Introduction[1-2]

Sotrovimab (Xevudy®) is provisionally registered by the Therapeutic Goods Administration for use in Australia for the treatment of COVID-19.

Sotrovimab is not an alternative or substitute for vaccination. **Vaccination is the preferred and primary option for the prevention of COVID-19.**

Clinical trials for sotrovimab were conducted when the early variants of SARS-CoV-2 were in circulation. Clinicians should consider the SARS-CoV-2 variant being targeted and the possibility of reduced efficacy.

This guideline requires endorsement by your local Drug and Therapeutics Committee (DTC) prior to implementation. Additional resources to support the safe and appropriate use of sotrovimab are available here.

Drug class and mechanism of action[1-2]

Recombinant human IgG1 monoclonal antibody targeting the spike protein of SARS-CoV-2, which is thought to prevent membrane fusion after the virus binds to the human ACE2 receptor. Sotrovimab appears to retain activity against the Alpha; Beta; Gamma; Epsilon; Iota; Delta and Omicron variants of SARS-CoV-2.

Approved indications[1-4]

Use of sotrovimab in NSW must be in accordance with the ACI Model of Care. The information below is derived from the Approved Product Information and National COVID-19 Clinical Evidence Taskforce recommendations and may differ from restrictions currently in place in NSW.

Treatment of COVID-19 in adults and adolescents (aged 12 years and over and weighing at least 40 kg) who do not require initiation of oxygen due to COVID-19 and who are at increased risk of progression to hospitalisation or death.

Adult patients *(from COMET-ICE trial)*	**Adolescents aged 12 years and over** *(from National COVID-19 Clinical Evidence Taskforce consensus recommendation)*
• Diabetes requiring medication • Obesity (BMI > 30m^2) • Chronic kidney disease (eGFR < 60 mL/min) • Congestive heart failure (NYHA ≥ class 2) • Chronic obstructive pulmonary disease • Moderate to severe asthma (requiring inhaled steroids to control the symptoms or has been prescribed a course of oral corticosteroids in the past year) • Aged 55 years and older	• Paediatric Complex Chronic Conditions (PCCC): congenital and genetic, cardiovascular, gastrointestinal, malignancies, metabolic, neuromuscular, renal and respiratory conditions • Severe asthma • Obesity

The efficacy of sotrovimab is unclear in partially or fully vaccinated individuals (individuals who had received one or more doses of SARS-CoV-2 vaccine were excluded from the trial).

See ACI Model of Care for further advice on use in vaccinated patients.

NSW Health clinicians seeking advice and guidance surrounding the use of sotrovimab in children and adolescents, can contact The Sydney Children's Hospital Network COVID-19 Clinical Treatment Review Panel by calling the switch of the Children's Hospital at Westmead (02 9845 0000) or Sydney Children's Hospital, Randwick (02 9382 1111) and asking for 'COVID-19 on-call'.

Contraindications and precautions[1,2,4,8]

- Contraindicated in patients with known hypersensitivity to sotrovimab, or any of the excipients (histidine, histidine hydrochloride monohydrate, sucrose, methionine, polysorbate 90) in the product, Chinese Hamster Ovary cell products or other recombinant human or humanised antibodies.
- Exercise caution in patients with a history of anaphylaxis to other medicines.
- Safety and efficacy of sotrovimab in children less than 12 years of age or weighing less than 40 kg has not yet been established, therefore use in these patients is not recommended.
- See *Pregnancy and breastfeeding* section for recommendations in pregnancy and breastfeeding.

Pregnancy and breastfeeding[2,4]

The National COVID-19 Clinical Evidence Taskforce has made a conditional recommendation regarding the use of sotrovimab in pregnant and breastfeeding women. Treatment should be considered if the benefit outweighs the possible but unknown risks. The most up to date advice can be found here.

Pregnancy

Sotrovimab should be used in only in the second and third trimesters of pregnancy if the expected benefit to the mother justifies the potential risk to the foetus.

Sotrovimab has been classified **pregnancy category B2** by the Therapeutic Goods Administration. There is potential for placental transfer of sotrovimab from the mother to the developing foetus.

Breastfeeding

There are insufficient data on the presence of sotrovimab in human milk and there are no data in lactating animals. The amount present in breastmilk is likely to be very low as sotrovimab is a large protein molecule. The median elimination half-life of sotrovimab is 49 days. A decision must be made whether to discontinue breastfeeding or to abstain from sotrovimab therapy considering the benefit of breastfeeding for the child and the benefit of therapy for the mother.

Drug interactions[1,9,10]

- No formal drug interaction studies have been conducted involving sotrovimab and other medications. Sotrovimab is not renally excreted or metabolised by the CYP450 enzymes. Sotrovimab is degraded by proteolytic enzymes widely distributed in the body and not restricted to hepatic tissue.
- As at 22 March 2022, drug interaction resources such as Liverpool COVID-19 Drug Interactions tool and Micromedex drug interaction tool do not identify any drug interactions. Contact the local Pharmacy Department or medicines information service for further advice.
- Interaction with COVID-19 vaccination has not been determined. It is recommended that COVID-19 vaccines should not be administered for at least 90 days after a dose of sotrovimab. Follow this link for information on medical exemptions to COVID-19 vaccination.

Presentation, storage and stability[1,12]

- Available as a single use vial of 500 mg in 8 mL (62.5 mg/mL) concentrated injection solution for infusion (after diluting). The solution in the vial should be clear and colourless to yellow or brown.
- Store unopened vials refrigerated at 2 - 8°C in original package. Protect from light. Do not freeze.
- Use medicine immediately after dilution in an intravenous bag. If this is not possible, the diluted solution may be stored at room temperature for up to 6 hours (including infusion time) or stored in the refrigerator (between 2 – 8°C) for up to 24 hours (including infusion time).

Dose, timing and route of administration[1-2]

Recommended dose is 500 mg as a single intravenous infusion over 30 minutes.

Give as soon as possible after a positive viral test for SARS-CoV-2 and **not later than 5 days** after the onset of first symptoms.

Preparation and administration[1-2,12]

Preparation of vials

The occupational hazard of intermittent low dose exposure to sotrovimab is not known. To minimise exposure, gloves and surgical mask should be worn when preparing this medication. Please refer to local protocol or guidelines on this matter.

Dilution

Sotrovimab must be diluted prior to administration and must **not** be administered as intravenous push or bolus injection – for infusion only.

1. Remove one sotrovimab 500 mg/8 mL vial from refrigerated storage and allow to come to room temperature for approximately 15 minutes before dilution (leave in original packaging during this time).
2. Visually inspect vial to ensure no particulate matter is present or damage to the vial (discard if present).
3. Gently swirl the vial several times without creating air bubbles before using.
4. Obtain an IV infusion bag containing 50 mL or 100 mL of either 0.9% sodium chloride or glucose 5% . Withdraw 8 mL from the infusion bag – if local protocols allow, this step may be omitted.
5. Using aseptic technique, withdraw 8 mL sotrovimab solution from the vial and inject into the infusion bag.
6. Gently mix infusion bag by gently rocking back and forth 3 to 5 times. Do not shake or invert the bag. Do not allow air bubbles to form.

Administration

1. Do not use the same IV line to administer other medications at the same time.
2. Attach an infusion set (PVC, PE or PU) to the infusion bag with an in-line or add-on 0.2–5 micrometre filter polyethersulfone, polysulfone, or polyamide end filter.
3. Prime the infusion set with sotrovimab infusion and then infuse intravenously over 30 minutes (until the bag is finished) via a central or peripheral line.
4. After the sotrovimab infusion is completed, flush the giving set with at least 20 mL of sodium chloride 0.9% or glucose 5% (at the same rate as the sotrovimab infusion).

Monitoring requirements[1,7,8,12]

Monitor the patient for adverse effects (see *Adverse Effects* section below).

Observe the patient's vital signs during the infusion and for 60 minutes after infusion cessation in case of hypersensitivity reactions or anaphylaxis.

Infusion reactions include fever, chills, dizziness, dyspnoea, pruritis and rash.

- For mild to moderate infusion reactions, slow or stop the infusion and treat accordingly. Note in the COMET-ICE trial, mild hypersensitivity reactions did not require pausing or discontinuation of the infusion.
- Anaphylactic reactions are rare but are a medical emergency. Stop the infusion and commence treatment immediately.

Adverse effects[1,7]

It may be difficult to distinguish between adverse effects of sotrovimab and signs and symptoms of COVID-19. As the proposed use is for a provisionally approved medicine which has no relevant post-marketing data, it is important to document and report all (from possible to confirmed) adverse effects experienced by the patient during treatment to inform its safety profile and future use. Refer to the Approved Product Information for complete list of possible adverse effects.

- **Common (≥ 1% to < 10%):** diarrhoea, hypersensitivity reactions (includes rash), infusion-related reaction, bronchospasm).
- **Rare (< 0.1%):** anaphylaxis.

Reporting[3]

- Sotrovimab is subject to additional monitoring in Australia – this will allow rapid identification of new safety information. Healthcare professionals are asked to report any suspected adverse events to the TGA, GlaxoSmithKline (drug sponsor) and via their facility's incident management system.
- Drug and Therapeutics Committee oversight in the access process will enable appropriate medicines governance and ensure the collection and analysis of patient outcomes and systematic monitoring of medicines use. Sotrovimab use and outcome reporting should occur as per local governance processes.

Summary of major changes made in version 1.4 – March 2022

- Statement regarding consideration of variant being targeted added to introduction.
- Highlighted that this drug guideline is based on the approved Product Information and National COVID-19 Clinical Evidence Taskforce advice, but that use in NSW **MUST** be in accordance with the ACI Model of Care and consider any other restrictions in place.
- Table of risk factors included for adults and adolescents at risk of progression to hospitalisation or death.
- Updated pregnancy and breastfeeding information as per National COVID-19 Clinical Evidence Taskforce advice at time of publishing. Moved to standalone section.
- General formatting changes and rewording/condensing of information (without loss of content).

References

1. Australian Product Information - Xevudy (Sotrovimab). TGA; 2021. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2021-PI-01995-1. Accessed 2022 March 8
2. Therapeutic Goods Administration. AusPAR: Sotrovimab. 2021. https://www.tga.gov.au/auspar/auspar-sotrovimab. Accessed 2022 March 8.
3. NSW Sotrovimab Clinical Working Group. Model of care for the use of sotrovimab in adults in NSW, Version 4. https://www.health.nsw.gov.au/Infectious/covid-19/communities-of- practice/Pages/model-care-adults-sotrovimab.aspx. Published 2021 August 31. Accessed 2022 March 8.
4. National COVID-19 Clinical Evidence Taskforce. Australian guidelines for the clinical care of people with COVID-19. https://covid19evidence.net.au/#living-guidelines. Published 2021. Accessed 2022 March 8.
5. Maynard SE, Thadhani R. Pregnancy and the Kidney. 2009;20(1):14-22. doi:10.1681/ASN.2008050493. Published 2008 Dec 31.
6. Wiles K, Bramham K, Seed PT, Nelson-Piercy C, Lightstone L, LC. C. Serum Creatinine in Pregnancy: A Systematic Review. 2018;4(3):408-419. doi:10.1016/j.ekir.2018.10.015. Published 2018 Oct 29.
7. Gupta A, Gonzalez-Rojas Y, Juarez E, et al. Early Covid-19 Treatment With SARS-CoV-2 Neutralizing Antibody Sotrovimab. *medRxiv.* 2021:2021.2005.2027.21257096. doi:10.1101/2021.05.27.21257096.
8. GlaxoSmithKline LLC. FDA Fact Sheet for Healthcare Providers: Emergency Use Authorization (EUA) of Sotrovimab. 2021. https://www.fda.gov/media/149534/download. Accessed 2022 March 8.
9. COVID-19 Drug Interactions Checker. https://www.covid19-druginteractions.org/checker. Accessed 2022 March 8.
10. IBM Micromedex ®. https://www.micromedexsolutions.com.acs.hcn.com.au/micromedex2/librarian/ND_PR/evidencexpert/CS/8D1E9A/ND_P/evidencexpert/DUPLICATIONSHIELDSYNC/200B3D/ND_PG/evidencexpert/ND_B/evidencexpert/ND_AppProduct/evidencexpert/ND_T/evidencexpert/PFActionId/pf.HomePage?navitem=topHome&isToolPage=true. Accessed 2022 March 8.
11. Centers for Disease Control and Prevention. Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States. CDC. https://www.cdc.gov/vaccines/covid- 19/clinical-considerations/covid-19-vaccines-us.html. Updated 2021 August 25. Accessed 2022 March 8.
12. Society of Hospital Pharmacists of Australia. Australian Injectable Drugs Handbook [Online]. In: 8th ed. Collingwood: Society of Hospital Pharmacists of Australia; 2021: https://aidh.hcn.com.au/browse/s. Accessed 2022 March 8.
13. GlaxoSmithKline. Use of Filter for Administration of Sotrovimab. In. Data on file, reference number: 01325452.
14. Cathcart AL, Havenar-Daughton C, Lempp FA, et al. The dual function monoclonal antibodies VIR-7831 and VIR-7832 demonstrate potent in vitro and in vivo activity against SARS-CoV-2. *bioRxiv*. 2021;Preprint. Available at: https://www.biorxiv.org/content/10.1101/2021.03.09.434607v9.