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

Remdesivir (Veklury®) has provisional registration in Australia for use in COVID-19. It is currently being evaluated in ongoing Phase 3 clinical trials for COVID-19. Further evidence of benefit and safety will be required for full registration.

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

Supply of remdesivir for clinical trials takes precedence over supply for use outside the clinical trial setting. Supply, if approved, is currently from the National Medical Stockpile (NMS).

Contact Margaret.noris@health.gov.au (Commonwealth Department of Health) for an application form to access. There is no cost to hospitals as the supply has been donated by Gilead and the Commonwealth will cover delivery costs.

This guideline aims to provide supportive information for clinicians if they decide to prescribe remdesivir for use in hospitalised patients with a COVID-19 infection, outside a clinical trial. This guideline should be used in conjunction with the patient consent form and patient and family information leaflet - link. Use of remdesivir is not recommended in the Hospital in the Home setting or in community-based patients with COVID-19.

*This guidance does **not** apply to use in children. Contact the ANZPID Working Group (Asha.Bowen@health.wa.gov.au) to access remdesivir for use in children < 12 years of age or weighing < 40 kg.*

Drug Class

Antiviral [1], a nucleotide analogue prodrug that inhibits RNA polymerases [2]

Authorised Prescribers

- Infectious diseases physicians,
- Intensivists, and
- Respiratory physicians.

Indication for applying this guidance [3; 4; 5; 17]

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

- With confirmed SARS-CoV2 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 and < 18 years of age weighing ≥ 40 kg; AND,
    - With oxygen saturation (SpO_2) ≤ 92% on room air and requiring supplemental oxygen. (Excluded are patients who have required mechanical ventilation longer than 48 hours or those receiving Extracorporeal Membrane Oxygenation (ECMO).

Factors where the benefit of remdesivir is uncertain and requires careful consideration before use are:

- Mechanical ventilation for less than 48 hours;
- 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.

Contraindications and Precautions [1; 4; 6; 7; 17]

- In compliance with conditions granted for supply under an Emergency Exemption (Section 18A of the Therapeutic Goods Act 1989), use is contraindicated in patients with:
  - known **hypersensitivity** to any ingredient of remdesivir product or remdesivir metabolites
  - **renal impairment:** eGFR < 30 mL/min/1.73m^2, on dialysis or continuous veno-venous hemofiltration
    - remdesivir solution is formulated with excipient sulfobutylether-β-cyclodextrin sodium salt, which is renally cleared and accumulates in patients with decreased renal function.
  - **hepatic impairment**: ALT ≥ 5 times the upper limit of normal (ULN) at baseline or ALT > 3 x ULN and bilirubin > 2 x ULN.
  - **evidence of multiorgan failure** including but not limited to coagulopathy (significant thrombocytopenia), hepatic failure, renal failure or significant cardiomyopathy (low cardiac output).
- Consider use in **pregnancy** only if the potential benefit justifies the potential risk of harm to the mother and foetus. If patient is breastfeeding, seek advice and discuss options.

Drug Interactions [4; 8; 9; 10; 11] Refer to University of Liverpool interactions checker.

- 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 whenever possible. [11]
- The combination of remdesivir and dexamethasone has not been evaluated. A clinically significant drug interaction is not anticipated. [8]
- Concomitant use with hydroxychloroquine or chloroquine (noting that current guidelines do not recommend the use of these medicines in COVID-19 outside a clinical trial) is not recommended as it may result in reduced antiviral activity of remdesivir [4; 8]
- In vitro, remdesivir is a substrate for various drug metabolizing enzymes e.g. CYP2C8, CYP2D6 and CYP3A4 and P-glycoprotein (P-gp) transporters as well as 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 or benzodiazepines) should be monitored. Doses may need to be adjusted to avoid toxicity.
  - Strong inducers of CYP3A4 (e.g. carbamazepine, phenytoin, rifampicin) may reduce remdesivir efficacy.

Dose [3; 9; 12; 13]

The suggested dose and duration (which may be updated as data from clinical trials becomes available) is:

200 mg 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 will be required to access stock.

Presentation

- Solution: 100 mg/20 mL concentrate solution (clear colourless to yellow) vial; requires refrigerated storage between 2-8 °C.
  (NB. Although use in children < 12 years of age or weighing < 40kg is outside the scope of this guidance, please note this formulation should not be used in this patient population.)
- Powder: 100 mg sterile, preservative-free, white to off-white to yellow lyophilized powder vial; requires storage below 30 °C.

Preparation and administration [4; 9; 16]

- 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 the two formulations of remdesivir (concentrate solution and powder).
  - If made in an aseptic environment, independent of which formulation has been used, the diluted remdesivir infusion solution 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.

Remdesivir – 100 mg/20 mL CONCENTRATE SOLUTION

The following process for dose preparation and administration is recommended:

1. Select the required number of single-dose vial(s). Equilibrate to room temperature.
   a. Sealed vials can be stored up to 12 hours at room temperature prior to dilution.
   b. If unused do not return to the fridge, contact the manufacturer for the expiry date.
2. Inspect the vial to ensure the container closure is free from defects and the solution is free of particulate matter.
3. Withdraw the required volume of 0.9% sodium chloride from the infusion bag and discard (see **Table 1**).
4. Withdraw the required volume of remdesivir injection solution from the remdesivir vial(s) (see **Table 1**).
   a. Pull the syringe plunger rod back to fill the syringe with approximately 10 mL of air.
   b. Inject the air into the remdesivir injection vial above the level of the solution.
   c. Invert the vial and withdraw the required volume of remdesivir injection solution into the syringe. The last 5 mL of solution requires more force to withdraw.
5. Discard any unused solution remaining in the remdesivir vial.
6. DILUTION: Transfer the required volume of remdesivir injection solution to the infusion bag.
7. Gently invert the bag 20 times to mix the solution in the bag. Do NOT shake.
8. Administer the diluted solution over 30 to 120 minutes using the infusion rate described in **Table 3** (a slow infusion of up to 120 minutes may help prevent infusion reactions).

Table 1 – Recommended dilution instructions for remdesivir concentrate solution

Remdesivir dose	0.9% sodium chloride infusion bag volume to be used	Volume of 0.9% sodium chloride to be withdrawn and discarded from 0.9% sodium chloride infusion bag	Required volume of remdesivir concentrate solution
200 mg (2 vials)	250 mL	40 mL	40 mL (2 x 20 mL)
100 mg (1 vial)		20 mL	20 mL

Remdesivir – 100 mg POWDER

The following process for dose preparation and administration is recommended:

1. Select the required number of powder vial(s).
2. Aseptically RECONSTITUTE remdesivir lyophilized powder by adding 19 mL of Sterile Water for Injection using a suitably sized syringe and needle per vial. Discard the vial if a vacuum does not pull the Sterile Water for Injection into the vial.
   a. Immediately shake the vial for 30 seconds
   b. Allow the contents of the vial to settle for 2 to 3 minutes. A clear solution should result. If the contents of the vial are not completely dissolved, shake the vial again for 30 seconds and allow the contents to settle for 2 to 3 minutes. Repeat this procedure as necessary until the contents of the vial are completely dissolved.
   c. Following reconstitution, each vial contains 100 mg/20 mL (5 mg/mL)
3. Withdraw the required volume of 0.9% sodium chloride from the infusion bag and discard (see **Table 2**)
4. Withdraw the required volume of reconstituted remdesivir from the vial(s) (see **Table 2**).
   a. Pull the syringe plunger rod back to fill the syringe with approximately 10 mL of air.
   b. Inject the air into the vial above the level of the reconstituted solution.
   c. Invert the vial and withdraw the required volume of reconstituted remdesivir into the syringe. The last 5 mL of solution may require more force to withdraw.
5. Discard any unused reconstituted remdesivir remaining in the vial(s).
   a. DILUTION: Transfer the required volume of reconstituted remdesivir into the infusion bag.
   b. Gently invert the bag 20 times to mix the solution in the bag. Do NOT shake.
   c. Administer the diluted solution over 30 to 120 minutes using the infusion rate described in **Table 3** (a slow infusion of up to 120 minutes may help prevent infusion reactions).
   d. 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 – Recommended dilution instructions for remdesivir powder vials (once reconstituted)

Remdesivir dose	0.9% sodium chloride infusion bag volume to be used	Volume of 0.9% sodium chloride to be withdrawn and discarded from 0.9% sodium chloride infusion bag	Required volume of reconstituted remdesivir
200 mg (2 vials)	250 mL	40 mL	40 mL (2 x 20 mL)
	100 mL*		
100 mg (1 vial)	250 mL	20 mL	20 mL
	100 mL*		
*The powder for reconstitution can be given in a volume of 100 mL of 0.9% sodium chloride and should be reserved for patients with extreme fluid restrictions.			

Table 3 – Recommended rate of infusion for remdesivir

Infusion bag volume	Infusion time	Rate of infusion	
250 mL	30 minutes	8.33 mL/min	On completion, flush with at least 30 mL of 0.9% sodium chloride via the giving set (at the same rate as the remdesivir infusion)
	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	
A slow infusion of up to 120 minutes may help prevent infusion reactions			

Monitoring Requirements [9]

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.
- Perform baseline and DAILY hepatic laboratory testing.
  NB: 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
- Observe for infusion-related reactions (described below). If present, immediately discontinue administration of remdesivir and initiate appropriate treatment.

Adverse Effects [1; 4; 9; 10; 14]

It may be difficult to distinguish remdesivir's adverse effects and 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%)

- 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 commence treatment immediately)
- infusion-related reactions may include hypotension, nausea, vomiting, diaphoresis, shivering.

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, the hospital IIMS+ or RiskMan system and Gilead.
- Remdesivir use and outcome reporting should occur as per local governance processes. A NSW TAG-developed drug registry using an outcome reporting process is in development. See http://www.nswtag.org.au/resources-for-experimental-medicines-for-the-treatment-of-covid-19/

Additional information [15]

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

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