Remdesivir
For neonates in New South Wales

2021

Alert	If treatment with remdesivir is considered— it should be in consultation with ANZPID COVID-19 Clinical Reference Group. For New South Wales, please contact Philip.Britton@health.nsw.gov.au or Brendan.mcmullan@health.nsw.gov.au about accessing remdesivir for use in children. New South Wales Therapeutic Advisory Group (TAG) has developed patient information and consent forms and can be accessed at https://www.nswtag.org.au/resources-for-experimental-medicines-for-the-treatment-of-covid-19/ Consult the local Drug and Therapeutic Committee and/or pharmacy department for the relevant pathway for remdesivir approval via IPU (Individual Patient Use)
Indication	Acute COVID-19 disease
Action	Prodrug of an adenosine nucleotide analogue. Remdesivir has a broad-spectrum antiviral activity against SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV).(1, 2)
Drug type	Antiviral
Trade name	Veklury (Gilead Sciences)
Presentation	Veklury 100mg powder for injection. **Use only powder formulation for paediatric patients**.
Dose	**Neonates 3.5 kg and over***(3, 4) Loading dose: 5 mg/kg once on day 1, followed by Maintenance: 2.5 mg/kg once daily for day 2 to day 5 (5-8) **Neonates <3.5 kg***(6, 7, 9, 10) To discuss with ANZPID COVID-19 Clinical Reference Group. *See the alert section for access to remdesivir in hospitals in New South Wales
Dose adjustment	**Therapeutic hypothermia** - No information. **ECMO** - No information. **Hepatic impairment** – See precautions section. **Renal impairment** – See precautions section.
Maximum dose	No information.
Total cumulative dose	No information.
Route	IV
Preparation	**Veklury® powder for injection** **(ONLY Powder formulation is suitable for paediatric use; DO NOT USE concentrate solution formulation)** **Reconstitute**: Veklury® powder by addition of 19 mL of sterile water for injection. Immediately shake the vial for 30 seconds. 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. The concentration of the reconstituted solution is 100mg in 20mL (5mg/mL). The reconstituted solution should be diluted *immediately* as below. (11) **Further dilute:** Draw up 20mL of reconstituted solution and add to 30 mL of sodium chloride 0.9% to make a final concentration of 2 mg/mL in 50mL. (ANMF Consensus)
Administration	Infuse the required dose over 60 minutes (30 – 120 minutes)(11)
Monitoring	Regular monitoring for anaemia, renal and hepatic functions.
Contraindications	Known hypersensitivity to any ingredient of remdesivir product or remdesivir metabolites.
Precautions	• Renal impairment – Remdesivir is not recommended for patients aged > 28 days with an eGFR < 30 mL/min or term neonates (7 to 28 days of life) with a serum creatinine ≥ 1 mg/dL, unless the benefit outweighs the risk of harm.(5) • Hepatic impairment with elevated liver enzymes. Remdesivir should not be administered to patients with ALT ≥ 5 times the upper limit of normal OR to patients with ALT elevations associated with elevated conjugated bilirubin, alkaline phosphatase, or international normalized ratio.(5) • Multi-organ failure
Drug interactions	Dexamethasone is reported to be a moderate inducer of CYP3A and P-gp. Induction is dose-dependent and occurs after multiple doses. However, dexamethasone is unlikely to have a clinically

	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.(11) There is a potential for remdesivir to interact with medicines that are substrates of CYP3A or OATP 1B1/1B3. Discuss with Infectious Diseases consultant and pharmacist for up to date information.
Adverse reactions	Anaemia. Impaired renal function. Elevated liver enzymes.
Compatibility	ONLY COMPATIBLE WITH SODIUM CHLORIDE 0.9%. Must not be mixed with other medicinal products.
Incompatibility	Must not be mixed with other medicines.
Stability	Reconstituted solution should be diluted immediately and administered as soon as possible. Discard the unused potion.
Storage	Veklury® powder for injection – store below 30°C.
Excipients	Sulfobutyl betadex sodium, hydrochloric acid, sodium hydroxide.
Special comments	
Evidence	**Efficacy** The COVID-19 evidence is rapidly emerging and it is advised to consult ANZPID COVID-19 Clinical Reference Group or the local paediatric infectious diseases specialist for up to date information on antiviral therapy for children. As of 2nd August 2021, no randomised trials have been published on the efficacy and safety of remdesivir in neonates and children with confirmed COVID-19. Children receiving remdesivir have been included in several paediatric case series. **Children:** A recent case series reported on the outcomes of 77 children and adolescents <18 years of age with confirmed severe COVID19 disease and received remdesivir. The intended remdesivir treatment course was 10 days (200 mg on day 1 and 100 mg daily subsequently for children ≥40 kg and 5 mg/kg on day 1 and 2.5 mg/kg daily subsequently for children <40 kg, given intravenously). Median age was 14 years (interquartile range 7–16, range, 2 months to 17 years). Seventy-nine percent of patients had ≥1 comorbid condition. At baseline, 90% of children required supplemental oxygen and 51% required invasive ventilation. By day 28 of follow-up, 88% of patients had a decreased oxygen-support requirement, 83% recovered, and 73% were discharged. Among children requiring invasive ventilation at baseline, 90% were extubated, 80% recovered, and 67% were discharged. There were 4 deaths, of which 3 were attributed to COVID-19. Remdesivir was well tolerated, with a low incidence of serious adverse events (16%). Most adverse events were related to COVID-19 or comorbid conditions. Laboratory abnormalities, including elevations in transaminase levels, were common.(3, 4) **Neonates:** Use of remdesivir in neonates with COVID19 is limited to case reports. [LOE V, GOR D]. A case report described use of remdesivir (RDV) on 3 preterm neonates with positive SARS-Cov-2-RNA.(9, 10) Parents of all three neonates were positive for SARS-CoV-2 RNA - all adults had mild symptoms and were isolating at home. Case 1 was born at 31/40 weeks, presented at 6 weeks of age and the weight at presentation was 2.5 kg. Case 2 was born at 33/40 weeks and presented at 2.5 weeks of age with a weight of 1.9 kg. Case 3 was born at 33/40 weeks and presented at 5 weeks of age at a weight of 2.8 kg. All of them needed oxygen and ventilator support. All three had a negative screen for other common respiratory viruses and also had negative blood cultures. C-reactive protein (CRP), lactate dehydrogenase, ferritin, d-dimer and NT pro-BNP were elevated in all babies. Remdesivir was given at a dose of 2.5mg/kg on day 1 and 1.25mg/kg between days 2 to 5. There were no significant side effects noted in the cohort except for case 2 who showed a 3- fold elevation of aspartate transaminase, AST (highest 162 IU/L) that came back to normal after completion of five days of RDV therapy. All three patients were discharged home successfully and have remained well. In another case report, an ex-preterm neonate with severe COVID-19 pneumonia was treated with a 10 day course of remdesivir (5 mg/kg loading dose followed by 2.5 mg/kg daily) at 5 weeks postnatal age. (6) A term neonate was given remdesivir at a loading dose of 5 mg/kg followed by 2.5 mg/kg daily for a total of 7 doses. It was well tolerated with stable creatinine and liver function tests.(7)

	5-day versus 10-day course: An RCT in adult patients with severe Covid-19 not requiring mechanical ventilation, did not show a significant difference between a 5-day course and a 10-day course of remdesivir.(8) **Safety** In ACTT-1 study in adults, the most common adverse events (AEs) reported in remdesivir recipients were decreased haemoglobin (7.9% vs 9.0% of placebo recipients); decreased eGFR or creatinine clearance, or increased blood creatinine (7.4% vs 7.3%); pyrexia (5.0% vs 3.3%); hyperglycaemia (4.1% vs 3.3%); and increased ALT and/or aspartate aminotransferase (AST) [4.1% vs 5.9%]. (12) Serious respiratory failure occurred in 5% of remdesivir recipients and 8% of placebo recipients. No deaths were judged to be related to treatment. In SIMPLE-severe study in adults, AEs led to treatment discontinuation in 4% and 10% of patients in the 5-day and 10-day remdesivir groups, respectively. In adults, remdesivir is currently not recommended in patients with an estimated glomerular filtration rate (eGFR) < 30 mL/min or in patients with alanine aminotransferase (ALT) $\geq$ 5 times the upper limit of normal. (2) **Pharmacokinetics** The half-lives of remdesivir and its metabolite GS-441524 are 1 hr and 27 hours respectively in adults. Half-life in neonates is unclear.(2). It is mainly excreted renally.
Practice points	**Overview** Children are at similar risk of infection as the general population, although they are less likely to have severe symptoms.(13) In general, paediatric patients with COVID-19 have had a good prognosis and have recovered within 1 to 2 weeks after disease onset.(13) Children do not seem to be at higher risk of severe illness based on age and sex. However, at present, no data are available on the role of comorbidities in the severity of paediatric COVID-19.(13) **Australian National COVID-19 Clinical Evidence Task Force** (14) There is a conditional recommendation against the use of remdesivir in children and adolescents. It is unclear whether remdesivir influences mortality outcomes in patients who are hospitalised with COVID-19 and not requiring oxygen. The recommended regimen in adults is daily intravenous infusion (200 mg initial dose, 100 mg maintenance), and the optimal duration of remdesivir treatment is unclear, however current evidence does not suggest a clear benefit of 10 days over 5 days.(8) **USA Paediatric Infectious Diseases Society – 2020 Interim guidance on antivirals for children With COVID-19** (5) • Given the typically mild course of COVID-19 in children, supportive care alone is suggested for most cases. • For children with severe illness, defined as a supplemental oxygen requirement without need for non-invasive or invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO), remdesivir is suggested, preferably as part of a clinical trial, if available. • A duration of 5 days is appropriate for most patients. • The panel recommends against the use of hydroxychloroquine or lopinavir-ritonavir (or other protease inhibitors) for COVID-19 in children. • Paediatric dosing 3.5 to 40 kg: 5 mg/kg IV loading dose on day 1, followed by 2.5 mg/kg IV every 24 hours of lyophilized powder only. • Treatment duration: Severe disease: up to 5 days Critical disease: 5–10 days • Contraindications: o Hepatic impairment: Remdesivir should not be administered to patients with ALT ≥ 5 times the upper limit of normal OR to patients with ALT elevations associated with elevated conjugated bilirubin, alkaline phosphatase, or international normalized ratio. o Renal insufficiency: Remdesivir is not recommended for patients aged > 28 days with an eGFR < 30 mL/min or term neonates (7 to 28 days of life) with a serum creatinine ≥ 1 mg/dL, unless the benefit outweighs the risk; no dose adjustments have been performed for patients with eGFR > 30 mL/min

	• Use in Multisystem Inflammatory Syndrome in Children (MIS-C) o Remdesivir is not routinely indicated for patients with MIS-C. o Therapy could be considered on a case-by-case basis in the setting of positive SARS-CoV-2 viral testing if there is diagnostic uncertainty as to whether presenting symptoms are consistent with acute COVID-19 infection vs MIS-C or in the presence of extreme illness.
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