Remdesivir Prescribing Guideline

Last updated 28/11/2022

Background

Remdesivir (Veklury®) has been granted provisional approval by the Therapeutic Goods Administration (TGA) for treatment of COVID-19 in Australia.

For public hospitals, Remdesivir has a restricted listing on the Queensland Health Medicines Formulary. Please refer to the List of Approved Medicines (LAM) for details. Remdesivir is managed through the National Medical Stockpile and distributed by Central Pharmacy.

It is recommended this guideline is endorsed by local Medicines Management or Drug and Therapeutics Committees prior to use at your facility.

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.[1,2,3]

Indications

- Refer to Decision Pathway for drug treatment of mild to moderate COVID 19 and Guidance on the use of COVID-19 therapeutics for treatment or prophylaxis of SARS-CoV-2. For detailed information on rationale for use please refer to the National Clinical Evidence Taskforce (NCET) and the Pharmaceutical Benefits Scheme (PBS)
- For information on prescribing in children please refer to CHQ-GDL-63327- The management and treatment of children with acute SARS-CoV-2 infection (COVID-19)
- For information on use in pregnancy and breastfeeding please refer to advice in the NCET Guidelines and the Product Information for the individual COVID therapeutics as well as the Guideline for Treatment of mild to moderate COVID-19.

Contraindications and precautions

- Known hypersensitivity to remdesivir, its metabolites or any of the excipients: sulfobutyl betadex sodium (SBECD), hydrochloric acid, sodium hydroxide
- Liver impairment: ALT ≥ 5 x upper limit of normal at baseline
- Kidney impairment: eGFR < 30 mL/min/1.73m2. (refer to dosing section for details)
- Refer to pregnancy and breastfeeding section for information in pregnancy and breastfeeding

Please also refer to the product information for considerations and precautions[1].

Drug interactions

No formal drug-drug interaction studies have been conducted with remdesivir and the potential for drug interactions is currently unknown.[1] Based on its rapid distribution, metabolism and clearance the likelihood of clinically significant interactions is low[4].

- Concomitant prescribing of chloroquine or hydroxychloroquine is **not recommended** due to antagonism observed in vitro which may result in reduced antiviral activity.[1,4]
- In vitro, remdesivir is a substrate of drug metabolising enzymes CYP2C8, CYP2D6 and CYP3A4, organic anion transporting polypeptides 1B1 and p-glycoprotein transporters[1]. 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.

Refer to the Liverpool COVID-19 Drug Interactions Checker for advice on specific drugs.

Dosing and duration (adults)

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

For treatment of COVID-19 in hospitalised adult patients requiring oxygen with an eGFR above 30mL/min
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 early treatment of mild to moderate COVID-19 within 7 days of symptom onset with an eGFR above 30mL/min:
Loading dose of **200 mg IV** on day 1, then **100 mg IV daily** on day 2 and 3
(maximum of 3 days treatment)

Kidney impairment

Remdesivir should be used with caution in patients with eGFR < 30 mL/min/1.73m^2 due to formulation with the excipient sulfobutylether-β-cyclodextrin (SBECD) which accumulates in patients with decreased kidney function.[1] SBECD is dialyzable, with approximately 46% removed in a 4-hour dialysis session[5]. The clinical significance of SBECD accumulation is unknown, particularly considering the short durations of therapy recommended for COVID-19 treatment and low concentrations of SBECD in remdesivir vials. However, patients should be monitored for kidney and liver toxicity.

Use in eGFR < 30 mL/min/1.73m2 is not recommended by the sponsor however, there are some limited studies on use of remdesivir in kidney impairment[6,7,8,9]. Dosing in this cohort should only be considered where the potential benefit outweighs risk. Consider seeking expert advice.

Based on extrapolation of pharmacokinetic data, an approach to dosing in adult patients with an eGFR less than 30mL/min/1.73m^2 is:

- for those not on dialysis for mild to moderate disease (not requiring oxygen): give 200mg IV loading dose once on day 1, then 100mg IV once on day 2, no further doses needed
- for those not on dialysis for moderate disease requiring oxygen: give 200mg IV loading dose once on day 1, then 100mg IV every 48 hours starting from day 2 until course complete (i.e. 200mg IV on day 1 and 100mg IV on day 2 and 4).
- For patients on dialysis: give the standard dose (see Box above), and maintain normal peritoneal dialysis or haemodialysis program (ensuring a dialysis session within the treatment course), administer remdesivir at least 4 hours before, or any time after, the haemodialysis session. Due to a lack of information, administration during dialysis is not recommended.

Liver impairment

The pharmacokinetics of remdesivir have not been evaluated in patients with liver impairment. It is not known if dose adjustment is required.[1]

Contraindicated in patients with ALT ≥ 5 times the upper limit of normal at baseline[1]

Prescribing and Ordering

Refer to Appendix 1 for examples of ieMR® and National Inpatient Medication Chart (non-ieMR®) ordering.

Adverse effects and reporting

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 local adverse event processes (e.g. Riskman).

Please refer to the remdesivir product information for a complete list of potential adverse effects.

The following adverse effects have been observed in clinical studies:[1,11,13]

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

Common (≥ 1% to <10%): prolonged prothrombin time, gastrointestinal symptoms (e.g.: nausea, vomiting, diarrhoea), headache, rash.

Rare (<0.1%): hypersensitivity and infusion reactions.

Monitoring

Observe for infusion reactions. Infusion reactions may include hypotension, hypertension, bradycardia, hypoxia, nausea, vomiting, angioedema, rash diaphoresis and shivering.[12] A slow infusion of up to two hours may help prevent these.[12] 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:
    - Significant decrease in eGFR to < 30 mL/min/1.73m^2 while on treatment
    - 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.

Access and Supply

Access to remdesivir is regulated by the National Medical Stockpile and is currently available through public and private hospital pharmacies. Australia has received a supply, from which Queensland has been allocated a number of doses for use in public and private hospital settings. Completion of the Request to Access Form is a requirement for supply.

QH facilities: use the MARP portal Login - Medication Access Request Portal (health.qld.gov.au)

For Private facilities: use the following link Clinical guidelines | Queensland Health and send completed forms to CTWG@health.qld.gov.au

Storage and Stability

Please refer to the remdesivir product information for advice on storage and stability[1].

Preparation and administration for adults

Preparation Steps [1,10,11]

1. Aseptically reconstitute the vial with **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, then allow to stand for 2 to 3 minutes.
4. Repeat the process of shaking and standing until completely dissolved and the solution is clear.
5. Following reconstitution, the vial contains: remdesivir 100 mg/20 mL (5 mg/mL)
6. Dilute immediately.
7. Prepare infusion bag: Withdraw the required volume of fluid from a 250 mL bag of 0.9% sodium chloride. * See table 1, below.
8. Withdraw the required dose of reconstituted remdesivir from the vial (see Table 1). Discard remaining vial(s).
9. 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 1 – dilution instructions for remdesivir

Remdesivir dose	Volume of infusion 0.9% sodium chloride infusion bag	Volume to be removed from bag	Volume of remdesivir reconstituted solution
200 mg	250 mL*	40 mL	2 x 20 mL (2 vials)
100 mg	250 mL*	20 mL	1 x 20 mL (1 vial)

*Remdesivir can be given in 100 mL for patients with severe fluid restriction. Refer to instructions in the Product Information available via the TGA website.

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)

References

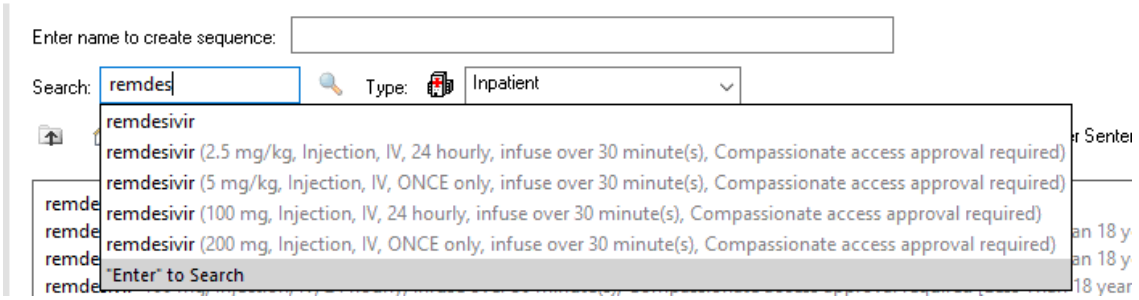
1. Gilead Sciences Pty Ltd. Australian product information – Veklury (remdesivir) concentrate for injection. 2020. Published 2020 July 20.
2. Beigel JH, Tomashek KM, Dodd LE *et al.* Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med 2020; 383:1813-1826.
3. Spinner CD, Gottlieb RL, Criner GJ *et al.* Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. JAMA 2020; 324:1048-1057.
4. Liverpool COVID 19 Drug Interactions Group. Evaluating the drug-drug interaction risk of COVID-19 therapies. Liverpool (UK): University of Liverpool; [Updated 2021 June 18; cited 2022 Jan 24]. Available from: https://www.covid19-druginteractions.org/
5. Luke D, Wood N, Tomaszewski, Damle B. Pharmacokinetics of sulfobutylether-β-cyclodextrin (SBECD) in subjects on hemodialysis. Nephrol Dial Transplant. 2012 Mar;27(3):1207-12
6. Butt, B.; Hussain, T.; Jarrar, M.; Khalid, K.; Albaker,W.; Ambreen, A.;Waheed, Y. Efficacy and Safety of Remdesivir in COVID-19 Positive Dialysis Patients. Antibiotics 2022, 11, 156. https://doi.org/10.3390/antibiotics11020156
7. Pettit NN, Pisano J, Nguyen CT, Lew AK, Hazra A, Sherer R, Mullane KM. Remdesivir Use in the Setting of Severe Renal Impairment: A Theoretical Concern or Real Risk? Clin Infect Dis. 2021 Dec 6;73(11):e3990-e3995..
8. Ackley TW, McManus D, Topal JE, Cicali B, Shah S. 2021. A valid warning or clinical lore: an evaluation of safety outcomes of remdesivir in patients with impaired renal function from a multicenter matched cohort. Antimicrob Agents Chemother 65:e02290-20.https://doi.org/10.1128/AAC.02290-20.
9. Choe PG, Jeong SI, Kang CK, Yang L, Lee S, Cho JY, Han SS, Kim DK, Lee SM, Park WB, Oh MD, Kim NJ. Exploration for the effect of renal function and renal replacement therapy on pharmacokinetics of remdesivir and GS-441524 in patients with COVID-19: A limited case series. Clin Transl Sci. 2022 Mar;15(3):732-740.
10. NSW Therapeutic Advisory Group. Use of remdesivir for COVID-19 in hospitalised patients, drug guideline version 1.6 [internet] NSW: NSW Health; 2021 [updated 2021 Sep 30; cited 2022 Jan 10]. Available from: 3.-GUIDELINE-for-use-of-REMDESIVIR-in-COVID-19_V1.6_30Sep21-Copy_.pdf (nswtag.org.au)
11. Society of Hospital Pharmacists of Australia. Australian Injectable Drugs Handbook [Online]. In: 8th ed. Collingwood: Society of Hospital Pharmacists of Australia; 2021: https://aidh.hcn.com.au/browse/r/remdesivir. Accessed 2022 January 10.
12. Gilead Sciences Pty Ltd. Remdesivir. Quality and safe use of medicine factsheet. Melbourne: Gilead Sciences; 31/07/2020.

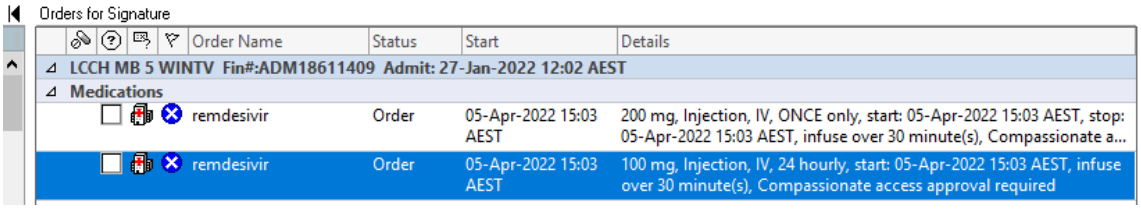
Appendix 1 – Prescribing in ieMR® and the National Inpatient Medication Chart (non-ieMR®)

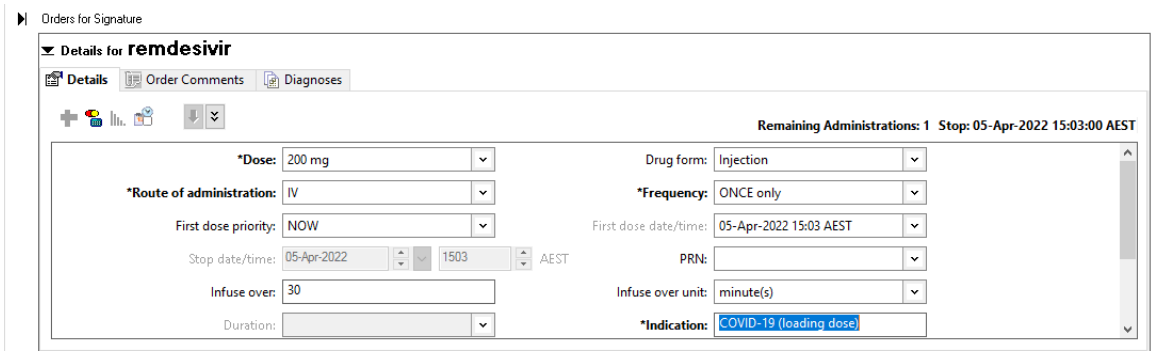
Ordering in the ieMR®

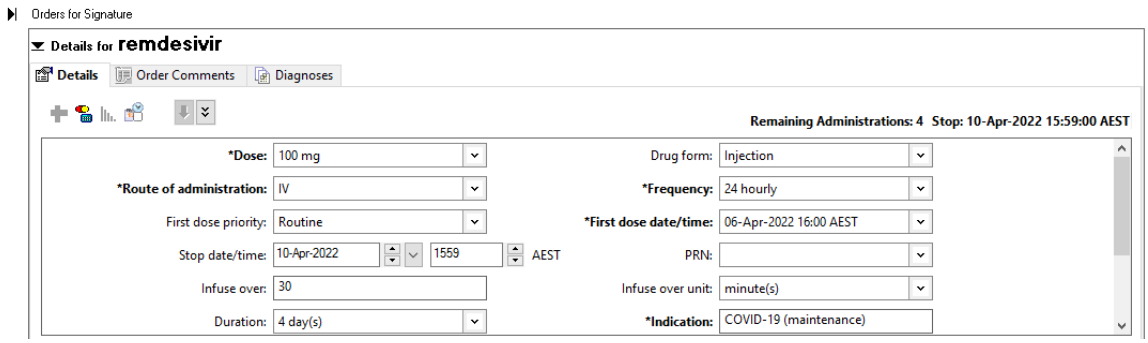
To prescribe remdesivir select “Add order” and search for drug name “remdesivir”.

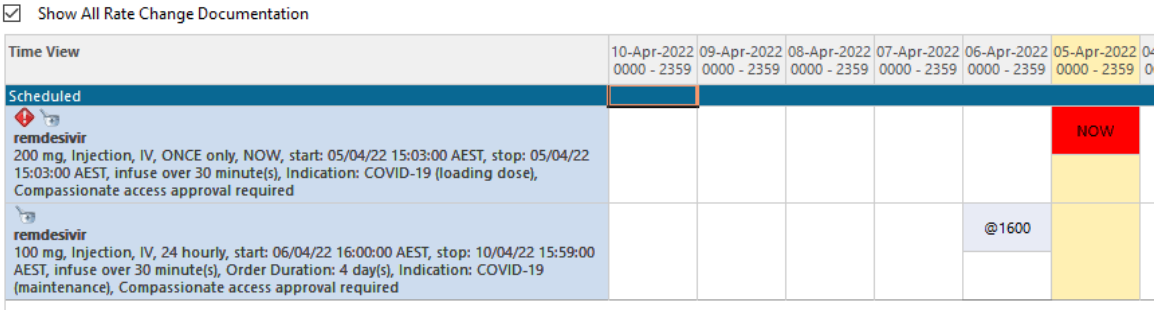
- For adults: Choose the appropriate order set – “stat order” Loading Dose followed by Maintenance Doses (Day 2 and 3 or 2-5) and complete prescription.
- For children: Select appropriate weight-based order set and complete prescription











Show All Rate Change Documentation

Time View	10-Apr-2022 0000 - 2359	09-Apr-2022 0000 - 2359	08-Apr-2022 0000 - 2359	07-Apr-2022 0000 - 2359	06-Apr-2022 0000 - 2359	05-Apr-2022 0000 - 2359	04 0
Scheduled							
remdesivir 200 mg, Injection, IV, ONCE only, NOW, start: 05/04/22 15:03:00 AEST, stop: 05/04/22 15:03:00 AEST, infuse over 30 minute(s), Indication: COVID-19 (loading dose), Compassionate access approval required						NOW	
remdesivir 100 mg, Injection, IV, 24 hourly, start: 06/04/22 16:00:00 AEST, stop: 10/04/22 15:59:00 AEST, infuse over 30 minute(s), Order Duration: 4 day(s), Indication: COVID-19 (maintenance), Compassionate access approval required					@1600		

National Inpatient Medication Chart (non ieMR®) ordering

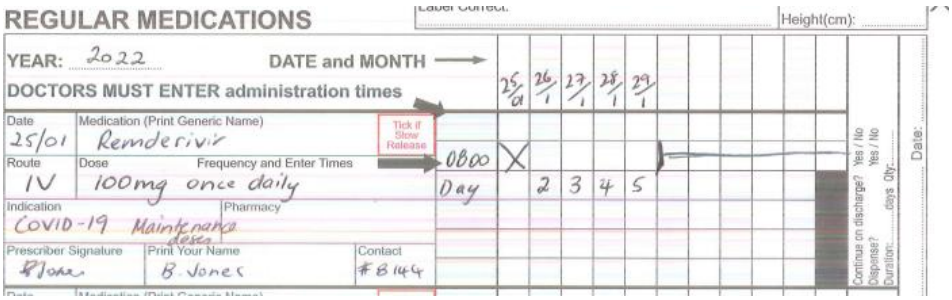
Remdesivir should be prescribed on the National Inpatient Medication Chart.

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.

Year: 2022 Ward / Unit: 3D-Resp ☐ Palliative Care ☐ Chemotherapy ☐ IV Heparin ☐ Other

ONCE ONLY, PRE-MEDICATION, TELEPHONE ORDERS AND NURSE INITIATED MEDICINES
(Telephone orders MUST be signed within 24 hours of order)

Date Prescribed	Medication (Print Generic Name)	Route	Dose	Date / Time of dose	Prescriber / Nurse Initiator (NI) Signature	Prescriber / Nurse Initiator (NI) Print Your Name	Given by	Time Given	Pharmacy
25/01	Remdesivir Loading Dose	IV	200mg	25/01 08:00	BJones	B. Jones			



REGULAR MEDICATIONS Height(cm):

YEAR: 2022 DATE and MONTH → 25/01 26/1 27/1 28/1 29/1

DOCTORS MUST ENTER administration times

Date 25/01 | Medication (Print Generic Name) Remdesivir | Tick if Slow Release

Route IV | Dose 100mg | Frequency and Enter Times once daily → 0800 Day | X | 2 3 4 5

Indication COVID-19 Maintenance dose | Pharmacy

Prescriber Signature BJones | Print Your Name B. Jones | Contact #8144

Continue on discharge? Yes / No | Dispense? Yes / No | Duration: ..... days Qty: ..... | Date: .....

Version	Amendments	Author/s	Approved for Publication
1.0	New document	Ashlea McCarron Panteha Voussoughi Dr Andrew Henderson	Approved by: Prof. Keith McNeil, Chief Medical Officer, Queensland Health 27/10/22
1.1	Minor update - Name change from NCCET to NCET - Update NCET link	Panteha Voussoughi	CTWG Chair 28/11/22