2.4 Dose Preparation and Administration

Preparation

Sotrovimab is supplied in a single-dose vial and **must be diluted** prior to IV infusion.

Sotrovimab infusion solution should be prepared by a qualified healthcare professional using aseptic technique.

- Gather the materials for preparation:
  - Polyvinyl chloride (PVC) or polyolefin (PO), sterile, prefilled 50-mL or 100-mL infusion bag containing 0.9% Sodium Chloride Injection or 5% Dextrose Injection, and
  - One vial of sotrovimab (500 mg/8 mL).
- Remove one vial of sotrovimab from refrigerated storage and allow to equilibrate to room temperature, protected from light, for approximately 15 minutes.
- Inspect the vial of sotrovimab visually for particulate matter and discoloration prior to administration. Should either be observed, the solution must be discarded and fresh solution prepared. Sotrovimab is a clear, colorless or yellow to brown solution.
- Gently swirl the vial several times before use without creating air bubbles. **Do not shake the vial.**
- Withdraw 8 mL of sotrovimab from one vial and inject into the prefilled infusion bag.
- Discard any product remaining in the vial.
- Prior to the infusion, gently rock the infusion bag back and forth by hand 3 to 5 times. **Do not invert the infusion bag.** Avoid forming air bubbles.
- This product is preservative-free; 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 [up to 77°F]) or refrigerated up to 24 hours (2°C to 8°C [36°F to 46°F]).

Administration

Sotrovimab infusion solution should be administered by a qualified healthcare professional *[see Warnings and Precautions (5.1)]*.

Sotrovimab may only be administered in settings in which healthcare providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary *[see Warnings and Precautions (5.1)]*.

- Gather the materials for infusion via infusion pump or gravity:
  - Polyvinyl chloride (PVC) or polyolefin (PO) infusion set, and

- Use of a 0.2 micron polyethersulfone (PES) filter is strongly recommended.

- Attach the infusion set to the IV bag using standard bore tubing.
- Prime the infusion set.
- Administer the entire infusion solution in the bag over 15 minutes for 50-mL infusion bag or 30 minutes for 100-mL infusion bag. Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.
- 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 Injection and 5% Dextrose Injection is not known.
- Once infusion is complete, **flush the tubing** with 0.9% Sodium Chloride or 5% Dextrose to ensure delivery of the required dose.
- If the infusion must be discontinued due to an infusion reaction, discard unused product.
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

3 DOSAGE FORMS AND STRENGTHS

Sotrovimab is a sterile, preservative-free, clear, colorless or yellow to brown solution available as:

- Injection: 500-mg/8-mL (62.5-mg/mL) solution in a single-dose vial.

4 CONTRAINDICATIONS

Sotrovimab is contraindicated in patients who have a history of anaphylaxis to sotrovimab or to any of the excipients in the formulation.

5 WARNINGS AND PRECAUTIONS

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

5.1 Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of sotrovimab *[see Overall Safety Summary (6.1)]*. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-related reactions, occurring during the infusion and up to 24 hours after the infusion, have been observed with administration of sotrovimab. These reactions may be severe or life

threatening.

Signs and symptoms of infusion-related reactions may include *[see Overall Safety Summary (6.1)]*:

- fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vaso-vagal reactions (e.g., pre-syncope, syncope), dizziness, and diaphoresis.

If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care. Clinically monitor patients for at least 1 hour after completion of the infusion for signs and symptoms of hypersensitivity.

Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported with the use of SARS-CoV-2 monoclonal antibodies under Emergency Use Authorization.

5.2 Clinical Worsening After SARS-CoV-2 Monoclonal Antibody Administration

Clinical worsening of COVID-19 after administration of SARS-CoV-2 monoclonal antibody treatment has been reported and may include signs or symptoms of fever, hypoxia or increased respiratory difficulty, arrhythmia (e.g., atrial fibrillation, tachycardia, bradycardia), fatigue, and altered mental status. Some of these events required hospitalization. It is not known if these events were related to SARS-CoV-2 monoclonal antibody use or were due to progression of COVID-19.

5.3 Limitations of Benefit and Potential for Risk in Patients with Severe COVID-19

Benefit of treatment with sotrovimab has not been observed in 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. Therefore, sotrovimab is not authorized for use in the following patient populations *[see Limitations of Authorized Use]*:

- Adults or pediatric patients who are hospitalized due to COVID-19, OR
- Adults or pediatric patients who require oxygen therapy and/or respiratory support due to COVID-19, OR
- Adults or pediatric patients who require an increase in baseline oxygen flow rate and/or respiratory support due to COVID-19 in those patients on chronic oxygen.

6 OVERALL SAFETY SUMMARY

6.1 Clinical Trials Experience

The safety of sotrovimab in subjects with mild-to-moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized) is based on analyses from COMET-ICE, a Phase 1/2/3 trial, and COMET-TAIL, a Phase 3 trial *[see Clinical Trial Results and Supporting Data for EUA (18)]*.

In COMET-ICE, subjects received a single 500-mg infusion of sotrovimab (n = 523) or placebo (n = 526). Two subjects experienced treatment interruptions due to infusion site extravasation; infusion was completed for each. In COMET-TAIL, subjects received a single 500-mg IV infusion of sotrovimab (n = 393).

Infusion-Related Reactions Including Hypersensitivity

Infusion-related reactions, including immediate hypersensitivity reactions, were observed in 1% of subjects treated with sotrovimab and 1% of subjects treated with placebo in COMET-ICE and in <1% of subjects treated with IV sotrovimab in COMET-TAIL. Reported events that started within 24 hours of study treatment were pyrexia, chills, dizziness, dyspnea, pruritus, rash, and infusion-related reactions; all events were Grade 1 (mild) or Grade 2 (moderate).

One case of anaphylaxis was reported following sotrovimab infusion in a study in hospitalized subjects; the infusion was immediately discontinued, and the subject received epinephrine. The event resolved but recurred within 2 hours; the subject received another dose of epinephrine and improved with no additional reactions. Other serious infusion-related reactions (including immediate hypersensitivity reactions) reported following sotrovimab infusion in the hospitalized study included Grade 3 (serious) or Grade 4 (life-threatening) bronchospasm and shortness of breath. These events were also reported following infusion of placebo. Sotrovimab is not authorized for use in subjects hospitalized due to COVID-19 *[see Warnings and Precautions (5.1, 5.3)]*.

Hypersensitivity adverse reactions (i.e., adverse events assessed as causally related) were observed in 2% of subjects treated with sotrovimab and 1% of subjects treated with placebo in COMET-ICE and in <1% of subjects treated with sotrovimab in COMET-TAIL. All were Grade 1 (mild) or Grade 2 (moderate), and none of the reactions in either trial led to permanent discontinuation of the infusions. One reaction led to pausing of the infusion *[see Warnings and Precautions (5.1)]*.

Common Adverse Events

The most common treatment-emergent adverse events observed in the sotrovimab treatment group in COMET-ICE were rash (1%) and diarrhea (2%), all of which were Grade 1 (mild) or Grade 2 (moderate). No other treatment-emergent adverse events were reported at a higher rate with sotrovimab compared to placebo.

6.2 Post-Authorization Experience

The following adverse reactions have been identified during post-authorization use of sotrovimab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders

Anaphylaxis *[see Contraindications (4), Warnings and Precautions (5.1)]*.

7 PATIENT MONITORING RECOMMENDATIONS

Clinically monitor patients during dose administration and observe patients for at least 1 hour after IV infusion is complete *[see Warnings and Precautions (5.1, 5.2) and Overall Safety Summary (6.1)]*.

8 ADVERSE REACTIONS AND MEDICATION ERRORS REPORTING REQUIREMENTS AND INSTRUCTIONS

Clinical trials evaluating the safety of sotrovimab are ongoing *[see Overall Safety Summary (6)]*.

The prescribing healthcare provider and/or the provider's designee is/are responsible for the mandatory reporting of all serious adverse events* and medication errors potentially related to sotrovimab within 7 calendar days from the healthcare provider's awareness of the event, using FDA Form 3500 (for information on how to access this form, see below). The FDA requires that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race)
- A statement "Sotrovimab use for COVID-19 under Emergency Use Authorization (EUA)" under the **"Describe Event, Problem, or Product Use/Medication Error"** heading
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes)
- Patient's preexisting medical conditions and use of concomitant products
- Information about the product (e.g., dosage, route of administration, NDC #)

Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:

- Complete and submit the report online at www.fda.gov/medwatch/report.htm, or

- Complete and submit a postage-paid FDA Form 3500 (https://www.fda.gov/media/76299/download) and return by:
  - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
  - Fax (1-800-FDA-0178), or
- Call 1-800-FDA-1088 to request a reporting form.
- In addition, please provide a copy of all FDA MedWatch forms to:

  GlaxoSmithKline, Global Safety
  Fax: 919-287-2902
  Email: WW.GSKAEReportingUS@gsk.com

  Or call the GSK COVID Contact Center at 1-866-GSK-COVID (866-475-2684) to report adverse events.

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of sotrovimab.

*Serious Adverse Events are defined as:

- death;
- a life-threatening adverse event;
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital anomaly/birth defect;
- other important medical event, which may require a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

IMPORTANT: When reporting adverse events or medication errors to MedWatch, please complete the entire form with detailed information. It is important that the information reported to FDA be as detailed and complete as possible. Information to include:

- Patient demographics (e.g., patient initials, date of birth)
- Pertinent medical history
- Pertinent details regarding admission and course of illness
- Concomitant medications
- Timing of adverse event(s) in relationship to administration of sotrovimab
- Pertinent laboratory and virology information

- Outcome of the event and any additional follow-up information if it is available at the time of the MedWatch report. Subsequent reporting of follow-up information should be completed if additional details become available.

The following steps are highlighted to provide the necessary information for safety tracking:

- In section A, box 1, provide the patient's initials in the Patient Identifier
- In section A, box 2, provide the patient's date of birth
- In section B, box 5, description of the event:
    - Write "Sotrovimab use for COVID-19 under Emergency Use Authorization (EUA)" as the first line
    - Provide a detailed report of medication error and/or adverse event. It is important to provide detailed information regarding the patient and adverse event/medication error for ongoing safety evaluation of this unapproved drug. Please see information to include listed above.
- In section G, box 1, name and address:
    - Provide the name and contact information of the prescribing healthcare provider or institutional designee who is responsible for the report.
    - Provide the address of the treating institution (NOT the healthcare provider's office address).

9 OTHER REPORTING REQUIREMENTS

Healthcare facilities and providers will report therapeutics information and utilization data as directed by the U.S. Department of Health and Human Services.

10 DRUG INTERACTIONS

Clinical drug-drug interaction studies have not 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.

11 USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to sotrovimab during pregnancy. Pregnant and recently pregnant individuals can go to https://covid-pr.pregistry.com to enroll or call 1-800-616-3791 to obtain information about the registry.

Risk Summary

There are insufficient data to evaluate a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcome. Sotrovimab should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy *(see Clinical Considerations)*.

Nonclinical reproductive toxicity studies have not 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 for sotrovimab. Since sotrovimab is a recombinant human immunoglobulin G (IgG) containing the LS modification in the Fc domain, 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.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo-Fetal Risk: COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

11.2 Lactation

Risk Summary

There are no available data on the presence of sotrovimab in human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for sotrovimab and any potential adverse effects on the breastfed infant 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.

11.3 Pediatric Use

Sotrovimab is not authorized for use in pediatric patients under 12 years of age or weighing less than 40 kg. The safety and effectiveness of sotrovimab have not been assessed in pediatric patients. The recommended dosing regimen in patients 12 years to less than 18 years of age, weighing at least 40 kg, is expected to result in comparable serum exposures of sotrovimab as those observed in adults.

11.4 Geriatric Use

Of the 528 subjects randomized to receive sotrovimab in COMET-ICE, 20% were 65 years of

age and older and 11% were over 70 years of age. Of the 378 subjects in the primary analysis population receiving sotrovimab in COMET-TAIL, 25% were 65 years of age or older and 8% were over 75 years of age. The difference in pharmacokinetics (PK) of sotrovimab in geriatric patients compared to younger patients has not been quantified.

11.5 Renal Impairment

No clinical trials have been conducted to evaluate the effects of renal impairment on the PK of sotrovimab. Sotrovimab is not eliminated intact in the urine, thus renal impairment is not expected to affect the exposure of sotrovimab.

11.6 Hepatic Impairment

No clinical trials have been conducted to evaluate the effects of hepatic impairment on the PK of sotrovimab. The impact of hepatic impairment on the PK of sotrovimab is unknown.

12 OVERDOSAGE

There is no human experience of acute overdosage with sotrovimab.

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

13 PRODUCT DESCRIPTION

Sotrovimab is a human immunoglobulin G-1 (IgG1-kappa) monoclonal antibody consisting of 2 identical light chain (LC) polypeptides composed of 214 amino acids each and 2 identical heavy chain (HC) polypeptides, each composed of 457 amino acids. Sotrovimab is produced by a Chinese Hamster Ovary cell line and has a molecular weight of approximately 149 kDa.

Sotrovimab injection is a sterile, preservative-free, clear, colorless or yellow to brown solution supplied in a single-dose vial for IV infusion after dilution.

Each mL contains sotrovimab (62.5 mg), L-histidine (1.51 mg), L-histidine monohydrochloride (2.15 mg), L-methionine (0.75 mg), polysorbate 80 (0.4 mg), and sucrose (70 mg). The solution of sotrovimab has a pH of 6.0.

14 CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

Sotrovimab is a recombinant human IgG1-kappa mAb that binds to a conserved epitope on the spike protein receptor binding domain of SARS-CoV-2 with a dissociation constant (K_D = 0.21 nM) but does not compete with human ACE2 receptor binding (IC_{50} value >33.6 nM [5 µg/mL]). Sotrovimab inhibits an undefined step that occurs after virus attachment and prior to fusion of the viral and cell membranes. The Fc domain of sotrovimab includes M428L and N434S amino acid substitutions (LS modification) that extend antibody half-life, but do not impact wild-type Fc-mediated effector functions in cell culture.

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 EC_{50} value.

The potential for ADE was also evaluated in a hamster model of SARS-CoV-2 using sotrovimab. Intraperitoneal administration prior to inoculation resulted in a dose-dependent improvement in all measured outcomes (body weight, total viral RNA in the lungs, or infectious virus levels based on $TCID_{50}$ measurements). No evidence of enhancement of disease was observed at any dose evaluated, including sub-neutralizing doses down to 0.05 mg/kg.

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 choose an authorized therapeutic option with activity against circulating SARS-CoV-2 variants in their state. SARS-CoV-2 variant frequency data for states and jurisdictions can be accessed on the CDC website [4].

Spike protein amino acid substitution E340A 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 epitope amino acid substitutions P337H/K/L/R/T, E340A/I/K/G/Q/V, T345P, K356T, and L441N conferred reduced susceptibility to sotrovimab based on observed fold-increase in EC_{50} value shown in parentheses: P337H (5.13), P337K (>304), P337L (>192), P337R (>192), P337T (10.62), E340A (>100), E340G (18.21), E340I (>190), E340K (>297), E340Q (>50), E340V (>200), T345P (225), K356T (5.90), and L441N (72). The presence of the highly prevalent D614G substitution, either alone or in combination, did not alter neutralization of sotrovimab. Pseudotyped VLP assessments indicate that sotrovimab retains activity against the B.1.1.7 (Alpha, UK origin: H69-, V70-, Y144-, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H; 2.3-fold change in EC_{50} value), B.1.351 (Beta, South Africa origin: L18F, D80A, D215G, R246I, K417N, E484K, N501Y, D614G, A701V; 0.6-fold change in EC_{50} value), P.1 (Gamma, Brazil origin: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F; 0.35-fold change in EC_{50} value), B.1.427/B.1.429 (Epsilon, California origin: S13I, W152C, L452R, D614G; 0.7-fold change in EC_{50} value), B.1.526 (Iota, New York origin: L5F, T95I, D253G, E484K, D614G, A701V; 0.6-fold change in EC_{50} value), B.1.617.1 (Kappa, India origin: T95I, G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H; 0.7-fold change in EC_{50} value), B.1.617.2 (Delta, India origin: T19R, G142D, E156G, F157-, R158-, L452R, T478K, D614G, P681R, D950N; 1-fold change in EC_{50} value), AY.1 (Delta [+K417N], India origin: T19R, T95I, G142D, E156G, F157-, R158-, W258L, K417N, L452R, T478K, D614G, P681R, D950N; 1.1-fold change in EC_{50} value), AY.2 (Delta [+K417N], India origin: T19R, V70F, G142D, E156G, F157-, R158-, A222V, K417N, L452R, T478K, D614G, P681R, D950N; 1.3-fold change in

[4] https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html

What other treatment choices are there?

Veklury (remdesivir) is FDA-approved for the treatment of mild-to-moderate COVID-19 in certain adults and children. Talk with your doctor to see if Veklury is appropriate for you.

Like sotrovimab, FDA may allow for the emergency use of other medicines to treat people with COVID-19. Go to https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization for information on the emergency use of other medicines that are authorized by FDA to treat people with COVID-19. Your healthcare provider may talk with you about clinical trials for which you may be eligible.

It is your choice for you or your child to be treated or not to be treated with sotrovimab. Should you decide not to receive it or your child not to receive it, it will not change you or your child's standard medical care.

What if I am pregnant or breastfeeding?

There is no experience treating pregnant women or breastfeeding mothers with sotrovimab. For a mother and unborn baby, the benefit of receiving sotrovimab may be greater than the risk from the treatment. If you are pregnant or breastfeeding, discuss your options and specific situation with your healthcare provider.

Pregnancy Registry

There is a pregnancy registry for individuals who receive sotrovimab during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk with your healthcare provider about how to take part in this registry. For more information visit https://covid-pr.pregistry.com or call 1-800-616-3791.

How do I report side effects with sotrovimab?

Contact your healthcare provider if you have any side effects that bother you or do not go away. Report side effects to **FDA MedWatch** at www.fda.gov/medwatch or call 1-800-FDA-1088, or call the GSK COVID Contact Center at 1-866-GSK-COVID (866-475-2684).

How can I learn more?

- Ask your healthcare provider
- Visit https://www.cdc.gov/COVID19
- Call the GSK COVID Contact Center at 1-866-GSK-COVID (866-475-2684)

What is an Emergency Use Authorization (EUA)?

The United States FDA has made sotrovimab available under an emergency access mechanism called an Emergency Use Authorization (EUA). The EUA is supported by a Secretary of Health and Human Service (HHS) declaration that circumstances exist to justify the emergency use of drugs and biological