



DRUG GUIDELINE- REMDESIVIR FOR TREATMENT OF COVID-19

Remdesivir is a prodrug that undergoes intracellular conversion to an active analogue of adenosine triphosphate to inhibit viral RNA polymerase. This antiviral has demonstrated inhibitory effects on pathogenic animal and human coronaviruses, including SARS-CoV-2 replication in animal models.

[Remdesivir](#) has been granted provisional Therapeutic Goods Administration (TGA) approval on the basis of preliminary clinic data only, as a treatment option for:

- adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg) who have pneumonia due to SARS-CoV-2, who require supplemental oxygen, and;
- adults and paediatric patients (12 years and over and weighing at least 40 kg) who do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19.

Remdesivir is not recommended in adults hospitalised with COVID-19 who require non-invasive or invasive ventilation.

Remdesivir is only to be used for the treatment of mild to moderate disease (within 7 days of symptom onset) in patients at significant risk of disease progression who do not require oxygen, where logistically feasible and where oral antiviral therapies are contraindicated (for example, in pregnant or breastfeeding women), or in children and adolescents aged 12 years and over and weighing at least 40 kg.

The [National COVID-19 Clinical Evidence Taskforce](#) (current as at 22/06/2022) provides a conditional recommendation for use of remdesivir in

- adults with COVID-19 who require oxygen but do not require non-invasive or invasive ventilation
- unvaccinated adults with COVID-19 within 7 days of symptom onset who do not require oxygen and who have one or more risk factors for diseases progression¹
- hospitalised women who are pregnant or breastfeeding with COVID-19 who require oxygen but do not require non-invasive or invasive ventilation.
- exceptional circumstances for the treatment of COVID-19 within 7 days of symptom onset in children and adolescents aged 28 days and over and weighing at least 3 kg who do not require oxygen and are at high risk of deterioration, where other treatments are not available or appropriate.

This medication is regulated by the National Medical Stockpile. Access to stock requires completion of a WA Emergency COVID-19 Treatment Approval for Remdesivir and confirmation by the prescriber that the patient fulfils required criteria.

Supply of COVID-19 therapeutics via the National Medical Stockpile (NMS) is uncertain and availability is expected to fluctuate with demand and constraints in the supply chain.

To ensure equity of access and conserve Remdesivir therapy for those patients at the highest risk of progression, a tiered access criterion is in place to allocate stock based upon current supply.

This guideline should be used in conjunction with the Remdesivir resources available:

- WA Emergency COVID-19 Treatment Approval for Remdesivir Form
- Patient Consent Form and further information regarding consent, and
- Patient Medicine Information Leaflet (MIL)

Drug Class:

Remdesivir is a prodrug that undergoes intracellular conversion to an active analogue of adenosine triphosphate to inhibit viral RNA polymerase.

Indication for Use:

The [TGA has granted provisional approval for use of remdesivir](#) in the treatment of:

- adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg) who have pneumonia due to SARS-CoV-2, who require supplemental oxygen, and;
- 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.

Remdesivir can be used for the treatment of mild to moderate disease (within 7 days of symptom onset) in patients at significant risk of disease progression who do not require oxygen, where logistically feasible and where oral antiviral therapies are contraindicated (for example, in pregnant or breastfeeding women), or in children and adolescents aged 12 years and over and weighing at least 40 kg.

Eligibility Criteria:

- As per TGA criteria listed above (depending on patient's clinical status).
- Positive COVID-19 PCR or RAT
- Within 7 days of symptom onset if for mild to moderate COVID-19 infection for patients who do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19.
- Oxygen saturation (SpO₂) \leq 94% on room air or requiring supplemental oxygen
- Alanine aminotransferase (ALT) $<$ 5 x upper limit of normal (ULN) by local laboratory measure and/or ALT $<$ 3 x ULN and bilirubin $<$ 2 x ULN

Remdesivir is **not** recommended in adults hospitalised with COVID-19 who require non-invasive or invasive ventilation. Within this population, ventilation includes invasive or non-invasive mechanical ventilation and extracorporeal membrane oxygenation (ECMO).

Any treatment must be accompanied by approval from an Infectious Diseases Physician following referral through the WA Emergency COVID-19 Treatment Approval for Remdesivir Form

- Further information can be found on the [National COVID-19 Clinical Evidence Taskforce website](#), including [remdesivir](#) specific information.

Contraindications and Precautions²:

- There are two available formulations with differences in preparation. Follow the product specific instructions for reconstitution and dilution⁵
- Remdesivir should be used cautiously in patients with hepatic or renal impairment.
- Remdesivir is not approved for use in patients with Alanine aminotransferase (ALT) $>$ 5 x upper limit of normal (ULN) by local laboratory measure^{4,6}.

- Both IV formulations of remdesivir contain sulfobutylether- β -cyclodextrin (SBECD) as a solubility enhancer which is renally cleared and accumulates in patients with decreased renal function. Remdesivir should not be commenced in patients with an eGFR of <30mL/minute^{5,6}.
- Remdesivir 100mg/20mL concentrate for injection should not be used for paediatric or neonatal patients (from 4 weeks of age and weighing at least 3 kg to 12 years of age and weighing less than 40 kg) due to the higher amount of SBECD present and resulting higher tonicity of the solution concentrate compared to the lyophilized formulation⁴. Consult your Pharmacy Department and Paediatric Infectious Disease Physician before commencing remdesivir.
- Remdesivir is not recommended in patients with:
 - Evidence of multiorgan failure including but not limited to:
 - Coagulopathy (significant thrombocytopenia)
 - Hepatic failure (elevated bilirubin)
 - Renal failure (low urine output or estimated glomerular filtration rate (eGFR) < 30 mL/min)
 - Significant cardiomyopathy (low cardiac output)
 - Renal failure (eGFR < 30 mL/min or dialysis or Continuous Veno-Venous Hemofiltration (CVVHF)
 - Mechanical ventilation for longer than 48 hours at time of application
 - Receiving Extracorporeal Membrane Oxygenation (ECMO)
 - Known hypersensitivity to the study drug, the metabolites, or formulation excipient.

Drug Interactions:

- Drug-Drug Interactions with remdesivir are not known. Due to antagonism observed in vitro, concomitant use of remdesivir with chloroquine or hydroxychloroquine is not recommended.
- In vitro, remdesivir is a substrate of CYP2C8, CYP2D6 and PGP. It is an inhibitor of CYP3A4, and OATp1B1/B3. It is suggested that substrates of these should be administered at least 2 hours after remdesivir, however clinical relevance of these potential interactions is not known. The use of strong CYP inducers such as rifampicin or lopinavir/ritonavir may decrease plasma concentrations of remdesivir and is not recommended.

Presentation and Storage²:

Remdesivir 100mg lyophilized powder for injection

- Used for Neonates and Children \geq 3 kg.
- Powder for injection
- Preservative-free
- White to off-white to yellow lyophilised powder.
- Store below 30°C
- The prepared infusion solution of remdesivir is stable for up to 4 hours at room temperature or up to 24 hours at 2-8°C.

Dose^{2,3}:

Key considerations

- For adults with pneumonia due to SARS-CoV-2, who require supplemental oxygen (**moderate to severe disease**) duration of treatment is 5 days but can be extended to a total of 10 days with infectious disease physician review if patient doesn't demonstrate clinical improvement.
- For adults and paediatric patients (12 years and over and weighing at least 40 kg) who do not require supplemental oxygen (**mild to moderate**) and who are at high risk of progressing to severe COVID-19 total duration of treatment is 3 days.
- No dose adjustment is required in patients >65 years.
- Remdesivir is not recommended in patients with eGFR less than 30 mL per minute unless the potential benefit outweighs the potential risk
- Hepatic laboratory testing should be performed prior to and monitored while receiving remdesivir as clinically appropriate. Remdesivir not recommended with ALT >5x ULN.
- Prothrombin time should be determined prior to and monitored while receiving remdesivir as clinically appropriate.
- For patient 18 years and under, approval is required from a Paediatric Infectious Diseases Physician at Perth Children's Hospital to determine appropriateness of adolescent risk factors (paediatric complex chronic conditions (PCCC): congenital and genetic, cardiovascular, gastrointestinal, malignancies, metabolic, neuromuscular, renal and respiratory conditions, severe asthma and obesity) and need for remdesivir.

For adults and paediatric patients (weighing at least 40 kg) who have pneumonia due to SARS-CoV-2 requiring supplemental oxygen:

- Day 1 - a single loading dose of VEKLURY 200 mg given by intravenous (IV) infusion
- Day 2 onwards - 100 mg given once daily by intravenous infusion for 4 days. This can be extended to a total of 10 days with infectious disease physician review if patient doesn't demonstrate clinical improvement.

For neonates and paediatric patients (at least 4 weeks of age and weighing at least 3 kg) * hospitalised with severe SARS-CoV-2 infection:

- 5mg/kg/dose (to a maximum of 200mg) as a single IV loading dose on day one followed by 2.5mg/kg/dose (to a maximum of 100mg) IV once daily for FOUR (4) days.
- Application may be made to extend the treatment out to a TEN (10) day course if there is no clinical improvement with infectious disease physician review.

*Must use remdesivir 100mg lyophilized powder for injection formulation for this patient group.

For adults and paediatric patients (≥ 12 years AND weighing at least 40 kg) AND at an increased risk of hospitalisation or death and who do not currently require initiation of oxygen:

- 200mg as a single IV loading dose on day one followed by 100mg IV once daily for a total duration of treatment of 3 days.

Preparation and Administration²:

Preparation Steps

Remdesivir must be administered in a location with suitable access to personnel and equipment to manage suspected infusion related reactions or anaphylaxis during the infusion and for the 60-minute observation period after completion of the infusion⁴.

This product contains no preservative, any unused portion of a single-dose remdesivir vial should be discarded after a diluted solution is prepared^{3,5}.

Remdesivir 100mg lyophilized powder for injection^{4,6}

1. Aseptically reconstitute remdesivir lyophilised powder by addition of 19 mL of sterile water for injection
2. Discard the vial if a vacuum does not pull the sterile water for injection into the vial
3. Immediately shake the vial for 30 seconds
4. Allow the contents of the vial to settle for 2 to 3 minutes. A clear solution should result
5. 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
6. Repeat this procedure as necessary until the contents of the vial are completely dissolved
7. Inspect the vial to ensure the container closure is free from defects and the solution is free of particulate matter
8. Once reconstituted each vial contains 100mg/20mL (5mg/mL) of remdesivir
9. **Dilute immediately after reconstitution** as per the table below
10. Remove the required volume of sodium chloride 0.9% as per the table below
11. Withdraw the required volume of remdesivir solution from the vial(s) and add to the 0.9% sodium chloride infusion bag
12. Gently invert the bag approximately 20 times to mix the solution once diluted.
Do not shake.

For children and adolescents 12 years and over:

- For a 200mg dose of remdesivir, withdraw 40mL of sodium chloride 0.9% from the appropriate infusion bag prior to adding the required 40mL of remdesivir solution.
- For a 100mg dose of remdesivir, withdraw 20mL of sodium chloride 0.9% from the appropriate infusion bag prior to adding the required 20mL of remdesivir solution.
- A volume of 250mL is preferred, but a volume of 100mL may be used for patients with severe fluid restrictions.

Remdesivir Dose	Sodium chloride 0.9% infusion bag volume to be used	Volume to be withdrawn and discarded from sodium chloride 0.9% infusion bag	Required volume of reconstituted Remdesivir
200mg (2 vials)	250mL	40mL	40mL (2x20mL)
	100mL*		
100mg (1 vial)	250mL	20mL	20mL
	100mL*		

*Note: 100mL infusion volume should be reserved for patients with severe fluid restriction

Please Note: When programming infusion pumps, even after removing the 20 or 40mL from the infusion bags there may still be an overage included which will need to be administered.

For children under 12 years:

- Further dilute the reconstituted 100 mg/20 mL (5 mg/mL) remdesivir to a fixed concentration of 1.25 mg/mL using 0.9% sodium chloride.
- The total required infusion volume of the 1.25 mg/mL remdesivir solution for infusion is calculated from the paediatric weight-based dosing regimens of 5 mg/kg for the Loading Dose and 2.5 mg/kg for each Maintenance Dose.
- Small 0.9% sodium chloride infusion bags (e.g., 25, 50, or 100 mL) or an appropriately sized syringe should be used for paediatric dosing. The recommended dose is administered via IV infusion in a total volume dependent on the dose to yield the target remdesivir concentration of 1.25 mg/mL.
- A syringe may be used for delivering volumes.

Administration Steps²

1. Remdesivir is to be administered intravenously over 30-120 minutes. It must not be given as an intramuscular (IM) injection.
2. After infusion is complete, flush with at least 30mL 0.9% sodium chloride.
3. If the patient develops an infusion-related hypersensitivity reaction, depending on the severity of the reaction, if it is deemed clinically appropriate to continue therapy the rate of infusion may be reduced to a maximum infusion time of 120 minutes to help minimise symptoms.

Recommended rate of infusion – diluted VEKLURY powder for injection in adults and paediatric patients (weighing at least 40 kg)

Infusion Bag Volume	Infusion Time	Rate of Infusion
250mL	30 min	8.33 mL/min
	60 min	4.17 mL/min
	120 min	2.08 mL/min
100mL	30 min	3.33 mL/min
	60 min	1.67 mL/min
	120 min	0.83 mL/min

Recommended rate of infusion – diluted VEKLURY powder for infusion in paediatric patients at least 4 weeks of age and weighing 3 kg to less than 40 kg

Infusion Bag Volume	Infusion Time	Rate of Infusion
100mL	30 min	3.33 mL/min
	60 min	1.67 mL/min
	120 min	0.83 mL/min
50mL	30 min	1.67 mL/min
	60 min	0.83 mL/min
	120 min	0.42 mL/min
25mL	30 min	0.83 mL/min
	60 min	0.42 mL/min
	120 min	0.21 mL/min

Monitoring Requirements²:

- Infusion-related reactions have been reported during and following administration of intravenous remdesivir.
 - Signs and symptoms to assess for include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnoea, wheezing, angioedema, rash, nausea, vomiting, diaphoresis and shivering.
 - Slower infusion rates (e.g. over 120 minutes) may assist to minimise these reactions.
- Anaphylactic reactions are rare but are a medical emergency. If an anaphylactic reaction occurs, stop the infusion immediately and initiate appropriate treatment.
- Given the limited experience with remdesivir patients should have ongoing monitoring of appropriate clinical and laboratory levels to aid in the early detection of any potential adverse effects. These should include baseline and daily urea and electrolytes, full blood picture and liver function tests⁴.
- Patients must be monitored and observed for possible anaphylactic and infusion related reactions throughout the infusion and for one hour after completion of the infusion⁴.

Note: Remdesivir should be discontinued in patients who develop:

- ALT greater than or equal to 5 times the upper limit of normal during treatment with remdesivir (may be restarted when ALT is less than 5 times the upper limit of normal⁵.)
- ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalised ratio (INR)⁵.
- Patients with an eGFR of <30mL/minute³.

Drug Interactions

- Drug-drug interaction trials of VEKLURY and other concomitant medications have not been conducted.
- Chloroquine and hydroxychloroquine reduced the conversion of remdesivir to the active triphosphate form in vitro and concomitant use not recommended.
- Remdesivir is a substrate for esterases in plasma and tissue and drug metabolizing enzyme CYP3A4 and is a substrate for Organic Anion Transporting Polypeptides 1B1 (OATP1B1) and P-glycoprotein (P-gp) transporters.
- The potential of interaction of remdesivir with inhibitors/inducers of the hydrolytic pathway (esterase) or 3A4 has not been studied. Strong inhibitors may result in increased remdesivir exposure. The use of strong inducers (e.g. rifampicin) may decrease plasma concentrations of remdesivir and is not recommended.
- Dexamethasone is reported to be a moderate inducer of CYP3A and P-gp. Induction is dose-dependent and occurs after multiple doses. Dexamethasone is unlikely to have a significant effect on remdesivir as remdesivir has a moderate-high hepatic extraction ratio and is used for a short duration in the treatment of COVID-19.

Adverse Effects²:

Common: headache, nausea, increased liver transaminases, rash, anaemia, hyperglycaemia, lymphopenia^{3,4,7}.

Rare: hypersensitivity reactions (including hypo and hypertension, tachycardia, bradycardia, hypoxia, fever, shivering, dyspnoea, wheezing, angioedema, rash, nausea and vomiting have been reported, slower infusion rates may potentially prevent these reactions, infusion related reactions^{3,4,6,7}.

Adverse events related to medicines should be reported to the [TGA](#) and via the [Datix CIMS](#) (WA Health).

Practice Points²:

- Compatibility of remdesivir with other medications is not known. Use a dedicated IV line only
- Compatibility of remdesivir with diluents other than sodium chloride is not known. Remdesivir should ONLY be diluted with 0.9% sodium chloride
- No data available of effects of remdesivir on fertility, pregnancy (category B2) and lactation.

Access to medications:

Please refer to your local health care facility guidelines as each facility will have their own internal processes and policies.

- Treating team will need to complete WA Emergency COVID-19 Treatment Approval – Remdesivir form which will need review by an Infectious Disease Physician for approval for use
- Once approval is obtained, the treating team will need to consent patient using the WA Health Patient Consent Form - Remdesivir before initiating treatment.

References

1. Gottlieb RL et al Early remdesivir to prevent progression to severe Covid-19 in outpatients. *New England Journal of Medicine* 2022;386(4):305-315
2. [VEKLURY Product Information](http://www.tga.gov.au). Available from www.tga.gov.au . Accessed 14/06/2022
3. Clinical Evidence Taskforce Guidelines. Available from https://covid19evidence.net.au/wp-content/uploads/FLOWCHART-MODERATE-SEVERE.pdf?_=220615-00907 . Accessed 11/01/2021
4. Gilead. VEKLURY Powder for Injection Product Information. 2020.
5. Clinical Pharmacology [Internet]. Elsevier BV. 2021 [cited 08/02/2022]. Available from: <http://www.clinicalpharmacology-ip.com.pklibresources.health.wa.gov.au/default.aspx> .
6. MIMS Australia. MIMS online [full product information]. St Leonards, N.S.W: CMP Medica Australia.; 2021. p. 1v. (various pages).
7. Symons K. Ermer J. (editors). Australian injectable drugs handbook. Collingwood: The Society of Hospital Pharmacists of Australia; 2020.
8. Paediatric Formulary Committee. BNF for Children: 2021. London: BMJ Group Pharmaceutical Press; 2021.
9. https://www.health.gov.au/sites/default/files/documents/2020/07/criteria-for-access-to-remdesivir-based-on-global-expanded-access-program_0.pdf
10. Criteria for access to remdesivir from the National Medical Stockpile; updated 31/7/20: https://www.health.gov.au/sites/default/files/documents/2020/07/criteria-for-access-to-remdesivir-from-the-national-medical-stockpile_0.pdf

Version Control

Version	Date	Comments
1.0	14/6/22	Endorsed by COVID-19 EAG

This guidance is correct at the time of publishing. However, as it is subject to updates, please use the hyperlinks to confirm the information is accurate.

WA guidance may be amended as additional federal guidance is finalised and/or further information becomes available.

© Department of Health 2022

Copyright to this material is vested in the State of Western Australia unless otherwise indicated. Apart from any fair dealing for the purposes of private study, research, criticism or review, as permitted under the provisions of the *Copyright Act 1968*, no part may be reproduced or re-used for any purposes whatsoever without written permission of the State of Western Australia.