DRUG GUIDELINE
Use of casirivimab and imdevimab injection for COVID-19

Introduction¹,²
Casirivimab and imdevimab (Ronapreve®) injection is provisionally registered by the Therapeutic Goods Administration for use in Australia for the treatment of COVID-19 and post-exposure prophylaxis against COVID-19. The National COVID-19 Clinical Evidence Taskforce also provides a conditional recommendation for the use of casirivimab and imdevimab in seronegative patients hospitalised with moderate to critical COVID-19. This indication will not be addressed in this guideline. Casirivimab and imdevimab are not an alternative or substitute for vaccination. Vaccination is the preferred and primary option for the prevention of COVID-19.

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

Drug class and mechanism of action¹,²
Casirivimab and imdevimab are IgG1 monoclonal antibodies that target the SARS-CoV-2 virus by simultaneously binding to distinct regions of the spike protein, thereby preventing the virus from infecting healthy cells. Clinical trials were conducted before the widespread circulation of variants of concern. Clinicians should consider the SARS-CoV-2 variant being targeted and the possibility of reduced sensitivity, e.g. early tests show casirivimab and imdevimab is not as effective against the Omicron variant.

Approved indications²,³,⁴
The use of casirivimab and imdevimab in NSW Health facilities must be in accordance with the restricted indications in NSW (see SN:024/21 accessible via the SABS register) and is contingent on local DTC approval.

FOR TREATMENT – in adults and adolescents (aged 12 years and older and weighing at least 40 kg) who have a current diagnosis of COVID-19, do not require supplemental oxygen for COVID-19 and who are at increased risk of progressing to severe disease.

Based on inclusion criteria of the three-phase REGEN-COV trial, the risk factors for disease progression in adults are:

- Age ≥ 50 years
- Obesity (BMI ≥ 30 kg/m²)
- Cardiovascular disease (including hypertension)
- Chronic lung disease (including asthma)
- Type 1 or 2 diabetes mellitus
- Chronic kidney disease, including those that are on dialysis
- Chronic liver disease
- Immunocompromised patients (including individuals with rheumatoid arthritis, HIV/AIDS and systemic lupus erythematosus).

The National COVID-19 Clinical Evidence Taskforce has arrived at a consensus recommendation based on their combined clinical expertise to guide clinical decisions about which children and adolescents are most likely to benefit. Potential risk factors for disease progression in children and adolescents include:

- Paediatric Complex Chronic Conditions (PCCC): congenital and genetic, cardiovascular, gastrointestinal, malignancies, metabolic, neuromuscular, renal and respiratory conditions
- Severe asthma
- Obesity (above 95th percentile on BMI for age growth chart)

FOR POST-EXPOSURE PROPHYLAXIS – in adults and adolescents (aged 12 years and older and weighing at least 40 kg) who have been exposed to SARS-CoV-2 and who either have a medical condition making them unlikely to respond to or be protected by vaccination OR who have not been vaccinated against COVID-19.

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Contraindications and precautions\(^2\)

- Known allergy to casirivimab, imdevimab or any of the excipients of this medicine (histidine, histidine monohydrochloride monohydrate, polysorbate 80, sucrose, water for injections).
- Safety and efficacy of casirivimab and imdevimab in children < 12 years of age has not yet been established.
- Casirivimab and imdevimab are classified as pregnancy category B2 (see below for further information).

Drug interactions\(^2,5\)

- No formal drug interaction studies have been conducted involving casirivimab and imdevimab. Casirivimab and imdevimab are not renally excreted or metabolised by the CYP450 enzymes. Texts such as Liverpool COVID-19 Drug Interactions tool and Micromedex drug interactions tool do not currently (correct as of 2 December 2021) identify any drug interactions. Contact your local Pharmacy Department or Medicines Information Service for further advice.
- Interaction with COVID-19 vaccination has not been determined. Casirivimab and imdevimab binds to epitopes on the SARS-CoV-2 spike protein used as an immunogen in all COVID-19 vaccines; therefore, it may be possible that casirivimab and imdevimab could interfere with the development of effective immune responses to COVID-19 vaccines. It is recommended that COVID-19 vaccines should not be administered for at least 90 days after a dose of casirivimab and imdevimab. Follow [this link](#) for information on medical exemptions to COVID-19 vaccination.

Dose, timing and route of administration\(^2,5\)

Casirivimab and imdevimab must be given together (either in the same intravenous bag or as concurrent subcutaneous injections).

**Treatment (for patients who do not require supplemental oxygen for COVID-19 and are at increased risk of progressing to severe disease)**

Recommended dose is 600 mg casirivimab and 600 mg imdevimab.

- Give as soon as possible after a positive viral test for SARS-CoV-2 and not later than 7 days after the onset of first symptoms.
- Intravenous infusion is strongly recommended. Subcutaneous injection is an alternative route of administration when intravenous infusion is not feasible and waiting would lead to delay in treatment.

**Post-exposure prophylaxis (initial dosing)**

Recommended dose is 600 mg casirivimab and 600 mg imdevimab.

- Give as soon as possible after SARS-CoV-2 exposure.
- For administration via intravenous infusion or subcutaneous injection.

**Post-exposure prophylaxis (repeat dosing)**

Recommended subsequent dosing for post-exposure prophylaxis is 300 mg of casirivimab and 300 mg of imdevimab once every 4 weeks. Commence 4 weeks after initial post-exposure prophylaxis dose.

- In individuals in whom repeat dosing is determined to be appropriate for ongoing SARS-CoV-2 exposure (longer than 4 weeks) and who have a medical condition making them unlikely to respond to or be protected by vaccination, continue until prophylaxis is no longer required.
- There is no data on repeat dosing beyond 24 weeks (6 doses).
- For administration via intravenous infusion or subcutaneous injection.
Use in pregnant and breastfeeding women\textsuperscript{2, 4}

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

Pregnancy – casirivimab and imdevimab is classified as pregnancy category B2 by the TGA. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by treating health professionals.

Breastfeeding – there is no available data on the excretion of casirivimab plus imdevimab in human milk, and the potential benefits and risks to a breastfed baby are not known. A decision whether to discontinue breastfeeding or to abstain from casirivimab plus imdevimab therapy should consider the benefit of breastfeeding for the baby and the benefit of therapy for the woman.

Presentations\textsuperscript{2, 5, 6}

Please note, casirivimab and imdevimab will be supplied in individual vials (i.e., NOT co-formulated). Casirivimab and imdevimab injection is available as:

Co-packed multidose vials - contain 11.1 mL of the active ingredient, cartons are labelled as 20 mL which refers to the vial capacity.
- Each casirivimab multidose vial contains 1332 mg casirivimab per 11.1 mL (120 mg/mL).
- Each imdevimab multidose vial contains 1332 mg imdevimab per 11.1 mL (120 mg/mL).

Co-packed single-use vials - contain 2.5 mL of the active ingredient, cartons are labelled as 6 mL which refers to the vial capacity.
- Each casirivimab vial contains 300 mg casirivimab per 2.5 mL (120 mg/mL).
- Each imdevimab vial contains 300 mg imdevimab per 2.5 mL (120 mg/mL).

Storage and stability\textsuperscript{2}

- Store unopened vials at 2 – 8 °C in original package. Protect from light. Do not freeze.
- After initial puncture, multidose vials can be stored for 16 hours at room temperature (up to 25 °C), or for 48 hours refrigerated between 2 °C to 8 °C. Due to potential risk of microbial contamination, it is not recommended that punctured vials are kept for more than 24 hours.
- Casirivimab and imdevimab is preservative-free and therefore once diluted the solution should be administered immediately. However, if necessary:
  - bags of diluted solution can be stored for 12 hours at room temperature (up to 25 °C) and 48 hours at 2 °C to 8 °C. Due to potential risk of microbial contamination, it is not recommended that diluted solution is stored for more than 24 hours. If refrigerated, allow the IV infusion bag to come to room temperature for approximately 30 minutes prior to administration.
  - syringes prepared for subcutaneous injection can be stored for 6 hours at room temperature (up to 25 °C) and 24 hours at 2 °C to 8 °C. If refrigerated, allow the syringes to come to room temperature for approximately 10 - 15 minutes prior to administration.

Handling of multi-dose vials\textsuperscript{2, 7}

- As mentioned above, multi-dose vials should be used within 24 hours of initial puncture if stored in the refrigerator (2-8°C) or within 16 hours if stored at room temperature (<25°C).
- Vials must be clearly labelled with the date and time of initial puncture.
- Before each entry into multi-dose vials, the top must be cleaned (using an alcohol swab) and injected with a new unused sterile needle and syringe.

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Preparation\textsuperscript{2, 6}

The occupational hazard of intermittent low dose exposure to casirivimab and imdevimab 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.

For IV infusion:
1. Remove both the casirivimab and imdevimab vials from refrigerated storage and allow to come to room temperature for approximately \textit{20 minutes before} dilution.
2. Visually inspect vial to ensure no particulate matter is present or damage to the vial (discard if present).
3. Obtain a prefilled IV infusion bag [made from polyvinyl chloride (PVC) or polyolefin (PO)] containing up to 250 mL of either 0.9% sodium chloride or 5% dextrose.
4. Using aseptic technique, withdraw the appropriate volume of casirivimab and imdevimab solution from each respective vial (refer to Tables 1 and 2) and inject into the prefilled infusion bag.
5. Gently mix infusion bag by inversion. \textbf{Do not shake.}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
\textbf{Indication} & \textbf{Dose} & \textbf{Total volume for one dose} & \textbf{Volume to be withdrawn from each respective MULTIDOSE vial and injected into infusion bag for co-administration} \\
\hline
\textit{Treatment and post-exposure prophylaxis (initial dose)} & 600 mg casirivimab and 600 mg imdevimab & 5 mL casirivimab + 5 mL imdevimab in an infusion bag & 5 mL from one multidose vial of casirivimab 120 mg/mL + 5 mL from one multidose vial of imdevimab 120 mg/mL \\
\hline
\textit{Ongoing prophylaxis (repeat dose)} & 300 mg casirivimab and 300 mg imdevimab & 2.5 mL casirivimab + 2.5 mL imdevimab in an infusion bag & 2.5 mL from a multidose vial of casirivimab 120 mg/mL + 2.5 mL from a multidose vial of imdevimab 120 mg/mL \\
\hline
\end{tabular}
\caption{Preparation of casirivimab and imdevimab for administration via intravenous infusion using MULTIDOSE vials.}
\end{table}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
\textbf{Indication} & \textbf{Dose} & \textbf{Total volume for one dose} & \textbf{Volume to be withdrawn from each respective SINGLE USE vial and injected into infusion bag for co-administration} \\
\hline
\textit{Treatment and post-exposure prophylaxis (initial dose)} & 600 mg casirivimab and 600 mg imdevimab & 5 mL casirivimab + 5 mL imdevimab in an infusion bag & 2.5 mL from \textbf{two} single-use vials of casirivimab 120 mg/mL + 2.5 mL from \textbf{two} single-use vials of imdevimab 120 mg/mL \\
\hline
\textit{Ongoing prophylaxis (repeat dose)} & 300 mg casirivimab and 300 mg imdevimab & 2.5 mL casirivimab + 2.5 mL imdevimab in an infusion bag & 2.5 mL from a single-use vial of casirivimab 120 mg/mL + 2.5 mL from a single-use vial of imdevimab 120 mg/mL \\
\hline
\end{tabular}
\caption{Preparation of casirivimab and imdevimab for administration via intravenous infusion using SINGLE USE vials.}
\end{table}
For subcutaneous injection:
1. Remove both the casirivimab and imdevimab vials from refrigerated storage and allow to come to room temperature for approximately 20 minutes before dilution.
2. Visually inspect vial to ensure no particulate matter is present or damage to the vial (discard if present).
3. Obtain 3 mL syringes with luer connection and 21 Gauge transfer needles.
4. Using aseptic technique, withdraw the appropriate volume of casirivimab and imdevimab injection from each respective vial into each syringe (see Tables 3 and 4) – total of 4 syringes for a 600 mg casirivimab and 600 mg imdevimab dose, and a total of 2 syringes for a 300 mg casirivimab and 300 mg imdevimab dose.
5. Replace the 21 Gauge transfer needle with a 25 Gauge or 27 Gauge needle for subcutaneous injection.

Table 3: Preparation of casirivimab and imdevimab for administration via subcutaneous injection using MULTIDOSE vials.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Total volume for one dose</th>
<th>Volume* to be withdrawn from a MULTIDOSE vial to prepare syringes for subcutaneous injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment and post-exposure prophylaxis (initial dose)</td>
<td>600 mg casirivimab and 600 mg imdevimab</td>
<td>5 mL casirivimab + 5 mL imdevimab</td>
<td>Syringes 1 – 2.5 mL from a multidose vial of casirivimab 120 mg/mL Syringe 2 – 2.5 mL from a multidose vial of casirivimab 120 mg/mL Syringe 3 – 2.5 mL from a multidose vial of imdevimab 120 mg/mL Syringe 4 – 2.5 mL from a multidose vial of imdevimab 120 mg/mL</td>
</tr>
<tr>
<td>Ongoing prophylaxis (repeat dose)</td>
<td>300 mg casirivimab and 300 mg imdevimab</td>
<td>2.5 mL casirivimab + 2.5 mL imdevimab</td>
<td>Syringe 1 – 2.5 mL from a multidose vial of casirivimab 120 mg/mL Syringe 2 – 2.5 mL from a multidose vial of imdevimab 120 mg/mL</td>
</tr>
</tbody>
</table>

*Larger subcutaneous injection volumes are considered to be associated with injection pain and adverse events at the injection site. See this [review article](#) for further information.

Table 4: Preparation of casirivimab and imdevimab for administration via subcutaneous injection using SINGLE USE vials.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Total volume for one dose</th>
<th>Volume* to be withdrawn from a SINGLE USE vial to prepare syringes for subcutaneous injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment and post-exposure prophylaxis (initial dose)</td>
<td>600 mg casirivimab and 600 mg imdevimab</td>
<td>5 mL casirivimab + 5 mL imdevimab</td>
<td>Syringe 1 – 2.5 mL from a single-use vial of casirivimab 120 mg/mL Syringe 2 – 2.5 mL from a single-use vial of casirivimab 120 mg/mL Syringe 3 – 2.5 mL from a single-use vial of imdevimab 120 mg/mL Syringe 4 – 2.5 mL from a single-use vial of imdevimab 120 mg/mL</td>
</tr>
<tr>
<td>Ongoing prophylaxis (repeat dose)</td>
<td>300 mg casirivimab and 300 mg imdevimab</td>
<td>2.5 mL casirivimab + 2.5 mL imdevimab</td>
<td>Syringe 1 – 2.5 mL from a single-use vial of casirivimab 120 mg/mL Syringe 2 – 2.5 mL from a single-use vial of imdevimab 120 mg/mL</td>
</tr>
</tbody>
</table>

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Administration\textsuperscript{2, 6}

For IV infusion:

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 casirivimab and imdevimab infusion and then infuse intravenously over the minimum infusion time specified in Table 3, via a central or peripheral line.
4. After the casirivimab and imdevimab infusion is complete, flush the giving set with at least 20 mL 0.9% sodium chloride injection or 5% dextrose injection.
5. Observe the patient during the infusion and for 60 minutes after infusion cessation in case of hypersensitivity reactions or anaphylaxis.

Table 3: Minimum infusion time for IV infusion bag volumes for 600 mg of casirivimab and 600 mg of imdevimab or 300 mg of casirivimab and 300 mg of imdevimab.

<table>
<thead>
<tr>
<th>Volume of 0.9% sodium chloride or 5% dextrose infusion bag</th>
<th>Minimum infusion time – 600 mg casirivimab and 600 mg imdevimab</th>
<th>Minimum infusion time – 300 mg casirivimab and 300 mg imdevimab</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 mL</td>
<td>20 minutes</td>
<td>20 minutes</td>
</tr>
<tr>
<td>100 mL</td>
<td>20 minutes</td>
<td>20 minutes</td>
</tr>
<tr>
<td>150 mL</td>
<td>20 minutes</td>
<td>20 minutes</td>
</tr>
<tr>
<td>250 mL</td>
<td>30 minutes</td>
<td>30 minutes</td>
</tr>
</tbody>
</table>

For subcutaneous injection:

1. Administer the prepared subcutaneous injections consecutively, each at a different injection site. Use different quadrants of the abdomen or upper thighs or upper outer arms to space apart each.
   - The area around the waistline and 5 cm around the navel should be avoided.
   - Do not inject into skin that is tender, damaged, bruised, or scarred.

Monitoring requirements\textsuperscript{2, 3, 5}

- Monitor the patient for adverse effects (see Adverse Effects section below) during the infusion and for 60 minutes after infusion cessation in case of hypersensitivity reactions or anaphylaxis. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration, initiate appropriate medications and/or supportive care.
- Infusion-related reactions (IRRs) have been observed with IV administration of casirivimab and imdevimab. IRRs observed in clinical studies were mostly mild to moderate in severity and were typically observed during or within 24 hours of infusion. The commonly reported signs and symptoms for these reactions included nausea, chills, dizziness (or syncope), rash, urticaria and flushing. However, infusion related reactions may present as severe or life-threatening events and may include other signs and symptoms. If an IRR occurs, consider interrupting, slowing or stopping the infusion and administer appropriate medications and/or supportive care.
Adverse effects\textsuperscript{2, 3, 5}

- 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 a complete list of possible adverse effects.
- Common (>1%): injection site reactions were reported with subcutaneous administration including single and repeat dose studies. They were mainly local, mild to moderate in severity and resolved either without intervention or with usual standard of care. Commonly reported signs and symptoms for these reactions included erythema, pruritis, ecchymosis, oedema, pain/tenderness and urticaria.

Reporting\textsuperscript{2, 3, 5}

- Casirivimab and imdevimab 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, Roche (drug sponsor) and via their facility’s incident management system.
- DTC 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. Casirivimab and imdevimab use and outcome reporting should occur as per local governance processes.

References