USE OF SOTROVIMAB FOR COVID-19 IN ADULTS DRUG GUIDELINE

Sotrovimab (Xevudy®) is provisionally registered for use in Australia for the treatment of COVID-19 in adults and adolescents (age ≥12 years and weighing at least 40 kg), who do not require oxygen and are at risk of disease progression to hospitalisation or death.[1] The decision was made on the basis of short term efficacy and safety data. Sotrovimab appears to retain activity against Alpha; Beta; Gamma; Epsilon; Iota; and Delta variants of SARS-CoV-2.[1,2]

The National COVID-19 Clinical Evidence Taskforce (NCCET) (current as at 29/09/21) provides a conditional recommendation for use of sotrovimab as a neutralising antibody therapy for adults with COVID-19 who do not require initiation of oxygen and who have one or more risk factors for disease progression.[3,4] (Certainty of evidence for outcomes: moderate for a composite endpoint of hospitalisation or death).[4] This conditional recommendation is based on the results of the COMET-ICE trial, suggesting that there would be 46 fewer events (composite endpoint) per 1000 patients (CI 95% 52 fewer- 30 fewer).[1,7] Although pregnant women were not participants in the COMET-ICE trial, the NCCET has made a conditional recommendation for treatment of COVID-19 within 5 days if symptom onset in pregnant women in the second or third trimester who do not require oxygen and who have one or more risk factors for disease progression. Currently use in breastfeeding women or children and adolescents is NOT recommended outside randomised trials, which are currently underway.[4] In addition, the NCCET has made a consensus recommendation to address patients not included in the COMET-ICE trial, such as vaccinated and immunosuppressed patients.[1] The NCCET also recommended rigorous data collection on indications and key outcomes of patients who receive sotrovimab therapy.[4]

This guideline requires endorsement by your local Drug and Therapeutics Committee (DTC) prior to implementation.

Supply of sotrovimab for clinical trials takes precedence over supply for use outside of clinical trials. This guideline aims to provide supportive information for clinicians if they are considering prescribing sotrovimab when patients are not eligible for a clinical trial or when a clinical trial is not available.

This guideline should be used in conjunction with the sotrovimab resources available here:

- Individual Patient Use (IPU) Application Form,
- Outcomes Reporting Form,
- Patient Consent Form and further information regarding consent, and
- Patient Information Leaflet.

Drug Class[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.

Authorised Prescribers:

- Infectious disease physicians,
- Respiratory physicians,
- Other physicians in accordance with local governance regulations e.g. emergency physicians.

Indication for applying this guidance[3,4]:

In accordance with relevant DTC approval, sotrovimab may be considered for **non-pregnant adult patients** and **pregnant women in their second or third trimester**[#] with a current diagnosis of COVID-19:

- with symptom onset of no more than 5 days AND
- who do not require oxygen AND
- who have reduced immunity to COVID-19 e.g. not vaccinated, not fully vaccinated[##] or immunosuppressed[*] (irrespective of vaccine status) AND
- who have one or more of the following risk factors:
  - Diabetes (requiring medication)/Pre-gestational diabetes (requiring medication) in pregnant women
  - Obesity (BMI >30 kg/m^2)
  - Chronic kidney disease (i.e. eGFR <60 mL/min/1.73m^2[**] or equivalent renal impairment for pregnant women)[5,6]
  - Congestive heart failure (New York Heart Association (NYHA) class II or greater)
  - Chronic obstructive pulmonary disease (history of chronic bronchitis, chronic obstructive lung disease, or emphysema with dyspnoea on physical exertion)
  - Moderate-to-severe asthma (requiring an inhaled steroid to control symptoms or prescribed a course of oral steroids in the previous 12 months)
  - Age ≥55 years or age >35 years if Aboriginal and/or Torres Strait Islander

Clinical judgement should be used when assessing the severity of specific risk factors.

[#]Sotrovimab may cross the placenta from mother to baby. The impact of this on the unborn baby is not known. However, it is known that pregnant women with COVID-19 are at increased risk of developing severe disease, which can be detrimental to the health of the woman and her baby. Sotrovimab can therefore be considered if the likelihood of benefit justifies the risk of harm.[4]
[##]Not fully vaccinated includes adults who have had only 1 vaccine dose or those whose 2nd dose was administered less than 2 weeks prior.
*For the purposes of this guidance, immunosuppressed patients are those that a) have a primary or acquired immunodeficiency such as haematological neoplasms, are post-transplant [solid organ (on immunosuppressive therapy) or haematopoietic stem cell transplant within 24 months], or have HIV/AIDS or other significant immunocompromising condition or b) are on/have been on recent immunosuppressive therapy such as chemotherapy, radiotherapy, high dose corticosteroids (equivalent to 20 mg or more of prednisone per day for 14 days or more) or are on biologic immunotherapies including most disease-modifying anti-rheumatic drugs (DMARDs).
**The COMET-ICE study used eGFR values derived from the Modification of Diet in Renal Disease (MDRD) formula, which is not routinely used in Australia. For the purposes of this guidance, eGFR calculations derived from CKD-Epi formula, which is routinely reported, are acceptable.

Contraindications and Precautions[1,2,4,8]:

- **Hypersensitivity:** 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.
- **First trimester pregnancy and breastfeeding:** Sotrovimab is pregnancy category B2[1,4]. There is potential for placental transfer of sotrovimab from the mother to the developing foetus. No information is available on the use of sotrovimab during breastfeeding. 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.[2] Discontinuation of breastfeeding may be considered.
- **Paediatric population**: The safety and efficacy of sotrovimab has not been established in children <12 years of age or weighing <40 kg.

Drug Interactions[1]:

No formal interaction studies have been conducted with sotrovimab. 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 26/8/21, drug interaction texts such as Liverpool COVID-19 Drug Interactions tool[9] and Micromedex drug interaction tool[10] (CIAP link) 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. The US Centers for Disease Control and Prevention advises delaying COVID-19 vaccination until 90 days after administration of monoclonal

antibodies as part of COVID-19 treatment, to avoid potential interference with the immune response to the COVID-19 vaccination.[11] This advice applies to those who have not received any vaccine dose as well as those who have received the first dose but not the second dose.[11]

Presentation and Storage[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 refrigerated at 2 - 8°C in original package. Protect from light. Do not freeze.

Dose[1,2]:

The recommended dose is 500 mg as a single dose intravenous infusion over 30 minutes

No dose adjustments for renal or hepatic function or age are required.

Preparation and Administration[1,2,12]:

- The occupational hazard of intermittent low dose exposure to sotrovimab is not known. Wear a mask and gloves when preparing the infusion to minimise exposure.
- It is recommended that the name and the batch number of the administered product is clearly recorded in order to improve traceability.
- Preferably use immediately after dilution. If this is not possible, the diluted solution may be stored at room temperature for up to 6 hours (include infusion time) or stored in the refrigerator for up to 24 hours (include infusion time).
- Personnel and equipment to manage anaphylaxis must be present during infusion and for at least 60 minutes post-infusion.

Preparation Steps
1. Remove one vial containing 8 mL sotrovimab solution from refrigerator at least 15 minutes before preparation of the infusion. 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. (Do NOT shake vigorously). 4. Withdraw 8 mL from a 50 mL or 100 mL sodium chloride 0.9% infusion bag or glucose 5% infusion bag. If local protocols allow, this step may be omitted. 5. Withdraw 8 mL solution from the sotrovimab vial. 6. Inject 8 mL of sotrovimab solution into selected infusion bag. 7. Prior to infusion, to mix, gently rock the infusion bag back and forth 3 to 5 times. Do NOT invert the bag. Avoid forming air bubbles. 8. Discard the vial including any unused solution.
Administration Steps
1. Do not use the same IV line to administer other medications at the same time. 2. Attach an infusion set to the infusion bag using standard bore tubing. Information from the manufacturer states the additional use of a 0.2 micrometre in-line filter is recommended but not required; check local requirements regarding in-line filter use.[13] 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 0.9% sodium chloride/ glucose 5% (at the same rate as the sotrovimab infusion). 5. **Observe the patient during the infusion and for 60 minutes after infusion cessation** in case of hypersensitivity reactions or anaphylaxis.

Monitoring Requirements[1,7,8,12]:

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

Infusion reactions include fever, chills, dizziness, dyspnoea, pruritis and rash. For mild to moderate infusion reactions, slow or stop the infusion and treat accordingly[12], noting that in the COMET-ICE trial, mild hypersensitivity reactions did not require pausing or discontinuation of the infusion.[7] 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 product information for complete list of possible adverse effects.

- **Common (>1%):**
  Diarrhoea (1%), hypersensitivity reactions (includes rash (2%), infusion-related reaction, bronchospasm).
- **Rare:** Anaphylaxis.

Reporting[3]:

Access via the IPU/Prescribing Declaration pathway will enable appropriate medicines governance and ensure the collection and analysis of patient outcomes and systematic monitoring of medicines use. The prescribing clinician is responsible for reporting medication errors and adverse events occurring as a result of sotrovimab treatment:

- Adverse events related to medicines should be reported to the TGA & via the hospital ims+ or Riskman system.
- Use of Prescribing Declarations/ IPU applications as per local governance processes will assist reporting of clinical outcomes. A NSW TAG-developed drug registry using an online application-process for sotrovimab is available. See https://www.nswtag.org.au/covid-19-medicines-resources/ and contact your local DTC or pharmacist for further information. For further information regarding reporting of clinical outcomes, see latest version of ACI Model of Care or the use of sotrovimab in adults in NSW.

Summary of amendments/updates made in version 1.2 11 October 2021:

- Introductory section (page 1): added NCCET pregnancy and breastfeeding recommendations.
- Indication section (page 2): added NCCET pregnancy and breastfeeding recommendation detail; added note regarding equivalent renal impairment measurement in pregnant women.
- Contraindications and precautions section (page 2): added median elimination half-life.
- Preparation & Administration section (page 3): clarified need for in-line filter per manufacturer advice.

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