



EUA 000100

EMERGENCY USE AUTHORIZATION- REVISED HCP FACT SHEET

GlaxoSmithKline LLC
Attention: Debra H. Lake, MS
Senior Director, Global Regulatory Affairs
Five Moore Drive
PO Box 13398
Durham, North Carolina 27709

Dear Ms. Lake:

Please refer to your Emergency Use Authorization (EUA) for emergency use of sotrovimab for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older, weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, issued on May 26, 2021, under section 564 of the Federal Food, Drug, and Cosmetic Act (FDCA) (21 U.S.C. 360bbb-3).

We refer to your submission dated October 1, 2021, wherein you submitted proposed revisions to update the authorized Fact Sheet for Healthcare Providers (HCP) and the Fact Sheet for Patients, Parents and Caregivers (Patient) with available virology and post-EUA authorization safety information. Further reference is made to your amendment dated October 21, 2021.

We have completed our review and concur with the following revisions to the HCP and Patient Fact Sheets:

HCP Fact Sheet

- Contraindications (Section 4): Previously read “None” changed to include contraindication language whereby it now states that sotrovimab is contraindicated in patients with a prior history of anaphylaxis to sotrovimab or to the excipients in the formulation. The Patient Fact sheet was updated to list the sotrovimab ingredients
- Post-Authorization Experience (Section 6.2): This new section was added to include the subsection titled “Immune System Disorders” under which anaphylaxis is added as an adverse reaction following post- EUA authorization reporting of this event following sotrovimab administration
- Microbiology/Resistance Information (Section 15): Updated with the addition of information regarding SARS-CoV-2 variants of concern/variants of interest. The revision provided summary data of

sotrovimab antiviral activity against the SARS-CoV-2 Lambda (C.37, Peru origin); Mu (B.1.621, Columbia origin); B.1.617.1 (Kappa, India origin); and B.1.617.2 (Delta, India origin) variants

Patient Fact Sheet

- The following subheaders were added
 - “Who should not receive sotrovimab?” with language added that sotrovimab should not be taken if prior serious allergic reactions to sotrovimab or ingredients have occurred.
 - “What are the ingredients in sotrovimab?” with the ingredients of sotrovimab listed
- Under header titled “What should I tell my healthcare provider before I receive sotrovimab?” language added for patient to tell provider of any prior allergic reaction to sotrovimab or sotrovimab ingredients
- Under header titled “What other treatment choices are there?” an editorial correction to the URL for the FDA website for further information on the emergency medicines available for COVID-19 treatment

The updated Fact Sheets for Healthcare Providers and the Fact Sheet for Patients, Parents and Caregivers are attached to this correspondence for your reference.

By submitting these amendments for review by the Food and Drug Administration (FDA), you have complied with the Conditions of Authorization stated in the May 26, 2021, letter authorizing the emergency use of sotrovimab for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) patients.

Sincerely,

{See appended electronic signature page}

John Farley, MD MPH
Director
Office of Infectious Diseases
Center for Drug Evaluation and
Research

FACT SHEET FOR HEALTHCARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF SOTROVIMAB

AUTHORIZED USE

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of the unapproved product sotrovimab for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.

LIMITATIONS OF AUTHORIZED USE

- 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).
- 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.

RECENT MAJOR CHANGES

- | | |
|--|-----------------|
| • <u>Overall Safety Summary, Post-Authorization Experience (Section 6.2):</u> addition of anaphylaxis | Revised 11/2021 |
| • <u>Microbiology/Resistance Information, Antiviral Resistance (Section 15):</u> addition of information on susceptibility of SARS-CoV-2 variants to sotrovimab | Revised 11/2021 |
| • <u>Dosage and Administration, Dosage Preparation and Administration (Section 2.4):</u> addition of 5% Dextrose injection and updated storage of diluted solution of sotrovimab | Revised 09/2021 |
| • <u>Overall Safety Summary, Clinical Trials Experience (Section 6.1):</u> addition of hypersensitivity adverse reaction data | Revised 09/2021 |
| • <u>Clinical Trial Results and Supporting Data for EUA (Section 18):</u> updated with efficacy results for the full population | Revised 09/2021 |

Sotrovimab has been authorized by FDA for the emergency use described above.

Sotrovimab is not FDA-approved for this use.

Sotrovimab is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of sotrovimab under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

This EUA is for the use of the unapproved product sotrovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-COV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death [see *Limitations of Authorized Use*].

The following medical conditions or other factors may place adults and pediatric patients (12 to 17 years of age weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example ≥ 65 years of age)
- Obesity or being overweight (for example, adults with BMI > 25 kg/m², or if 12 to 17 years of age, have BMI ≥ 85 th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID 19])

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19, and authorization of sotrovimab under the EUA is not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website: <https://www.cdc.gov/coronavirus/2019->

[ncov/need-extra-precautions/people-with-medical-conditions.html](https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html). Healthcare providers should consider the benefit-risk for an individual patient.

Circulating SARS-CoV-2 viral variants may be associated with resistance to monoclonal antibodies. Healthcare providers should review the Antiviral Resistance information in Section 15 of this Fact Sheet for details regarding specific variants and resistance, and refer to the CDC website (<https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html>) as well as information from state and local health authorities regarding reports of viral variants of importance in their region to guide treatment decisions.

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.

Sotrovimab must be administered after dilution by intravenous (IV) infusion.

Healthcare providers must submit a report on all medication errors and **ALL SERIOUS ADVERSE EVENTS** potentially related to sotrovimab. See Sections 8 and 9 of the Full EUA Prescribing Information for reporting instructions below.

- See the Full EUA Prescribing Information for complete dosage, administration, and preparation instructions.
- The authorized dosage for sotrovimab is one single IV infusion of 500 mg administered as soon as possible after a positive viral test for SARS-CoV-2 and within 10 days of symptom onset [*see Dosage and Administration (2.2) and Clinical Trial Results and Supporting Data for EUA (18)*].
- Sotrovimab is available as a concentrated solution and must be diluted prior to administration.
- Administer 500 mg of sotrovimab by IV infusion over 30 minutes.
- Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.
- Patients treated with sotrovimab should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect “high touch” surfaces, and frequent handwashing) according to CDC guidelines.

The authorized dosage may be updated as additional data from clinical trials becomes available.

For information on clinical trials that are testing the use of sotrovimab in COVID-19, please see www.clinicaltrials.gov.

Contraindications

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

Dosing

Patient Selection and Treatment Initiation

This section provides essential information on the unapproved product sotrovimab, for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death [*see Limitations of Authorized Use*].

The following medical conditions or other factors may place adults and pediatric patients (12 to 17 years of age weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example ≥ 65 years of age)
- Obesity or being overweight (for example, adults with BMI >25 kg/m², or if 12 to 17 years of age, have BMI ≥ 85 th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis, and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID 19])

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19, and authorization of sotrovimab under the EUA is not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website: <https://www.cdc.gov/coronavirus/2019-ncov/need->

[extra-precautions/people-with-medical-conditions.html](#). Healthcare providers should consider the benefit-risk for an individual patient.

Dosage

The dosage of sotrovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) is 500 mg of sotrovimab. Sotrovimab should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset. Sotrovimab must be diluted and administered as a single IV infusion over 30 minutes.

Dosage Adjustment in Specific Populations

No dosage adjustment is recommended based on renal impairment, during pregnancy or while lactating [see Full EUA Prescribing Information, Use in Specific Populations (11)].

Preparation and Administration

Preparation

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

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

- Gather the materials for preparation:
 - Choose from the following:
 - Polyvinyl chloride (PVC) or polyolefin (PO), sterile, prefilled 50-mL or 100-mL infusion bag containing 0.9% Sodium Chloride Injection, or
 - PVC, sterile, prefilled 50-mL or 100-mL infusion bag containing 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 a 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.

- Gather the materials for infusion:
 - 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 30 minutes. Due to potential overflow 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.

Storage

Refrigerate unopened vials at 2°C to 8°C (36°F to 46°F) in original carton. Do not freeze or shake. Protect from light.

Warnings

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

Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been observed with

administration of sotrovimab [see Full EUA Prescribing Information, 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:

- 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.

Consider slowing or stopping the infusion and administer appropriate medications and/or supportive care if an infusion-related reaction occurs.

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.

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.

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 patients [see *Limitations of Authorized Use*]:

- 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).

Side Effects

Adverse events have been reported with sotrovimab [see Full EUA Prescribing Information, Overall Safety Summary (6.1)].

Additional adverse events associated with sotrovimab may become apparent with more widespread use.

INSTRUCTIONS FOR HEALTHCARE PROVIDERS

As the healthcare provider, you must communicate to your patient or parent/caregiver, as age appropriate, information consistent with the “Fact Sheet for Patients, Parents, and Caregivers” (and provide a copy of the Fact Sheet) prior to the patient receiving sotrovimab, including:

- FDA has authorized the emergency use of sotrovimab for treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death [see *Limitations of Authorized Use*].
- The patient or parent/caregiver has the option to accept or refuse sotrovimab.
- The significant known and potential risks and benefits of sotrovimab and the extent to which such risks and benefits are unknown.
- Information on available alternative treatments and the risks and benefits of those alternatives, including clinical trials.
- Patients treated with sotrovimab should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect “high touch” surfaces, and frequent handwashing) according to CDC guidelines.

For information on clinical trials that are testing the use of sotrovimab for COVID-19, please see www.clinicaltrials.gov.

MANDATORY REQUIREMENTS FOR ADMINISTRATION OF SOTROVIMAB UNDER EMERGENCY USE AUTHORIZATION

In order to mitigate the risks of using this unapproved product under the EUA and to optimize the potential benefit of sotrovimab, the following steps are required. Use of sotrovimab under this EUA is limited to the following (all requirements **must** be met):

1. Treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death [see *Limitations of Authorized Use*].

2. As the healthcare provider, communicate to your patient or parent/caregiver information consistent with the “Fact Sheet for Patients, Parents, and Caregivers” prior to the patient receiving sotrovimab. Healthcare providers (to the extent practicable given the circumstances of the emergency) must document in the patient’s medical record that the patient/caregiver has been:
 - a. Given the “Fact Sheet for Patients, Parents, and Caregivers”,
 - b. Informed of alternatives to receiving authorized sotrovimab, and
 - c. Informed that sotrovimab is an unapproved drug that is authorized for use under this Emergency Use Authorization.
3. Patients with known hypersensitivity to any ingredient of sotrovimab must not receive sotrovimab.
4. The prescribing healthcare provider and/or the provider’s designee is/are responsible for mandatory reporting of all medication errors and serious adverse events* potentially related to sotrovimab within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words “Sotrovimab use for COVID-19 under Emergency Use Authorization (EUA)” in the description section of the report.
 - 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.
 - Submitted reports should include in the field name, “Describe Event, Problem, or Product Use/Medication Error” the statement “Sotrovimab use for COVID-19 under Emergency Use Authorization (EUA).”

*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;
 - a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.
5. 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.
6. OTHER REPORTING REQUIREMENTS
- Healthcare facilities and providers must report therapeutics information and utilization data through HHS Protect, Teletracking or National Healthcare Safety Network (NHSN) as directed by the U.S. Department of Health and Human Services.
 - 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.

APPROVED AVAILABLE ALTERNATIVES

There is no adequate, approved and available alternative to sotrovimab for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death. Additional information on COVID-19 treatments can be found at <http://www.covid19treatmentguidelines.nih.gov/>. The healthcare provider should visit <https://clinicaltrials.gov/> to determine whether the patient may be eligible for enrollment in a clinical trial.

AUTHORITY FOR ISSUANCE OF THE EUA

The Secretary of the Department of Health and Human Services (HHS) has declared a public health emergency that justifies the emergency use of drugs and biological products during the COVID-19 pandemic. In response, the FDA has issued this EUA, as requested by GlaxoSmithKline, for the unapproved product, sotrovimab, for the treatment of mild-to-moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-COV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.¹ As a healthcare provider,

¹ The healthcare provider should visit <https://clinicaltrials.gov/> to determine whether there is an active clinical trial for the product in this disease/condition and whether enrollment of the patient(s) in a clinical trial is more appropriate than product use under this EUA.

you must comply with the mandatory requirements of this EUA (see above).

Although limited scientific information is available, based on the totality of the scientific evidence available to date, it is reasonable to believe that sotrovimab may be effective for the treatment of mild-to-moderate COVID-19 in certain at-risk patients as specified in this Fact Sheet. You may be contacted and asked to provide information to help with the assessment of the use of the product during this emergency.

This EUA for sotrovimab will end when the Secretary determines that the circumstances justify the EUA no longer exist or when there is a change in the approval status of the product such that an EUA may no longer be needed.

CONTACT INFORMATION

For additional information visit www.sotrovimabinfo.com

If you have questions, please call the GSK COVID Contact Center at 1-866-GSK-COVID (866-475-2684).

END SHORT VERSION FACT SHEET

Long Version Begins on Next Page

FULL EUA PRESCRIBING INFORMATION

FULL EUA PRESCRIBING INFORMATION: CONTENTS*

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*Sections or subsections omitted from the full prescribing information are not listed.

1 AUTHORIZED USE

Sotrovimab is authorized for use under an Emergency Use Authorization (EUA) for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death [see *Clinical Trial Results and Supporting Data for EUA (18)*].

LIMITATIONS OF AUTHORIZED USE

- 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).
- 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 [see *Warnings and Precautions (5.2)*].

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Sotrovimab should be administered as soon as possible after a positive viral test for SARS-CoV-2 and within 10 days of symptom onset in adults and pediatric patients (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death [see *Authorized Use (1) and Clinical Trial Results and Supporting Data for EUA (18)*].

The following medical conditions or other factors may place adults and pediatric patients (12 to 17 years of age weighing at least 40 kg) at higher risk for progression to severe COVID-19:

- Older age (for example, ≥ 65 years of age)
- Obesity or being overweight (for example, adults with BMI >25 kg/m², or if 12 to 17, have BMI ≥ 85 th percentile for their age and gender based on CDC growth charts, https://www.cdc.gov/growthcharts/clinical_charts.htm)
- Pregnancy
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or immunosuppressive treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (for example, chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis, and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (for example, cerebral palsy) or other conditions that confer medical complexity (for example, genetic or metabolic syndromes and severe congenital anomalies)
- Having a medical-related technological dependence (for example, tracheostomy, gastrostomy, or positive pressure ventilation [not related to COVID 19])

Other medical conditions or factors (for example, race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19, and authorization of sotrovimab under the EUA is not limited to the medical conditions or factors listed above. For additional information on medical conditions and factors associated with increased risk for progression to severe COVID-19, see the CDC website: <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>. Healthcare providers should consider the benefit-risk for an individual patient.

2.2 Dosage

The dosage of sotrovimab in adults and pediatric patients (12 years of age and older weighing at least 40 kg) is a single intravenous (IV) infusion of 500 mg. Sotrovimab should be given as soon as possible after positive results of direct SARS-CoV-2 viral testing and within 10 days of symptom onset. Sotrovimab must be diluted and administered as a single IV infusion over 30 minutes.

2.3 Dosage Adjustment in Specific Populations

Pregnancy or Lactation

No dosage adjustment is recommended in pregnant or lactating women [see *Use in Specific Populations (11.1, 11.2)*].

Pediatric Use

No dosage adjustment is recommended in pediatric patients who weigh at least 40 kg and are 12 years of age and older. Sotrovimab is not authorized for patients under 12 years of age or pediatric patients weighing less than 40 kg [see *Use in Specific Populations (11.3)*].

Geriatric Use

No dosage adjustment is recommended in geriatric patients [see *Use in Specific Populations (11.4)*].

Renal Impairment

No dosage adjustment is recommended in patients with renal impairment [see *Use in Specific Populations (11.5)*].

2.4 Dose Preparation and Administration

Preparation

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

Sotrovimab injection should be prepared by a qualified healthcare professional using aseptic technique:

- Gather the materials for preparation:
 - Choose from the following:
 - Polyvinyl chloride (PVC) or polyolefin (PO), sterile, prefilled 50-mL or 100-mL infusion bag containing 0.9% Sodium Chloride Injection, or
 - PVC, sterile, prefilled 50-mL or 100-mL infusion bag containing 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.

- Gather the materials for infusion:
 - 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 30 minutes. Due to potential overflow 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.

Storage

This product is preservative-free; therefore, the diluted infusion solution should be administered immediately. If immediate administration is not possible, store the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) or up to 6 hours at room temperature (up to 25°C [up to 77°F]) including transportation and infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 15 minutes prior to administration.

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 for IV infusion after dilution.

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.

Consider slowing or stopping the infusion and administer appropriate medications and/or

supportive care if an infusion-related reaction occurs.

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 patients [*see Limitations of Authorized Use*]:

- 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).

6 OVERALL SAFETY SUMMARY

6.1 Clinical Trials Experience

The ongoing Phase 1/2/3 double-blind, placebo-controlled, randomized study enrolled 1,057 non-hospitalized patients with COVID-19 (COMET-ICE). The safety of sotrovimab is based on an analysis from 1049 patients [*see Clinical Trial Results and Supporting Data for EUA (18)*].

All patients received a single 500-mg infusion of sotrovimab (n = 523) or placebo (n = 526).

Two patients experienced treatment interruptions due to infusion site extravasation; infusion was completed for each.

Infusion-related reactions, including immediate hypersensitivity reactions, have been observed in 1% of patients treated with sotrovimab and 1% of patients treated with placebo in COMET-ICE. 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 patients; the infusion was immediately discontinued, and the patient received

epinephrine. The event resolved but recurred within 2 hours; the patient 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 patients hospitalized due to COVID-19 [see *Warnings and Precautions (5.1, 5.3)*].

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

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 infusion and observe patients for at least 1 hour after infusion is complete.

8 ADVERSE REACTIONS AND MEDICATION ERRORS REPORTING REQUIREMENTS AND INSTRUCTIONS

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

Completion of an FDA MedWatch Form to report all medication errors and serious adverse events* occurring during sotrovimab use and considered to be potentially related to sotrovimab is mandatory and must be done by the prescribing healthcare provider and/or the provider's designee. These adverse events must be reported within 7 calendar days from the onset of the event:

*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;
- a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

If a serious and unexpected adverse event occurs and appears to be associated with the use of sotrovimab, the prescribing healthcare provider and/or the provider's designee should complete and submit a MedWatch form to FDA 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.

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 should 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:

1. In Section A, Box 1, provide the patient's initials in the Patient Identifier.

2. In Section A, Box 2, provide the patient's date of birth.
3. In Section B, Box 5, description of the event:
 - a. Write "Sotrovimab use for COVID-19 under Emergency Use Authorization (EUA)" as the first line.
 - b. 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.
4. In Section G, Box 1, name and address:
 - a. Provide the name and contact information of the prescribing healthcare provider or institutional designee who is responsible for the report.
 - b. Provide the address of the treating institution (NOT the healthcare provider's office address).

9 OTHER REPORTING REQUIREMENTS

- Healthcare facilities and providers must report therapeutics information and utilization data through HHS Protect, Teletracking or National Healthcare Safety Network (NHSN) as directed by the U.S. Department of Health and Human Services.
- 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.

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

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.

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.

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 based on an allometric scaling approach (which accounted for effect of body weight changes associated with age on clearance and volume of distribution).

11.4 Geriatric Use

Of the 528 patients receiving sotrovimab in COMET-ICE, 20% were 65 years of age and older and 11% were over 70 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 $\mu\text{g/mL}$]). 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.

14.2 Pharmacokinetics

In COMET-ICE, the geometric mean C_{max} following a 1 hour IV infusion was 117.6 $\mu\text{g/mL}$ ($N = 290$, CV% 46.5), and the geometric mean Day 29 concentration was 24.5 $\mu\text{g/mL}$ ($N = 372$, CV% 42.4) from all subjects with an available Day 29 sample.

Distribution

The mean steady-state volume of distribution of sotrovimab was 8.1 L.

Metabolism

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

Elimination

The mean systemic clearance was 125 mL/day with a median terminal half-life of approximately 49 days.

Specific Populations

The effect of different covariates (e.g., age, sex, race, body weight, disease severity, hepatic impairment) on the PK of sotrovimab is unknown. 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.

15 MICROBIOLOGY/RESISTANCE INFORMATION

Antiviral Activity

The 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 cell culture 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 cell culture 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.

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.

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 TCID₅₀ 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 website².

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 epitope amino acid substitutions P337H/L/R/T, E340A/K/G, and K356T 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), K356T (5.90), and P337T (5.4). 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 EC₅₀ value), B.1.351 (Beta, South Africa origin: L18F, D80A, D215G, R246I, K417N, E484K, N501Y, D614G, A701V; 0.6-fold change in EC₅₀ value), P.1 (Gamma, Brazil origin: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F; 0.35-fold change in EC₅₀ value), B.1.427/B.1.429 (Epsilon, California origin: S13I, W152C, L452R, D614G; 0.7-fold change in EC₅₀ value), B.1.526 (Iota, New York origin: L5F, T95I, D253G, E484K, D614G, A701V; 0.6-fold change in EC₅₀ value), B.1.617.1 (Kappa, India origin: T95I, G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H; 0.7-fold change in EC₅₀ value), B.1.617.2 (Delta, India origin: T19R, G142D, E156G, F157-, R158-, L452R, T478K, D614G, P681R, D950N; 1-fold change in EC₅₀ value), AY.1 (Delta Plus, India origin: T19R, T95I, G142D, E156G, F157-, R158-, W258L, K417N, L452R, T478K, D614G, P681R, D950N; 1.1-fold change in EC₅₀ value), AY.2 (Delta Plus, India origin: T19R, V70F, G142D, E156G, F157-, R158-, A222V, K417N, L452R, T478K, D614G, P681R, D950N; 1.3-fold change in EC₅₀ value), C.37 (Lambda, Peru origin: G75V, T76I, del246-252, L452Q, F490S, T859N; 1.5-fold change in EC₅₀ value), and B.1.621 (Mu, Colombia origin: T95I, Y144T, Y145S, ins146N, R346K, E484K, N501Y, D614G, P681H, D950N; 1.3-fold change in EC₅₀ value) variant spike proteins (Table 1). Microneutralization data using authentic SARS-CoV-2 variant viruses indicate that sotrovimab retains activity against the B.1.1.7 (Alpha, UK origin; 3-fold change in EC₅₀ value), B.1.351 (Beta, South Africa origin; 1.2-fold change in EC₅₀ value), P.1 (Gamma, Brazil origin; 1.6-fold change in EC₅₀ value), B.1.617.1 (Kappa, India origin; 0.9-fold change in EC₅₀ value), and B.1.617.2 (Delta, India origin; 0.4-fold change in EC₅₀ value) variants (Table 2).

². <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-proportions.html>

Table 1: Pseudotyped Virus-Like Particle Neutralization Data for SARS-CoV-2 Variant Substitutions with Sotrovimab

| Lineage with Spike Protein Substitution | Country First Identified | WHO Nomenclature | Key Substitutions Tested | Fold Reduction in Susceptibility |
|---|--------------------------|------------------|------------------------------------|----------------------------------|
| B.1.1.7 | UK | Alpha | N501Y ^a | No change ^b |
| B.1.351 | South Africa | Beta | K417N + E484K + N501Y ^c | No change ^b |
| P.1 | Brazil | Gamma | K417T + E484K + N501Y ^d | No change ^b |
| B.1.427/B.1.429 | USA (California) | Epsilon | L452R ^e | No change ^b |
| B.1.526 ^f | USA (New York) | Iota | E484K ^g | No change ^b |
| B.1.617.1 | India | Kappa | L452R + E484Q ^h | No change ^b |
| B.1.617.2 | India | Delta | L452R + T478K ⁱ | No change ^b |
| AY.1/AY.2 ^j | India | Delta [+K417N] | L452R + T478K + K417N ^k | No change ^b |
| C.37 | Peru | Lambda | L452Q, F490S ^l | No change ^b |
| B.1.621 | Colombia | Mu | R346K, E484K, N501Y ^m | No change ^b |

^a Pseudotyped VSV-luc expressing variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: del69-70, del144, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H.

^b No change: <5-fold reduction in susceptibility.

^c Pseudotyped VSV-luc expressing variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: L18F, D80A, D215G, R246I, K417N, E484K, N501Y, A701V.

^d Pseudotyped VSV-luc expressing variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I, V1176F.

^e Pseudotyped VSV-luc expressing variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: S13I, W152C, L452R, D614G.

^f Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).

^g Pseudotyped VSV-luc expressing variant spike protein was tested. The following changes from

wild-type spike protein are found in the variant: L5F, T95I, D253G, E484K, D614G, A701V.

^h Pseudotyped VSV-luc expressing variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: T95I, G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H.

ⁱ Pseudotyped VSV-luc expressing variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: T19R, G142D, E156G, del157-158, L452R, T478K, D614G, P681R, D950N.

^j Commonly known as "Delta plus".

^k Pseudotyped VSV-luc expressing variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: AY.1 T19R, T95I, G142D, E156G, del157-158, W258L, K417N, L452R, T478K, D614G, P681R, D950N; AY.2. T19R, V70F, G142D, E156G, del157-158, A222V, K417N, L452R, T478K, D614G, P681R, D950N.

^l Pseudotyped VSV-luc expressing variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: G75V, T76I, del246-252, L452Q, F490S, T859N.

^m Pseudotyped VSV-luc expressing variant spike protein was tested. The following changes from wild-type spike protein are found in the variant: T95I, Y144T, Y145S, ins146N, R346K, E484K, N501Y, D614G, P681H, D950N.

Table 2: Authentic SARS-CoV-2 Neutralization Data for SARS-CoV-2 Variant Substitutions for Sotrovimab

| SARS-CoV-2 Lineage | Country First Identified | WHO Nomenclature | Key Substitutions^a | Fold Reduction in Susceptibility |
|---------------------------|---------------------------------|-------------------------|--------------------------------------|---|
| B.1.1.7 | UK | Alpha | N501Y | No change ^b |
| B.1.351 | South Africa | Beta | K417N + E484K + N501Y | No change ^b |
| P.1 | Brazil | Gamma | K417T + E484K + N501Y | No change ^b |
| B.1.617.1 | India | Kappa | L452R + E484Q | No change ^b |
| B.1.617.2 | India | Delta | L452R + T478K | No change ^b |

^a For variants with more than one substitution of concern, only the one(s) with the greatest impact on activity is (are) listed.

^b No change: <5-fold reduction in susceptibility.

Limited nucleotide sequencing data from a total of 539 COMET-ICE subjects indicated that 36 subjects (16 treated with placebo and 20 treated with sotrovimab) carried the B.1.1.7 (Alpha, UK origin) variant. Four subjects (2 treated with placebo and 2 treated with sotrovimab) carried the N501Y substitution. Thirty-one subjects (19 treated with placebo and 12 treated with

sotrovimab) carried the B.1.427/B.1.429 (Epsilon, California origin) variant. Eight additional subjects carried the L452R substitution (6 treated with placebo and 2 treated with sotrovimab). Eleven subjects carried the P.1 (Gamma, Brazil origin) variant (3 treated with placebo and 8 treated with sotrovimab). Three subjects carried the B.1.526 (Iota, New York origin) variant with the E484K substitution (2 treated with placebo and 1 treated with sotrovimab), while 9 subjects (4 treated with placebo and 5 treated with sotrovimab) carried the S477N substitution that has been associated with the B.1.526 (Iota, New York origin) variant. Additionally, 10 subjects carried the E484K substitution (4 treated with placebo and 6 treated with sotrovimab), 2 carried the S494P substitution (1 treated with placebo and 1 treated with sotrovimab), and 3 carried the S494P substitution with the N501Y substitution (2 treated with placebo and 1 treated with sotrovimab). Two subjects in the group receiving sotrovimab (1 carrying the B.1.427/B.1.429 [Epsilon, California origin] variant and 1 carrying the B.1.1.7 [Alpha, UK origin] variant) progressed to hospitalization. Four subjects in the placebo group (2 carrying the E484K substitution, 1 carrying the P.1 [Gamma, Brazil origin] variant, and 1 carrying the B.1.1.7 [Alpha, UK origin] variant) progressed to hospitalization. None of the subjects with currently available baseline sequences carried the full complement of substitutions characteristic of the B.1.351 (Beta, South Africa origin) or B.1.617 (Delta, India origin) variants.

In COMET-ICE, post-baseline epitope substitutions were detected in 20 subjects in the cohort receiving sotrovimab (spike protein substitutions P337L/E340K [49.4%/54.8% allele frequency]; E340A [99.0%]; E340K [5 subjects: 8.0% to 99.9%]; E340V [73.1%]; A344V [6.2%]; R346G [5.2%]; K356R [7.5%]; S359G [2 subjects: 12.2% and 8.3%]; C361T [7 subjects: 5.0% to 15.7%]). Of the substitutions detected at baseline and post-baseline, L335F, L335S, P337L, G339C, E340A, E340K, A344V, R346G, R346I, K356N, K356R, R357I, I358V and S359G substitutions have been assessed phenotypically using a pseudotyped VLP system. P337L, E340A, and E340K substitutions confer reduced susceptibility to sotrovimab (>180-fold, >100-fold, and >297-fold changes in EC₅₀ value, respectively). Sotrovimab retains activity against L335F (0.8-fold change in EC₅₀ value), L335S (0.9-fold change in EC₅₀ value), G339C (1.2-fold change in EC₅₀ value), A344V (1.1-fold change in EC₅₀ value), R346G (0.9-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 substitutions is not yet known. Data collection and analysis is still ongoing.

Immune Response Attenuation

There is a theoretical risk that antibody administration may attenuate the endogenous immune response to SARS-CoV-2 and make patients more susceptible to re-infection.

16 NONCLINICAL TOXICOLOGY

Carcinogenesis, mutagenesis, and reproductive toxicology studies with sotrovimab have not been conducted.

In a toxicology study in monkeys, sotrovimab had no adverse effects when administered intravenously.

In tissue cross reactivity studies using human and monkey adult tissues, no binding of clinical concern was detected for sotrovimab.

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

17 ANIMAL PHARMACOLOGIC AND EFFICACY DATA

In a Syrian Golden hamster model of SARS-CoV-2 infection, antiviral activity was demonstrated using a single dose of sotrovimab which was administered intraperitoneally at 24- or 48-hours prior to infection. Animals receiving 5 mg/kg or more of the 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 virus in the lung (as measured by TCID₅₀) were significantly decreased versus controls in hamsters receiving 0.5 mg/kg or more of the antibody.

Protection was also observed in the Syrian Golden hamster model using the SARS-CoV-2 B.1.351 (Beta, South Africa origin) variant. Significant reductions in total and replication competent virus were observed on Day 4 post-infection in animals receiving a single intraperitoneal dose of 0.5, 2, 5, or 15 mg/kg sotrovimab compared to isotype control antibody-treated animals.

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

The clinical data supporting this EUA are based on the analysis of the Phase 1/2/3 COMET-ICE trial (NCT #04545060). COMET-ICE is an ongoing, randomized, double-blind, placebo-controlled trial studying sotrovimab for the treatment of subjects with mild-to-moderate COVID-19 (subjects with COVID-19 symptoms who are not hospitalized). Eligible subjects were 18 years of age and older with at least one of the following comorbidities: diabetes, obesity (BMI >30), chronic kidney disease, congestive heart failure, chronic obstructive pulmonary disease, or moderate to severe asthma, or were 55 years of age and older regardless of 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 and severely immunocompromised patients were excluded from the trial.

A total of 1,057 eligible subjects were randomized to receive a single 500-mg infusion of sotrovimab (n = 528) or placebo (n = 529) over 1 hour (Intent to Treat [ITT] population at Day 29). At baseline, the median age was 53 years (range:17 to 96); 20% of subjects were 65 years of age or older and 11% were over 70 years of age; 46% of subjects were male; 87% were White, 8% Black or African American, 4% Asian, 65% Hispanic or Latino. Fifty-nine

percent of subjects received sotrovimab or placebo within 3 days of COVID-19 symptom onset and 41% within 4 to 5 days. The four most common pre-defined risk factors or comorbidities were obesity (63%), 55 years of age or older (47%), diabetes requiring medication (22%), and moderate-to-severe asthma (17%). Overall, baseline demographic and disease characteristics were well balanced between the treatment arms.

The primary endpoint, progression of COVID-19 at Day 29, was reduced by 79% (adjusted relative risk reduction) in recipients of sotrovimab versus placebo. Table 3 provides the results for the primary and key secondary endpoint of COMET-ICE.

Table 3. Efficacy Results in Adults with Mild-to-Moderate COVID-19 at Day 29

| | Sotrovimab n = 528 | Placebo n = 529 |
|---|-------------------------------|----------------------------|
| Progression of COVID-19 (defined as hospitalization for >24 hours for acute management of any illness or death from any cause) (Day 29)^a | | |
| Proportion (n, %) | 6 (1%) | 30 (6%) |
| Adjusted Relative Risk Reduction (95% CI) | 79% (50%, 91%) | |
| All-cause mortality (up to Day 29) | | |
| Proportion (n, %) | 0 | 2 (<1%) |

^a The determination of primary efficacy was based on a planned interim analysis of 583 patients, which had similar findings to those seen in the full population above. The adjusted relative risk reduction was 85% with a 97.24% CI of (44%, 96%) and p-value = 0.002.

Within the subset of the ITT population who had a central laboratory confirmed, virologically quantifiable nasopharyngeal swab at Day 1 and Day 8 (n = 639), the mean decline from baseline in viral load at Day 8 was greater in subjects treated with sotrovimab (-2.610 log₁₀ copies/mL) compared to that in subjects treated with placebo (-2.358); mean difference = -0.251, 95% CI: (-0.415, -0.087).

19 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Sotrovimab injection 500 mg (62.5 mg/mL) is a sterile, preservative-free, clear, colorless or yellow to brown solution supplied in a carton containing one single-dose glass vial with a rubber vial stopper (not made with natural rubber latex) and a flip-off cap (NDC 0173-0901-86).

Storage and Handling

Sotrovimab is preservative-free. Discard unused portion.

Store unopened vials refrigerated at 2°C to 8°C (36°F to 46°F) in original carton. Do not freeze or shake. Protect from light.

The solution of sotrovimab in the vial is preservative-free and requires dilution prior to administration. The diluted infusion solution of sotrovimab should be administered immediately. If immediate administration is not possible, store the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) or up to 6 hours at room temperature (up to 25°C [up to 77°F]) including transportation and infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 15 minutes prior to administration.

20 PATIENT COUNSELING INFORMATION

Patients treated with sotrovimab should continue to self-isolate and use infection control measures (e.g., wear mask, isolate, social distance, avoid sharing personal items, clean and disinfect “high touch” surfaces, and frequent handwashing) according to CDC guidelines. Also, see “Fact Sheet for Patients, Parents, and Caregivers”.

21 CONTACT INFORMATION

For additional information visit www.sotrovimabinfo.com

If you have questions, please call the GSK COVID Contact Center at 1-866-GSK-COVID (866-475-2684).



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FACT SHEET FOR PATIENTS, PARENTS, AND CAREGIVERS

Emergency Use Authorization (EUA) of Sotrovimab for the Treatment of Coronavirus Disease 2019 (COVID-19)

You are being given a medicine called **sotrovimab** for the treatment of coronavirus disease 2019 (COVID-19). This Fact Sheet contains information to help you understand the potential risks and potential benefits of taking sotrovimab, which you may receive.

Receiving sotrovimab may benefit certain people with COVID-19.

Read this Fact Sheet for information about sotrovimab. Talk to your healthcare provider if you have any questions. It is your choice to receive sotrovimab or stop it at any time.

What is COVID-19?

COVID-19 is caused by a virus called a coronavirus. People can get COVID-19 through contact with another person who has the virus.

COVID-19 illnesses have ranged from very mild (including some with no reported symptoms) to severe, including illness resulting in death. While information so far suggests that most COVID-19 illness is mild, serious illness can happen and may cause other medical conditions to become worse. People of all ages with severe, long-lasting (chronic) medical conditions like heart disease, lung disease, diabetes, for example, and other conditions including obesity, seem to be at higher risk of being hospitalized for COVID-19. Older age, with or without other conditions, also places people at higher risk of being hospitalized for COVID-19.

What are the symptoms of COVID-19?

The symptoms of COVID-19 are fever, cough, and shortness of breath, which may appear 2 to 14 days after exposure. Serious illness, including breathing problems, can occur and may cause your other medical conditions to become worse.

What is sotrovimab?

Sotrovimab is an investigational medicine used to treat mild-to-moderate symptoms of COVID-19 in adults and children (12 years of age and older weighing at least 88 pounds [40 kg]) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk of progression to severe COVID-19, including hospitalization or death. Sotrovimab is investigational because it is still being studied. There is limited information about the safety and effectiveness of using sotrovimab to treat people with mild-to-moderate COVID-19.

The U.S. Food & Drug Administration (FDA) has authorized the emergency use of sotrovimab for the treatment of COVID-19 under an Emergency Use Authorization (EUA). For more information on EUA, see the “**What is an Emergency Use Authorization (EUA)?**” section at the end of this Fact Sheet.

Who should not receive sotrovimab?

Do not take sotrovimab if you have had a serious allergic reaction to sotrovimab or to any of the ingredients in sotrovimab.

What are the ingredients in sotrovimab?

Active ingredient: sotrovimab

Inactive ingredients: L-histidine, L-histidine monohydrochloride, L-methionine, polysorbate 80, and sucrose

What should I tell my healthcare provider before I receive sotrovimab?

Tell your healthcare provider about all of your medical conditions, including if you:

- Have any allergies
- Have had a serious allergic reaction to sotrovimab or to any of the ingredients in sotrovimab
- Are pregnant or plan to become pregnant

- Are breastfeeding or plan to breastfeed
- Have any serious illnesses
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

How will I receive sotrovimab?

- You will receive 1 dose of sotrovimab.
- Sotrovimab will be given to you through a vein (intravenous or IV infusion) over 30 minutes.
- You will be observed by your healthcare provider for at least 1 hour after you receive sotrovimab.

What are the important possible side effects of sotrovimab?

Possible side effects of sotrovimab are:

- **Allergic reactions.** Allergic reactions can happen during and after infusion with sotrovimab. Tell your healthcare provider right away if you get any of the following signs and symptoms of allergic reactions: fever; difficulty breathing; low oxygen level in your blood; chills; tiredness; fast or slow heart rate; chest discomfort or pain; weakness; confusion; nausea; headache; shortness of breath; low or high blood pressure; wheezing; swelling of your lips, face, or throat; rash including hives; itching; muscle aches; dizziness; feeling faint; and sweating.

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

These are not all the possible side effects of sotrovimab. Not many people have been given sotrovimab. Serious and unexpected side effects may happen. Sotrovimab is still being studied, so it is possible that all of the risks are not known at this time.

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.

What other treatment choices are there?

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 not approved 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 to be treated or not to be treated with sotrovimab. Should you decide not to receive sotrovimab, or stop it at any time, it will not change your 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.

How do I report side effects with sotrovimab?

Tell your healthcare provider right away 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 www.sotrovimabinfo.com
- Call the GSK COVID Contact Center at 1-866-GSK-COVID (866-475-2684)

- Visit <https://www.covid19treatmentguidelines.nih.gov/>
- Visit <https://combatcovid.hhs.gov/i-have-covid-19-now/available-covid-19-treatment-options>
- Contact your local or state public health department

What is an Emergency Use Authorization (EUA)?

The FDA has made sotrovimab available under an emergency access mechanism called an 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 products during the COVID-19 pandemic.

Sotrovimab has not undergone the same type of review as an FDA-approved medicine. In issuing an EUA under the COVID-19 public health emergency, the FDA must determine, among other things, that based on the totality of scientific evidence available, it is reasonable to believe that the product may be effective for diagnosing, treating, or preventing COVID-19, or a serious or life-threatening disease or condition caused by COVID-19; that the known and potential benefits of the product, when used to diagnose, treat, or prevent such disease or condition, outweigh the known and potential risks of such product; and that there are no adequate, approved and available alternatives. All of these criteria must be met to allow for the medicine to be used in the treatment of patients during the COVID-19 pandemic.

The EUA for sotrovimab is in effect for the duration of the COVID-19 declaration justifying emergency use of these medicines, unless terminated or revoked (after which the products may no longer be used).



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