USE OF REMDESIVIR FOR COVID-19 IN HOSPITALISED PATIENTS DRUG GUIDELINE

Remdesivir (Veklury®), an antiviral, has provisional registration in Australia for use in COVID-19. Further evidence of benefit and safety will be required for full registration.

The National COVID-19 Clinical Evidence Taskforce (NCCET) (as at last update 6/9/21) provides a conditional recommendation for use of remdesivir in adults, including pregnant or breastfeeding women hospitalised with moderate to severe COVID-19 who do not require ventilation.[1] However, controversy about remdesivir's efficacy remains.[2,3] From the evidence available, if remdesivir is effective, it appears to be more likely to be of benefit when used within 10 days of symptom onset.[4] This is supported by the immunopathology of COVID-19, whereby an initial phase of antiviral replication progresses to respiratory failure at day 8-9 in severe infections due to the host inflammatory response.[5] The current evidence does not suggest a clear benefit of a 10 day course over a 5 day course of treatment.[1]

The Australian Government has provided specific criteria that need to be met in order to access remdesivir for clinical treatment.[6] These include age ≥18 years (or 12 to 17 years weighing ≥40 kg), an oxygen saturation of SpO2 ≤92% on room air and requiring supplemental oxygen, and alanine aminotransferase (ALT) <5 x upper limit of normal (ULN) and/or ALT <3 x ULN and bilirubin <2 ULN. Patients with evidence of multiorgan failure, renal failure, or those receiving mechanical ventilation for >48 hours at the time of initiation or extracorporeal membrane oxygenation (ECMO) cannot access remdesivir. Access for eligible patients is limited to a 5-day course.[6]

This guidance does **not** apply to use in children. The NCCET recommends that use of remdesivir in children or adolescents outside a trial setting should not be considered routinely.[1] Contact the ANZPID Working Group (NSW contact: Philip.Britton@health.nsw.gov.au) about accessing remdesivir for children <12 years of age or adolescents weighing <40 kg.

Use of remdesivir is not recommended in the Hospital in the Home setting or in community-based patients with COVID-19.

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

This guideline aims to provide supportive information for clinicians if they decide to prescribe remdesivir for hospitalised patients with COVID-19 outside a clinical trial. This guideline should be used with the patient consent form/verbal guide and patient and family information leaflet - link.

Drug Class[7,8]

Antiviral, a nucleotide analogue prodrug that binds to the viral RNA-dependent RNA polymerase and inhibits viral replication through premature termination of RNA transcription.

Authorised Prescribers

- Infectious disease physicians
- Intensivists
- Respiratory physicians
- Emergency Medicine physicians

Indication for applying this guidance[1]

At the treating clinician's discretion and in accordance with relevant DTC approval/formulary restrictions, remdesivir may be considered for patients, including pregnant or breastfeeding women:

- With confirmed diagnosis of COVID-19 or known contact of a confirmed case with syndrome consistent with COVID-19 awaiting confirmation by diagnostic testing; AND
- Aged ≥18 years, or aged 12 to 17 years and weighing >40 kg; AND
- With oxygen saturation (SpO2) ≤92% on room air and requiring supplemental oxygen. N.B. remdesivir is NOT indicated for patients requiring non-invasive or invasive mechanical ventilation or ECMO, although it may be continued if it was started prior to requiring ventilation; AND
- ≤10 days since symptom onset.[4]

Factors where the benefit of remdesivir is uncertain & requires careful consideration before use[6]:

- Presence of an intercurrent illness likely to lead to the patient's death within one year;
- Advanced age with limitations on activities of daily living; and
- Need for more than a 5-day treatment course.

Patients **with evidence of multiorgan failure,** including but not limited to coagulopathy (significant thrombocytopenia), hepatic failure, renal failure or significant cardiomyopathy (low cardiac output) are not eligible to access remdesivir from the National Medicines Stockpile.[6]

Contraindications

- Use is contraindicated in patients with:
  - Known **hypersensitivity** to any ingredient of remdesivir product or remdesivir metabolites.[8]
  - **Renal impairment[8]:** eGFR <30 mL/min/1.73m^2
    - remdesivir is formulated with the excipient sulfobutyl betadex sodium (SBECD), which is renally cleared and accumulates in patients with decreased renal function.[8]
  - **Hepatic impairment**: ALT ≥5 times the upper limit of normal (ULN) at baseline.[8]

Drug Interactions

- Drug-drug interaction trials of remdesivir and other concomitant medications have not been conducted in humans. It is prudent to minimise the concurrent use of any nonessential medications.
- A variety of resources are available to check specific drug combinations, e.g. Liverpool COVID-19 Drug Interactions tool[9] & summary chart[10] and Micromedex drug interaction tool (CIAP link). Contact the local pharmacy department or medicines information service for tailored advice.
- Concomitant use with hydroxychloroquine or chloroquine (not recommended for treatment of COVID-19) is not recommended as it may result in reduced antiviral activity of remdesivir.[8,11,12]
- In vitro, remdesivir is a substrate for various drug metabolising enzymes, e.g. CYP2C8, CYP2D6 and CYP3A4 and P-glycoprotein (P-gp) transporters and an inhibitor of various other enzymes, e.g. CYP3A4. The clinical relevance of these in vitro assessments has not been established.
  - Medicines which are metabolised via CYP3A4 (e.g. atorvastatin, warfarin, voriconazole or benzodiazepines) should be monitored. Doses may need to be adjusted to avoid toxicity.[10]
  - Strong inducers of CYP3A4 (e.g. carbamazepine, phenytoin, rifampicin) may reduce remdesivir efficacy.[10]

Dose and duration[1,6,8]

200 mg intravenous (IV) on day 1, then 100 mg IV daily for a further 4 days (Total 5 days treatment).

If insufficient clinical improvement, specialist advice should be sought about extending treatment to a 10-day course, noting further approval may be required to access stock.

Presentations, Storage & Stability[8,13,14]

There are 2 formulations that may be suitable for dosing (noting exceptions such as paediatric use below).

POWDER for reconstitution vial

- 100 mg sterile, preservative-free, white to off-white to yellow lyophilised powder vial.
- Requires storage below 30°C.
- Also contains sulfobutyl betadex sodium (SBECD 3 g), hydrochloric acid & sodium hydroxide.

CONCENTRATED SOLUTION vial

- 100 mg/20 mL concentrate solution (clear colourless to yellow) vial; sterile preservative-free.
- Requires refrigerated storage at 2–8°C. Stable for up to 12 hours at room temperature (20–25°C) prior to dilution.
- Also contains sulfobutyl betadex sodium (SBECD 6 g), hydrochloric acid & sodium hydroxide.

(N.B. Although remdesivir use in children <12 years of age or adolescents weighing <40 kg is outside the scope of this guidance, please note that the concentrated solution should not be used in this patient population.)

Preparation and administration[8,13,14]

- Administer by intravenous infusion.
- Do not use the same IV line to administer other medications at the same time as remdesivir.
- **Aseptic technique** is required during preparation as there is no preservative or bacteriostatic agent present in either formulation of remdesivir (concentrated solution or powder).
  - If made in an aseptic environment, independent of which formulation is used, the remdesivir infusion bag may be stored at room temperature (20–25°C) for 4 hours or at refrigerated temperature (2–8°C) for 24 hours prior to administration.

PREPARATION STEPS

Remdesivir 100 mg POWDER

The following process for reconstitution, dose preparation & administration is recommended.

RECONSTITUTE VIAL

1. Add **19 mL** of sterile Water for Injection (WFI) to remdesivir powder vial(s). (Discard vial if a vacuum does not pull the WFI into the vial.)
   a. Immediately shake the vial for 30 seconds.
   b. Allow the contents of the vial to settle for 2–3 minutes. A clear solution should result. Repeat shaking and standing until the contents of the vial are completely dissolved.
   c. Following reconstitution, each vial contains: 100 mg/20 mL (5 mg/mL).

Remdesivir 100 mg/20 mL CONCENTRATED SOLUTION

The following process for dose preparation & administration is recommended.

PREPARE VIAL

1. Remove required number of single-dose vial(s) from the fridge and equilibrate them to room temperature.
   a. Sealed vials can be stored for up to 12 hours at room temperature (20–25°C) prior to dilution.
   b. If unused, do not return to the fridge; contact manufacturer for the expiry date.
   c. Inspect the vial to ensure the container closure is free from defects and the solution is free of particulate matter.

PREPARE BAG

2. Withdraw the required volume of 0.9% sodium chloride (see **Table 1**) from the infusion bag and discard.

OBTAIN DOSE

3. Withdraw the dose from the remdesivir vial(s) by:
   a. Injecting 10 mL of air into the remdesivir vial; and
   b. Withdrawing the required volume of remdesivir (see **Table 1**). The last 5 mL of solution may require more force to withdraw. Discard leftover vial(s).

Table 1 – Dilution instructions for remdesivir vials

Remdesivir dose	0.9% sodium chloride infusion bag volume	Volume of 0.9% sodium chloride to be withdrawn and discarded from 0.9% sodium chloride infusion bag	Required volume of remdesivir to add to bag
200 mg (2 vials)	250 mL*	40 mL	40 mL (2 x 20 mL)
100 mg (1 vial)	250 mL*	20 mL	20 mL
*For patients with extreme fluid restrictions, the powder vials, once reconstituted, can be given in a bag volume of 100 mL of 0.9% sodium chloride (refer to Table 2 for administration times/duration below).			

PREPARE INFUSION BAG FOR ADMINISTRATION

4. Add the drawn-up volume of remdesivir into the 0.9% sodium chloride infusion bag.
5. Gently invert the bag 20 times to mix the solution in the bag. Do NOT shake.

ADMINISTRATION

6. Infuse over 30 to 120 minutes, see **Table 2**.
7. Flush with at least 30 mL of 0.9% sodium chloride via the giving set (at the same rate as the remdesivir infusion).

Table 2 – Rate of infusion for remdesivir

Infusion bag volume	Infusion time	Rate of infusion	
250 mL	30 minutes	8.33 mL/min	A slow infusion of up to 120 minutes may help prevent infusion reactions
	60 minutes	4.17 mL/min	
	120 minutes	2.08 mL/min	
100 mL	30 minutes	3.33 mL/min	
	60 minutes	1.67 mL/min	
	120 minutes	0.83 mL/min	

Monitoring Requirements[8,11,14]

Given the limited experience with remdesivir at the recommended dose and duration, patients should have appropriate clinical and laboratory monitoring to aid in early detection of any potential adverse events.

- Perform baseline and DAILY UECs and FBCs
  - Discontinue remdesivir if eGFR <30mL/min/1.73m^2.
- Perform baseline and DAILY LFTs
  N.B.: Remdesivir should be discontinued in patients who develop:
  - ALT ≥5 times ULN during treatment with remdesivir (remdesivir may be restarted when ALT is <5 times ULN); OR
  - ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR.
- Perform baseline and DAILY coagulation profile testing, including prothrombin time.[11]
- Heart rate.[11]
- Observe for infusion-related reactions (described below). If present, immediately discontinue administration of remdesivir and initiate treatment.

Adverse Effects[8,11,14]

It may be difficult to distinguish remdesivir's adverse effects from signs and symptoms of COVID-19. It is important to document and report all adverse effects (from possible to confirmed) experienced by the patient during treatment to inform its safety profile and future use. The following adverse effects have been observed:

Very Common (≥10%)

- graded elevations in ALT, AST and bilirubin—mechanism unknown, time to onset 1–16 days.

Common (≥1%)

- prolonged prothrombin time[11], gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea), headache, rash.

Rare (<0.1%)

- hypersensitivity reactions (anaphylactic reactions are rare but are a medical emergency; stop the infusion and begin treatment immediately).
- infusion-related reactions may include hypotension, nausea, vomiting, diaphoresis, shivering.

Post-marketing adverse effects reported include: bradycardia (including severe bradycardia and sinus bradycardia), cardiac failure and hypotension.[11]

Reporting

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. The prescribing clinician is responsible for reporting medication errors and adverse effects occurring as a result of remdesivir treatment.

- Adverse events related to remdesivir should be reported to the TGA and Gilead and also via the hospital ims+ or RiskMan system.
- Remdesivir use and outcome reporting should occur as per local governance processes.
  A NSW TAG-developed drug registry using an outcome reporting process has been developed. See https://www.nswtag.org.au/covid-19-medicines-resources/. Contact your local DTC or pharmacist for further information.

Additional information

Further information about remdesivir may be obtained from the Medical Affairs Department at Gilead Sciences Australia & New Zealand**:**

- Dr Paul Slade – Senior Director, Medical Affairs; M: 0452 241 653; E: paul.slade@gilead.com
- Dr Heshaam Mir – Director, Medical Affairs; M: 0428 154 750; E: heshaam.mir@gilead.com
- Medical Information Phone: 1800 806 112; Email: au.nz.medinfo@gilead.com

Summary of amendments/updates made in version 1.6 28 September 2021

- Introductory section (page 1): added detail to the recommendations and updated references; removed supply information
- Drug class (page 1): added detail regarding mechanism of action
- Indication for applying guidance (page 2): added ≤10-day symptom onset
- Contraindications (page 2): refined circumstances that would meet contraindications to use
- Drug interactions (page 2): added a reference
- Monitoring and Adverse Effects (page 5): Added prothrombin time, added heart rate and other post-marketing adverse effects such as bradycardia
- Throughout: changed terminology of SARS-CoV-2 to COVID-19 where appropriate.

References

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