 (7%) primary endpoint events [hospitalization for >24 hours for acute management of any illness or death from any cause (Day 29)] in the placebo group compared to 3 (1%) events in the sotrovimab group. Results are provided in Table 5.

Table 5. Interim Efficacy Results in Adults with Mild to Moderate COVID-19 (ITT population)^a

	Sotrovimab (n = 291)	Placebo (n = 292)
Primary Endpoint		
Progression of COVID-19 as defined by hospitalization for >24 hours for acute management of any illness or death from any cause (Day 29)		
Proportion (n, %) ^b	3 (1%)	21 (7%)
Adjusted relative risk reduction ^c (97.24% CI)	85% (44%, 96%)	
Adjusted Risk Difference ^c	-8.05	
p-value	0.002	
Secondary Endpoints		
Progression to develop Severe and/or Critical Respiratory COVID-19 ^d (Day 29)		
Proportion (n, %) ^e	2 (<1%)	19 (7%)
All-cause mortality (up to Day 29)		
Proportion (n, %)	0	1 (<1%)

^a Interim analysis data cut-off: 4 March 2021

^b No subjects required intensive care unit (ICU) stay in the group receiving sotrovimab versus 5 subjects in the group receiving placebo.

^c Adjusted for duration of symptoms (<=3, >=4 days), age (<=70, >70 years old) and gender (male, female)

^d Defined as the requirement for supplemental oxygen [low flow nasal cannula/face mask, high flow oxygen, non-invasive ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO)].

^e No subjects required use of high flow oxygen, non-rebreather mask or mechanical ventilation in the group receiving sotrovimab versus 7 subjects in the group receiving placebo.

The final study analysis of COMET-ICE included 1057 subjects. Based on this updated analysis, there were 30 primary endpoint events in the placebo group compared to 6 events in the sotrovimab group. The estimated adjusted relative risk reduction for the primary endpoint was 79% (95% CI: 50%, 91%), and the adjusted risk difference was 6.34.

14.4 Immunogenicity

Immunogenicity data are not currently available. Consistent with the potentially immunogenic properties of protein and peptide therapeutics, patients may develop antibodies to sotrovimab following treatment.

15 MICROBIOLOGY

Antiviral Activity

The cell culture neutralization activity of sotrovimab against SARS-CoV-2 (isolate USA WA1/2020) was measured in a concentration response model using cultured Vero E6 cells. Sotrovimab neutralized SARS

CoV-2 with an average EC₅₀ value of 0.67 nM (100.1 ng/mL) and an average EC₉₀ value of 1.2 nM (186.3 ng/mL).

Sotrovimab demonstrated *in vitro* FcγR activation using Jurkat reporter cells expressing FcγRIIa (low-affinity R131 and high affinity H131 alleles), FcγRIIIa (low-affinity F158 and high-affinity V158 alleles) and FcγRIIb). Sotrovimab exhibited antibody-dependent cell-mediated cytotoxicity (ADCC) *in vitro* using isolated human natural killer (NK) cells following engagement with target cells expressing spike protein. Sotrovimab also elicited antibody-dependent cellular phagocytosis (ADCP) in cell-based assays using CD14+ monocytes targeting cells expressing spike protein.

Antiviral activity in a Syrian Golden hamster model of SARS-CoV-2 infection was demonstrated using a single dose of an unmodified (no LS modification in the Fc domain) version of sotrovimab which was administered intraperitoneally at 24- or 48-hours prior to infection. Animals receiving 5 mg/kg or more of antibody showed a significant improvement in body weight loss and significantly decreased total lung SARS-CoV-2 viral RNA compared to vehicle only and control antibody-treated animals. Levels of infectious virus in the lung (as measured by TCID₅₀) were significantly decreased versus controls in hamsters receiving 0.5 mg/kg or more of antibody.

Antibody Dependent Enhancement (ADE) of Infection

The risk that sotrovimab could mediate viral uptake and replication by immune cells was studied in U937 cells, primary human monocytic dendritic cells and peripheral blood mononuclear cells. This experiment did not demonstrate productive viral infection in immune cells exposed to SARS CoV-2 in the presence of concentrations of sotrovimab from 1-fold down to 1000-fold below the EC₅₀ value.

No evidence of ADE was observed in a Syrian golden hamster model of SARS-CoV-2 as evidenced by improvement in the measured outcomes of body weight, total viral RNA in the lungs, or infectious virus levels based on TCID₅₀ measurements in hamsters administered an unmodified version of sotrovimab (no LS modification in the Fc domain) intraperitoneally.

Antiviral Resistance

There is a potential risk of treatment failure due to the development of viral variants that are resistant to sotrovimab. Prescribing healthcare providers should consider the prevalence of SARS-CoV-2 variants in their area, where data are available, when considering treatment options. An E340A amino acid substitution in the spike protein emerged in cell culture selection of resistant virus and had a >100-fold reduction in activity in a pseudotyped virus-like particle (VLP) assay. This substitution is in the conserved epitope of sotrovimab, which is comprised of 23 amino acids. A pseudotyped VLP assessment in cell culture showed that the epitope sequence polymorphisms P337H/L/R/T and E340A/K/G conferred reduced susceptibility to sotrovimab based on observed fold-increase in EC₅₀ value shown in parentheses: E340K (>297), P337R (>276), P337L (180), E340A (>100), E340G (27), P337H (7.5), and P337T (5.4). The presence of the highly prevalent D614G variant, either alone or in combination, did not alter neutralization of sotrovimab.

Pseudotyped virus *in vitro* assessments indicate that sotrovimab retains activity against the Alpha (2.3-fold change in EC₅₀ value; B.1.1.7: H69-, V70-, Y144-, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H), Beta (0.6-fold change in EC₅₀ value; B.1.351: L18F, D80A, D215G, R246I, K417N, E484K, N501Y, D614G, A701V), Gamma (0.35-fold change in EC₅₀ value; P.1: D138Y, D614G, E484K, H655Y, K417T, L18F, N501Y, P26S, R190S, T1027I, T20N, V1176F), Epsilon (0.7-fold change in EC₅₀ value; B.1.427/B.1.429: D614G, L452R, S13I, W152C), Iota (0.6-fold change in EC₅₀ value; B.1.526: L5F, T95I, D253G, E484K,

D614G, A701V), Kappa (0.7-fold change in EC₅₀ value; B.1.617.1; T95I, G142D, E154K, L452R, E484Q, D614G, P681R, and Q1071H), and Delta (1.0-fold change in EC₅₀ value; B.1.617.2; T19R, G142D, E156G, F157-, R158-, L452R, T478K, D614G, P681R, D950N) variant spike proteins. Microneutralization data available thus far using authentic SARS-CoV-2 variant virus indicate that sotrovimab retains activity against the Alpha (3-fold change in EC₅₀ value), Beta (1.2-fold change in EC₅₀ value) and Gamma (1.6-fold change in EC₅₀ value) variants.

Limited nucleotide sequencing data from a total of 218 participants indicated that 9 participants (5 placebo and 4 treated with sotrovimab) enrolled in COMET-ICE were infected with the Epsilon (B.1.427/B.1.429) variant (S13I, W152C, L452R), and one subject treated with sotrovimab progressed to require hospitalization. Two additional participants in the placebo group carried the L452R variant only. None of the participants were infected with SARS-CoV-2 that contained the full complement of spike substitutions characteristic of the Alpha (B.1.1.7), Beta (B.1.351) or Gamma (P.1) variants. One participant in the placebo group carried the N501Y variant at baseline.

In COMET-ICE, post-baseline epitope variants were detected in eight participants in the cohort receiving sotrovimab (spike protein substitutions E340K [4 subjects: ≥99.7% allele frequency]; A344V [6.2%]; K356R [7.5%]; S359G [2 subjects: 12.2% and 8.3%]). Of the variants detected at baseline and post-baseline, L335F, G339C, E340A, E340K, R346I, K356N, K356R, R357I, I358V and S359G substitutions have been assessed phenotypically using a pseudotyped VLP system. E340A and E340K substitutions confer reduced susceptibility to sotrovimab (>100-fold and >297-fold changes in EC₅₀ value, respectively). Sotrovimab retains susceptibility against L335F (0.8-fold change in EC₅₀ value), G339C (1.2-fold change in EC₅₀ value), R346I (1.7-fold change in EC₅₀ value), K356N (1.1-fold change in EC₅₀ value), K356R (0.8-fold change in EC₅₀ value), R357I (1-fold change in EC₅₀ value), I358V (0.7-fold change in EC₅₀ value), and S359G (0.8-fold change in EC₅₀ value) substitutions. The clinical impact of these variants is not yet known. Data collection and analysis is still ongoing.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

In a 2-week repeat-dose toxicity study in cynomolgus monkeys, sotrovimab had no adverse effects when administered intravenously up to 500 mg/kg.

In tissue cross reactivity studies using human and monkey adult tissues, no specific binding was detected.

In a cross-reactive binding assay using a protein array enriched for human embryofetal proteins, no off-target binding was detected for sotrovimab.

Carcinogenicity and Genotoxicity

Carcinogenicity and genotoxicity studies have not been conducted with sotrovimab.

Reproductive and Developmental Toxicology

Nonclinical reproductive and developmental toxicity studies have not been conducted with sotrovimab.

PATIENT MEDICATION INFORMATION

HEALTH CANADA HAS AUTHORIZED THE SALE OF THIS COVID-19 DRUG BASED ON LIMITED CLINICAL TESTING IN HUMANS AND/OR QUALITY INFORMATION.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

^P**Sotrovimab for injection**

Read this carefully before you start taking **sotrovimab**. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **sotrovimab**.

What is sotrovimab used for?

Sotrovimab is a medicine being studied to prevent worsening of COVID-19. Sotrovimab may be given if you or your child are 12 years of age or older and weigh at least 40 kg (kilograms) and are not already in the hospital. Sotrovimab is only given to patients at high risk of being hospitalized or dying due to COVID-19, because of their age or medical conditions. Your healthcare professional will decide if you or your child should take sotrovimab.

Sotrovimab is not authorized for use in patients:

- who are in the hospital to treat their COVID-19, OR
- who are given oxygen to help them breathe because of COVID-19.

How does sotrovimab work?

COVID-19 is caused by a coronavirus (SARS-CoV-2). You can get COVID 19 through contact with another person who has the virus.

Sotrovimab is a monoclonal antibody, a type of protein that attaches to the spike protein of the coronavirus (SARS-CoV-2) that causes COVID-19, and prevents the virus from entering and infecting healthy cells within your body. Sotrovimab may help reduce your risk of progressing from mild or moderate COVID-19 to severe infection that requires hospitalization.

What are the ingredients in sotrovimab?

Medicinal ingredients: sotrovimab

Non-medicinal ingredients: L-histidine, L-histidine monohydrochloride, L-methionine, sucrose, polysorbate 80, and water for injection.

Sotrovimab comes in the following dosage forms:

Sotrovimab solution, 500mg/8mL (62.5mg/mL).

Do not use sotrovimab if:

You have had an allergic reaction to sotrovimab or any of the non-medicinal ingredients listed above.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take sotrovimab. Talk about any health conditions or problems you may have, including if you:

- are allergic to any medicines;
- are pregnant or plan to become pregnant;
- are breastfeeding a child or plan to breastfeed;
- have any serious illness;
- are taking any medicines (prescription, over-the-counter, vitamins, or herbal products).

Pregnancy

- Tell your health professional if you are pregnant or if you plan to become pregnant
 - There is not enough information to be sure that sotrovimab is safe for use in pregnancy.
 - Sotrovimab will only be given if the potential benefits of treatment outweigh the potential risks to you and your unborn child.

Breast-feeding

- Tell your health professional if you are breast-feeding or plan to breast-feed
 - It is not yet known whether sotrovimab or the COVID-19 virus pass into human breast milk, or what the effects might be on the baby or milk production.
 - Your health professional will help you decide whether to continue breast-feeding or to start treatment with sotrovimab.
 - You will need to consider the potential benefits of treatment for you, compared with the health benefits and risks of breast-feeding for your baby.

Other warnings you should know about:

A possible side effect of sotrovimab is **allergic reaction**, which can happen during and after infusion with sotrovimab. These reactions may be severe or life threatening. Tell your healthcare professional right away if you get any of the following signs and symptoms of allergic reactions: fever; chills; nausea; headache; shortness of breath; low or high blood pressure; rapid or slow heart rate; chest discomfort or pain; weakness; confusion; feeling tired; wheezing; swelling of your lips, face, or throat; rash including hives; itching; muscle aches; dizziness; and sweating.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take sotrovimab:

- Sotrovimab will be given to you by a qualified healthcare professional intravenously (through a vein) over 60 minutes.
- You will be observed by your healthcare professional during the infusion and for a period of one hour after you receive sotrovimab.

Usual dose:

Sotrovimab is given once. The recommended dose is 500 milligrams (mg).

Overdose:

If you think you, or a person you are caring for, have taken too much sotrovimab, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

What are possible side effects from using sotrovimab?

The side effects of getting any medicine through a vein may include brief pain from inserting the needle, bleeding, bruising of the skin, soreness, swelling, and possible infection at the injection site.

Tell your healthcare professional right away if you get any signs and symptoms of infusion reactions or allergic reactions (see table below).

Some people have had diarrhea when taking sotrovimab.

These are not all the possible side effects you may have when taking sotrovimab. If you experience any side effects not listed here, tell your healthcare professional. Not many people have been given sotrovimab. Serious and unexpected side effects may happen. It is possible that all of the risks of taking sotrovimab are not known at this time.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE			
<i>Infusion Reaction</i> Fever, chills, nausea or feeling sick, headache, difficulty breathing, chest tightness, fall or increase in blood pressure, swelling of the face, throat irritation, rash with hives, itching or an itchy rash, muscle pain, uneven heart-beat, low oxygen in blood, increased sweating, dizziness or light headedness.		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

It is possible that sotrovimab could interfere with your body's own ability to fight off a future infection of SARS-CoV-2. Similarly, sotrovimab may reduce your body's immune response to a vaccine for SARS-CoV-2. Specific studies have not been conducted to address these possible risks. Talk to your healthcare provider if you have any questions.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (<https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html>) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

If you want more information about sotrovimab:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (<https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html>); the manufacturer's website <http://www.gsk.ca/>, or by calling 1-800-387-7374.

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