Introduction[1,2]

Remdesivir (Veklury®) is provisionally registered by the Therapeutic Goods Administration for use in Australia for the treatment of COVID-19.

Remdesivir is not an alternative or substitute for vaccination. **Vaccination is the preferred and primary option for the prevention of COVID-19.**

Clinical trials for remdesivir were conducted when the early variants of SARS-CoV-2 were in circulation. Clinicians should consider the SARS-CoV-2 variant being targeted and the possibility of reduced efficacy.

This guideline requires endorsement by your local Drug and Therapeutics Committee (DTC) prior to implementation. Additional resources to support the safe and appropriate use of remdesivir are available here.

Drug class and mechanism of action[1,2]

Remdesivir is an adenosine nucleotide prodrug (antiviral) that inhibits the replication of SARS-CoV-2, the causative virus of COVID-19.

Approved indications[1-3]

Treatment of COVID-19 in:

- adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg) who have pneumonia due to SARS-CoV-2 requiring supplemental oxygen
- adults and paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19

Use of remdesivir for patients who do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19 must be in accordance with the ACI *Guidance for the use of anti-SARS-CoV-2 monoclonal antibodies and antiviral agents as prophylaxis or to prevent severe infection from COVID-19 in NSW*.

Contraindications and precautions[1]

- Known allergy to remdesivir or any of the excipients of this medicine (sulfobutyl betadex sodium, hydrochloric acid and sodium hydroxide).
- Patients with eGFR < 30 mL/min/1.73m^2. One of the excipients, sulfobutyl betadex sodium, is renally cleared and accumulates in patients with decreased renal function, which may potentially adversely affect renal function.
- Patients with hepatic impairment defined as alanine aminotransferase (ALT) ≥ 5 times the upper limit of normal at baseline.
- See *Pregnancy and breastfeeding* section for recommendations in pregnancy and breastfeeding.

Pregnancy and breastfeeding[3]

The National COVID-19 Clinical Evidence Taskforce has made two conditional recommendations regarding the use of remdesivir in pregnant and breastfeeding women:

- Consider using remdesivir in pregnant and breastfeeding women hospitalised with COVID-19 who require oxygen but do not require non-invasive or invasive ventilation
- Consider using remdesivir within 7 days of symptom onset in pregnant women with COVID-19 who do not require oxygen and who have one or more additional risk factors for disease progression. Treatment should be considered if the benefit justifies the possible but unknown risks.

Pregnancy

Remdesivir has been classified **pregnancy category B2** by the Therapeutic Goods Administration. No adequate or well-controlled studies of remdesivir use in pregnant women have been conducted. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by treating health professionals.

Breastfeeding

There is no information regarding the presence of remdesivir in human milk, the effects on the breastfed infant, or the effects on milk production. Evidence from animal studies suggests that remdesivir metabolite is excreted into the milk of lactating animals.

Drug interactions[1,5,6]

- No formal drug interaction studies have been conducted involving remdesivir and other medications. 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.
- Concomitant use with hydroxychloroquine or chloroquine (both of which are **not recommended** for treatment of COVID-19) is not recommended as it may result in reduced antiviral activity of remdesivir.
- Medicines which are metabolised via CYP3A4 (e.g., atorvastatin, warfarin, voriconazole or benzodiazepines) should be monitored and doses may need to be adjusted to avoid toxicity.
- Strong inducers of CYP3A4 (e.g., carbamazepine, phenytoin, rifampicin) may reduce remdesivir efficacy, and hence should be avoided during remdesivir treatment.
- Resources such as Liverpool COVID-19 drug interactions tool and Micromedex drug interactions tool can be used to identify drug interactions in a patient taking remdesivir.

Presentation, storage and stability[1,9]

Remdesivir is available as a powder for reconstitution vial containing remdesivir 100 mg. The powder vial must be stored below 30ºC. Once reconstituted and diluted, the infusion solution is stable for 4 hours below 25ºC or 24 hours at 2 to 8ºC.

Dose, timing and route of administration[1,7,8]

The recommended dose for adult and paediatric patients (weighing at least 40 kg) is:

200 mg intravenous (IV) on Day 1, then 100 mg IV daily

- In patients with pneumonia requiring supplemental oxygen the total duration of treatment should be **at least 5 days and not more than 10 days.** Note – treatment beyond five days did not improve outcomes in clinical trials.
- In patients who do not require supplemental oxygen and are at high risk of progressing to severe COVID-19 treatment should be initiated as soon as possible after diagnosis of COVID-19 and within 7 days after symptom onset. The total duration of treatment should be **3 days**.

The recommended dose for paediatric patients with pneumonia requiring supplemental oxygen who are at least 4 weeks of age and weighing 3 kg to less than 40 kg is:

5 mg/kg intravenous (IV) on Day 1, then 2.5 mg/kg IV daily for no more than 10 days

Preparation and administration[1,9, 10, 11]

Preparation of vials
1. Using aseptic technique, add 19 mL of sterile water for injection (WFI) to the remdesivir powder vial. 2. Immediately shake the vial for 30 seconds and 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 secondsand allow the contents to settle for 2 to 3 minutes. Repeatthis procedure as necessary until the contents of the vialare completely dissolved. 3. Repeat steps 1 and 2 for the number of vials required. Following reconstitution, each vial contains 100 mg/20 mL (5 mg/mL). Dilute immediately after reconstitution.
Dilution – adult and paediatric patients (weighing at least 40 kg)
1. Obtain a 0.9% sodium chloride 250 mL prefilled IV infusion bag. 2. Using aseptic technique, withdraw the required volume from the IV infusion bag (see below).

Remdesivir dose	Volume of sodium chloride 0.9% to be removed from the bag	Volume of remdesivir reconstituted solution
200 mg	40 mL	2 x 20 mL (2 vials)
100 mg	20 mL	20 mL (1 vial)

3. Withdraw the required dose of remdesivir (see above) and add to the 0.9% sodium chloride infusion bag. 4. Gently invert the bag 20 times to mix the solution in the bag. **Do NOT shake.** Note: For patients with extreme fluid restrictions, the powder for reconstitution vials, once reconstituted, can be given in a bag of 0.9% sodium chloride, total volume of **100 mL.**
Dilution - paediatric patients (at least 4 weeks of age and weighing 3 kg to less than 40 kg)
Dilute the prescribed dose of remdesivir 5 mg/mL solution with sodium chloride 0.9% to achieve a final concentration of 1.25 mg/mL (i.e.,1 part remdesivir 5 mg/mL solution and 3 parts sodium chloride 0.9%). For example: 50 mg dose of remdesivir. Required volume of remdesivir 5 mg/mL solution = 10 mL (1 part) Required volume of sodium chloride 0.9% to achieve 1.25 mg/mL concentration = 30 mL (3 parts i.e., 3 x 10 mL)
Administration
Administration of remdesivir is via intravenous infusion. • Do not use the same IV line to administer other medications at the same time. • Refer to **table below** for recommended infusion time • After the infusion is complete, flush the giving set with at least 30 mL of 0.9% sodium chloride (at the same rate as the remdesivir infusion).

Rate of infusion for remdesivir for adults and paediatric patients (weighing at least 40 kg)

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

Rate of infusion for remdesivir for paediatric patients at least 4 weeks of age and weighing 3 kg to less than 40 kg[12]

Infusion Volume	Infusion time (min)	Rate of infusion (mL/min)	
100 mL	30	3.33	A slow infusion of up to 120 minutes may help prevent infusion reactions
	60	1.67	
	120	0.83	
50 mL	30	1.67	
	60	0.83	
	120	0.42	
25 mL	30	0.83	
	60	0.42	
	120	0.21	
7 mL	30	0.23	
	60	0.12	
	120	0.06	

Monitoring requirements[1,9,12]

- Monitor the patient for adverse effects (see *Adverse Effects* section below). If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue, initiate appropriate medications and/or supportive care.
- Patients should have appropriate clinical and laboratory monitoring to aid in early detection of any potential adverse events.
    - Perform baseline and daily urea, electrolytes and creatinine (UEC) and full blood count (FBC)
        - Discontinue remdesivir if eGFR < 30mL/min/1.73m^2.
    - Perform baseline and daily liver function tests – remdesivir should be discontinued in patients who develop:
        - ALT ≥ 5 times upper limit of normal (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.
- Monitor heart rate every 4 - 6 hours.
- Observe for infusion-related reactions. If present, immediately discontinue administration of remdesivir and initiate treatment.

Adverse effects[1,12]

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 the Product Information for a complete list of possible adverse effects.

- **Very common (≥ 10%):** graded elevations in ALT, AST and bilirubin.
- **Common (≥ 1% to < 10%):** prolonged prothrombin time, gastrointestinal symptoms (e.g., nausea, vomiting, diarrhoea), headache, rash.
- **Rare (< 0.1%):** hypersensitivity and infusion related reactions (anaphylactic reactions are rare but are a medical emergency; stop the infusion and begin treatment immediately).

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

Reporting[3]

- Remdesivir 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, Gilead (drug sponsor) and via their facility's incident management system.
- Drug and Therapeutics Committee oversight in the access process will enable appropriate medicines governance and ensure the collection and analysis of patient outcomes and systematic monitoring of medicine use. Remdesivir use and outcome reporting should occur as per local clinical governance processes.

Summary of major changes made in version 1.8.1 – July 2022

- Inclusion of additional provisionally approved indications for remdesivir.
- Inclusion of paediatric dosing recommendations, and dilution instructions (from PIMH, reference 11).
- Updated conditional recommendations on use of remdesivir in pregnancy and breastfeeding.
- Removal of reference to the remdesivir concentrated solution vial as this product is no longer available.

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