Remdesivir prescribing guideline

Department of Health

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1. Purpose
This guideline has been developed by the Queensland Health COVID-19 Therapeutics Working Group to provide clinicians with information and guidance around the appropriate prescribing and safe administration of remdesivir (Veklury®) in patients diagnosed with COVID-19, and to ensure equity of access to new COVID-19 therapeutics. This guideline requires endorsement by local Drugs and Therapeutics Committees or equivalent prior to implementation.

2. Background
This guideline and procedure are based on the recommendations of the National COVID-19 Clinical Evidence Taskforce (NCCET) and the NIH (US) and NICE (UK) guidelines. This document will be updated frequently as new evidence is made available.

2.1 Regulatory status
Remdesivir has been granted provisional approval by the Therapeutic Goods Administration (TGA) for the treatment COVID-19 in adults and adolescents (age ≥12 years and weighing at least 40 kg); with pneumonia requiring supplemental oxygen. Approval has been made based on limited data. More comprehensive evidence is required to be submitted prior to full registration. The product is subject to additional monitoring in Australia.

2.2 Mechanism of action
Remdesivir is a nucleotide prodrug of an adenosine analogue. It binds to the viral RNA-dependent RNA polymerase and inhibits viral replication by terminating RNA transcription prematurely.

2.3 Efficacy
Although it has demonstrated in vitro activity against SARS-CoV-2, there is controversy around the efficacy of remdesivir. It is currently recommended by the National COVID-19 Clinical Evidence Taskforce (NCCET) for use in adults hospitalised with COVID-19 who require oxygen but do not require invasive or non-invasive ventilation. However, remdesivir is not recommended according to the WHO living guidelines. This discrepancy is due to the
method of analysis applied to the current evidence whereby the Australian NCCET assessed trial data according to disease severity classification, whereas WHO did not separate data by disease severity, instead formulating their recommendation using overall mortality data. If effective, remdesivir appears more likely to be of benefit when used early in the disease. The PINETREE study demonstrated efficacy of a three day course of remdesivir in preventing hospitalisation or progression to severe disease in non-hospitalised, high-risk COVID-19 patients who were within 7 days of symptom onset. Remdesivir treated patients had an 87% reduction in the risk of hospitalisation or death.

3. Prescription and governance

Remdesivir has a restricted listing on the Queensland Health Medicines Formulary (List of Approved Medicines): on the advice of a specialist physician for the treatment of COVID-19 in accordance with recommendations in the National COVID-19 Clinical Evidence Taskforce Guidelines.

3.1 Authorised prescribers

Prescribers are to complete a Remdesivir Request to Access Form appropriate to the indication (Hospitalised Patients or Mild-moderate Disease) for each patient, confirming patient suitability and consent to treatment.

For paediatric patients, high risk children should be assessed initially by their treating paediatrician, with patient suitability confirmed on discussion with on-call paediatric Infectious Diseases for your service or at Children’s Health Queensland (CHQ)

3.2 Patient consent

There are no additional requirements for consent to administer remdesivir than is usual practice for any other TGA registered pharmaceutical. Clinicians should discuss the risks and benefits of treatment with the patient and/or their carer and document that this has been done in the patient record. Some clinicians may wish to obtain formal written consent and a generic COVID-19 Therapeutics consent form has been developed for this purpose. Consent forms for adults and children are available online.
4. Access and supply

Access to remdesivir is regulated by the National Medical Stockpile and managed centrally in Queensland by Central Pharmacy. Supply of COVID-19 therapeutics including remdesivir is uncertain and vulnerable to constraints in the supply chain as demand fluctuates nationally and globally.

To ensure timely and equitable access across the state, a small amount of stock will be made available to healthcare facilities that have the capacity to appropriately store and monitor remdesivir. Access will be closely monitored, and prescribers will be required to complete a Remdesivir Request to Access form for each patient. Forms are available online: Hospitalised Patients or Mild-moderate Disease.

5. Clinical criteria for treatment

5.1 Indications

There are two clinical scenarios where remdesivir has been used in the management of COVID 19:

1. For the treatment of COVID-19 in hospitalized patients requiring oxygen
2. For the prevention of worsening of COVID-19 in patients with mild to moderate COVID-19 with risk factors for progression who are not fully vaccinated or immunosuppressed.

For the treatment of COVID-19 in hospitalized patients requiring oxygen, the Australian Government has outlined specific criteria that need to be met in order to access remdesivir. Treatment courses are limited to 5 days.  

1. Treatment: non-pregnant adults and pregnant women aged ≥ 18 years

- Hospitalised with confirmed SARS-CoV2
- Requiring supplemental oxygen (SpO2 ≤ 92% on room air) but are NOT ventilated. (invasive or non-invasive mechanical ventilation or ECMO)
- ALT < 5 x upper limit of normal (ULN) and/or ALT < 3 x ULN and bilirubin < 2 x ULN.
- < 10 days from onset of symptoms
- eGFR > 30 mL/min/1.73m²
Situations where patients should be prioritised include:

- Not requiring high flow nasal oxygen
- Life expectancy greater than one year.

2. Prevention: worsening of COVID-19 in patients with mild/moderate COVID-19 with risk factors for progression who are not fully vaccinated or immunosuppressed—see the recommendations in the COVID-19 Treatment guidelines for mild to moderate disease (Adults)

Note: The use of remdesivir for the prevention of disease progression in mild to moderate COVID-19 is off-label (i.e., not TGA approved for this indication) - discuss with an Infectious Diseases physician.

5.2 Contraindications

Use in contraindicated in patients with:

- Known hypersensitivity to remdesivir, its metabolites or any of the excipients: sulfobutyl betadex sodium (SBECDS), hydrochloric acid, sodium hydroxide
- Renal impairment: eGFR < 30 mL/min/1.73m²
- Hepatic impairment: ALT ≥ 5 x upper limit of normal

5.3. Children and adolescents aged ≥ 12 years and < 18 years, weighing ≥ 40 kg

Remdesivir should only start after multidisciplinary discussion with Paediatric Infectious Diseases. Refer to CHQ Guideline for prescribing guidelines and dosing advice.

5.4 Pregnancy and Breastfeeding

Category B2 – no adequate and well-controlled studies of remdesivir have been conducted in pregnant women. From the limited published data for remdesivir in pregnant women with COVID-19, maternal use of remdesivir has not been associated with an increased risk of congenital malformations or adverse pregnancy outcomes. However mild transaminitis has been observed. Remdesivir should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the foetus. Close monitoring and management by a multidisciplinary team is recommended.

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There is no information regarding the presence of remdesivir in human milk, the effects on the breastfed infant, or the effects on milk production. Based on animal studies, it can be assumed that there is excretion of remdesivir and/or metabolites into the milk of lactating animals. However as remdesivir is likely to have poor oral bioavailability, breastfed infants are unlikely to receive significant amounts of remdesivir from breast milk. No serious adverse reactions were reported in the small number of infants who directly received remdesivir therapy for Ebola and COVID-19 infections. Observe the breastfed infant for irritability, diarrhoea, skin rash and jaundice.

5.5 Drug interactions

No formal drug-drug interaction studies have been conducted with remdesivir and the potential for drug interactions is currently unknown. Based on its rapid distribution, metabolism and clearance the likelihood of clinically significant interactions is low.

- Concomitant prescribing of chloroquine or hydroxychloroquine is not recommended due to antagonism observed in vitro which may result in reduced antiviral activity.
- In vitro, remdesivir is a substrate of drug metabolising enzymes CYP2C8, CYP2D6 and CYP3A4, organic anion transporting polypeptides 1B1 and p-glycoprotein transporters. While the clinical relevance of this has not been established, rapid clearance and the IV route of administration suggests the potential for clinically significant interactions is low. However:
  - patients on concurrent medication metabolised via CYP3A4 (e.g. warfarin, voriconazole, benzodiazepines) should be monitored closely for signs of toxicity.
  - The use of strong CYP3A4 inducers (e.g. rifampicin) may result in result in decreased remdesivir exposure and the manufacturer cautions against their use. However the Liverpool Drug Interaction Group advises that while a decrease in plasma levels can be expected to a limited extent, no a priori dose adjustment of remdesivir is needed.

6. Prescribing and administration

6.1 Baseline tests

Baseline liver function tests and an eGFR should be determined prior to commencing remdesivir and during treatment.
6.2 Dose and duration

For treatment of COVID-19 in hospitalised patients requiring oxygen:

| Loading dose of **200 mg IV** on day 1, then **100 mg IV daily** for a further 4 days. (maximum of 5 days treatment) |

For prevention of worsening of COVID-19 in patients with mild to moderate disease:

| Loading dose of **200 mg IV** on day 1, then **100 mg IV daily** on day 2 and 3 (maximum of 3 days treatment) |

6.2.1 Dose in renal impairment

There is no dose adjustment in patients with eGFR $\geq 30$ mL/min/1.73m$^2$, however, remdesivir is contraindicated in patients with eGFR $< 30$ mL/min/1.73m$^2$ due to formulation with the excipient sulfobutylether-β-cyclodextrin (SBECOD) which accumulates in patients with decreased renal function.$^1$

6.2.2 Dose in hepatic impairment

The pharmacokinetics of remdesivir have not been evaluated in patients with hepatic impairment. It is not known if dose adjustment is required.$^1$

Contraindicated in patients with ALT $\geq 5$ times the upper limit of normal at baseline$^1$

6.2.3 Dose based on age

- **Elderly**: No dose adjustment is required in patients over the age of 65 years
- **Paediatric**: No dose adjustment for adolescent patients aged 12 to 17 years and weighing $> 40$ kg. The safety and efficacy of remdesivir in children under the age of 12 and weighing less than 40 kg has not been established.

6.3 Prescribing on ieMR

To prescribe remdesivir select “Add order” and search for drug name “remdesivir”.

- **For adults**: Choose the appropriate order set – “stat order” Loading Dose followed by Maintenance Doses (Day 2 and 3 or 2-5) and complete prescription.
• For children 12 years and older and weighing more than 40 kg: Select appropriate weight based order set and complete prescription

(See Appendix 1 for ieMR prescribing examples.)

**Non ieMR ordering: remdesivir** should be prescribed on the National Inpatient Medication Chart. The loading dose should be charted as a “stat” order on the front page, with maintenance doses charted under regular orders, with the days of therapy clearly numbered.

6.4 Presentation

Each pack contains a clear glass vial of remdesivir 100 mg lyophilised powder for reconstitution. The sterile powder is white to off-white to yellow.

6.5 Storage and stability

Store below 30°C. Reconstituted solution should be diluted immediately.\(^6\)

Diluted solution for infusion is stable for 4 hours below 25°C or 24 hours at 2 to 8°C.\(^5\)
6.6 Preparation and administration

Preparation Steps

1. Reconstitute the vial with **19 mL** of water for injections, immediately shake the vial for 30 seconds, then allow to stand for 2 to 3 minutes.

2. Repeat the process of shaking and standing until completely dissolved and the solution is clear.

3. Following reconstitution, the vial contains: remdesivir 100 mg/20 mL (5 mg/mL)

4. Dilute immediately.

5. Prepare infusion bag: Withdraw the required volume of fluid from a 250 mL bag of 0.9% sodium chloride.* See table 1, below.

6. Withdraw the dose from the remdesivir vials, by injecting 10 mL of air into the vial; and withdrawing the required volume of remdesivir (see Table 1). Note, the last 5 mL of solution may require more force to withdraw. Discard remaining vial(s).

7. Add the drawn-up volume of remdesivir to the prepared infusion bag. Gently invert the bag 20 times to mix the solution in the bag. Do NOT shake.

<table>
<thead>
<tr>
<th>Remdesivir dose</th>
<th>Volume of infusion 0.9% sodium chloride infusion bag</th>
<th>Volume to be removed from bag</th>
<th>Volume of remdesivir reconstituted solution</th>
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<tbody>
<tr>
<td>200 mg</td>
<td>250 mL*</td>
<td>40 mL</td>
<td>2 x 20 mL (2 vials)</td>
</tr>
<tr>
<td>100 mg</td>
<td>250 mL*</td>
<td>20 mL</td>
<td>1 x 20 mL (1 vial)</td>
</tr>
</tbody>
</table>

*Remdesivir can be given in 100 mL for patients with severe fluid restriction.

Administration Steps

1. Infuse over 30 minutes to 2 hours.

2. Flush with at least 30 mL of 0.9% sodium chloride via the giving set (at the same rate as the remdesivir infusion)
6.7 Observation and monitoring

Observe for infusion reactions. Infusion reactions may include hypotension, hypertension, bradycardia, hypoxia, nausea, vomiting, angioedema, rash diaphoresis and shivering. A slow infusion of up to two hours may help prevent these. Anaphylactic reactions are rare – if present, stop the infusion and commence treatment immediately.

- Perform baseline and daily UEC, FBC and LFT. Remdesivir should be discontinued if:
  - eGFR < 30mL/min/1.73m²
  - ALT ≥ 5 times upper limit of normal during treatment OR
  - ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR.

6.8 Adverse effects and reporting

The following adverse effects have been observed in clinical studies:

**Very common (≥10%):** graded elevations in ALT, AST and bilirubin – mechanism is unknown, time to onset 1-16 days.

**Common (≥1%):** prolonged prothrombin time, gastrointestinal symptoms (e.g.: nausea, vomiting, diarrhoea), headache, rash.

**Rare (<0.1%):** hypersensitivity reactions.

It may be difficult to distinguish between adverse effects of remdesivir and signs and symptoms of COVID-19. However, because remdesivir is a provisionally approved product with no post-marketing data, all possible and confirmed adverse events must be reported. These should be notified to the TGA Reporting adverse events | Therapeutic Goods Administration (TGA) and reported via Riskman.

6.9 Monitoring of treatment outcomes

The use of remdesivir requires reporting of clinical outcomes to the National Medical Stockpile Taskforce. Prescribers agree to these terms when completing a Remdesivir Request to Access Form. Data required includes eligibility, confirmation of dose delivered and outcome: recovery, ICU or death.

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7. Compliance and evaluation

Regular prescribing reports will be provided through interrogation of iPharmacy, ieMR and CHARM programs. Reports will be made available to Medication and Pharmacy Planning Response Group (MPPRG).
Appendix 1 – ieMR screenshots

Modify duration of therapy based on the indication.

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8. References


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10. Available from: 3.-GUIDELINE-for-use-of-REMDESIVIR-in-COVID-19_V1.6_30Sep21-
Copy_.pdf (nswtag.org.au)

## 9. Version control

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<td>New document</td>
<td>Tina Patterson, Andrew Henderson, Amy Legg</td>
<td>Jan 2022</td>
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<td>COVID-19 Therapeutics Working Group (CTWG)</td>
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<td>11/02/2022</td>
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