

Remdesivir

Remdesivir Injection 100 mg/20 mL

रिंमिडीविर

For use in hospital/institutional set up only

PRESCRIBING INFORMATION

1. GENERIC NAME

Remdesivir Injection 100 mg/20 mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Remdesivir Injection
Each Vial contains

3. DOSAGE FORM AND STRENGTH

Remdesivir Injection 100 mg/20 mL

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Remdesivir is indicated for treatment of patients hospitalized with suspected or laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and severe disease. Severe disease is defined as patients with oxygen saturation (SpO₂) \leq 94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO). Specifically, Remdesivir is only authorized for hospitalized adult and pediatric patients for whom use of an IV agent is clinically appropriate.

4.2 Posology and Method of Administration

Important Testing Prior to and During Treatment and Route of Administration

- Adult and pediatric patients (\geq 28 days old) must have an estimated glomerular filtration rate (eGFR) determined, and full-term neonates (at least 7 days to \leq 28 days old) must have serum creatinine determined before dosing of remdesivir and daily while receiving remdesivir.
- Hepatic laboratory testing should be performed in all patients prior to starting remdesivir and daily while receiving remdesivir.
- Remdesivir should be administered via IV (intravenous) infusion only. Do not administer as an intramuscular (IM) injection.

Adult Patients

- The recommended dosage in adults is a single loading dose of remdesivir 200 mg on Day 1 followed by once-daily maintenance doses of remdesivir 100 mg from Day 2 via IV infused over 30-120 minutes once daily for 4 days. Extension of administration of drug beyond 5 days to 10 days is not recommended.
- Administer remdesivir via IV infusion in a total volume of up to 250 mL 0.9% sodium chloride over 30 to 120 minutes. Extension of administration of drug beyond 5 days to 10 days is not recommended.

Pediatric Patients

For pediatric patients weighing 3.5 kg to less than 40 kg, the dose should be calculated using the mg/kg dose according to the patient's weight. Refer to Table 1 below for recommended dosage form and dosage in pediatric patients according to weight.

Table 1: Recommended Dosage Form and Dosage in Pediatric Patients

Body weight	Recommended dosage form	Loading dose (on Day 1)	Maintenance dose (from Day 2)
3.5 kg to less than 40 kg	Remdesivir for Injection	5 mg/kg	2.5 mg/kg
40 kg and higher	Remdesivir for Injection	200 mg	100 mg

Remdesivir IV should be infused over 30 to 120 minutes once daily. Extension of administration of drug beyond 5 days to 10 days is not recommended.

Remdesivir is not recommended in adult and paediatric patients ($>$ 28 days old) with eGFR less than 30 mL/min or in full-term neonates (\geq 7 days to \leq 28 days old) with serum creatinine greater than or equal to 1 mg/dL unless the potential benefit outweighs the potential risk.

Use in Special Populations

Pregnant Women

Remdesivir should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus.

Patients with Renal Impairment

Adult and pediatric patients (greater than 28 days old) must have an eGFR determined and full-term neonates (at least 7 days to less than or equal to 28 days old) must have serum creatinine determined before dosing and daily while receiving remdesivir.

Adults

- eGFR, Male: (140 – age in years) \times (weight in kg) / 72 \times (serum creatinine in mg/dL)
- eGFR, Female: (140 – age in years) \times (weight in kg) \times 0.85 / 72 \times (serum creatinine in mg/dL)

Pediatric patients (greater than 28 days old to less than 1 year of age)

- eGFR: 0.45 \times (height in cm) / serum creatinine in mg/dL

Pediatric patients (at least 1 year of age to less than 18 years of age)

- eGFR = 0.413 \times (height or length)/Scr if height/length is expressed in centimeters OR

41.3 \times (height or length)/Scr if height/length is expressed in meters

Because the excipient sulfobutylether- β -cyclodextrin sodium salt (SBECD) is renally cleared and accumulates in patients with decreased renal function, administration of drugs formulated with SBECD (such as remdesivir) is not recommended in adults and pediatric patients ($>$ 28 days old) with eGFR $<$ 30 mL per minute or in full-term neonates (\geq 7 days and \leq 28 days old) with serum creatinine \geq 1 mg/dL unless the potential benefit outweighs the potential risk.

Use of Remdesivir in patients with renal impairment is based on potential risk and potential benefit considerations. Patients with eGFR greater than or equal to 30 mL/min are reported to have received remdesivir for treatment of COVID-19 with no dose adjustment of remdesivir. All patients must have an eGFR determined before dosing. Remdesivir is not recommended in adult and paediatric patients ($>$ 28 days old) with eGFR less than 30 mL/min or in full-term neonates (\geq 7 days to \leq 28 days old) with serum creatinine greater than or equal to 1 mg/dL unless the potential benefit outweighs the potential risk.

Patients with Hepatic Impairment

It is not known if dosage adjustment is needed in patients with hepatic impairment and remdesivir should only be used in patients with hepatic impairment if the potential benefit outweighs the potential risk.

Hepatic laboratory testing should be performed in all patients prior to starting remdesivir and daily while receiving remdesivir.

Use of Remdesivir in patient with hepatic impairment: It is not known if dosage adjustment is needed in patients with hepatic impairment and remdesivir should only be used in patients with hepatic impairment if the potential benefit outweighs the potential risk. Hepatic laboratory testing should be performed in all patients prior to starting remdesivir and daily while receiving remdesivir.

Dose Preparation and Administration (Adults and Pediatric Patients Weighing \geq 40 kg) Remdesivir for Injection, 100 mg/20 mL (5 mg/ml)

Dilution Instructions

Care should be taken during admixture to prevent inadvertent microbial contamination. As there is no preservative or bacteriostatic agent present in this product, aseptic technique must be used in preparation of the final parenteral solution. It is always recommended to administer IV medication immediately after preparation when possible.

- Withdraw the required volume of 100 mg/20 mL (5 mg/mL), should be further diluted in 100 mL or 250 mL 0.9% sodium chloride infusion bags.
- Using Table 2, determine the volume of 0.9% saline to withdraw from the infusion bag.

Table 2: Recommended Dilution Instructions—Remdesivir for Injection in Adults and Pediatric Patients Weighing \geq 40 kg

Remdesivir dose	0.9% saline infusion bag volume to be used	Volume of sodium chloride to be withdrawn and discarded from 0.9% sodium chloride infusion bag	Required volume of reconstituted remdesivir for injection
200 mg (two vials)	250 mL	40 mL	40 mL (2 \times 20 mL)
	100 mL	40 mL	40 mL (2 \times 20 mL)
100 mg (one vial)	250 mL	20 mL	20 mL
	100 mL	20 mL	20 mL

- Withdraw the required volume of saline from the vial as per table 2 using an appropriately sized syringe and needle.
- Withdraw the required volume of reconstituted remdesivir for injection from the remdesivir vial using an appropriately sized syringe per Table 1. Discard any unused portion remaining in the remdesivir vial.
- Transfer the required volume of reconstituted remdesivir for injection to the selected infusion bag.
- Gently invert the bag 20 times to mix the solution in the bag. Do not shake.
- The prepared diluted solution is stable for 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 24 hours in the refrigerator at 2°C to 8°C (36°F to 46°F).

Administration Instructions

The prepared diluted solution should not be administered simultaneously with any other IV medication. The compatibility of remdesivir injection IV solutions and medications other than 0.9% sodium chloride is not known.

Administer the diluted remdesivir for injection as per the infusion rate described in Table 3.

Table 3: Recommended Rate of Infusion—Diluted Remdesivir for Injection in Adults and Pediatric Patients Weighing \geq 40 kg

Infusion bag volume	Infusion time	Rate of infusion
250 mL	30 minutes	8.33 mL/min
	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

Pediatric Dose Preparation and Administration

Remdesivir for Injection, 100 mg/20 mL (5 mg/ml)

For pediatric patients weighing 3.5 kg to $<$ 40 kg, use remdesivir for injection, 100 mg/20 mL (5 mg/ml), only.

Dilution Instructions

Care should be taken during admixture to prevent inadvertent microbial contamination. As there is no preservative or bacteriostatic agent present in this product, aseptic technique must be used in preparation of the final parenteral solution. It is always recommended to administer IV medication immediately after preparation when possible.

- For pediatric patients weighing 3.5 kg to less than 40 kg, the 100 mg/20 mL (5 mg/mL) remdesivir concentrate should be further diluted 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 pediatric 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 pediatric 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 less than 50 mL.

INFUSION WITH IV BAG

- Prepare an IV bag of 0.9% sodium chloride with volume equal to the total infusion volume minus the volume of reconstituted remdesivir solution that will be diluted to achieve a 1.25 mg/mL solution.
- Withdraw the required volume of reconstituted solution containing remdesivir for injection into an appropriately sized syringe.
- Transfer the required volume of reconstituted remdesivir for injection to the 0.9% sodium chloride infusion bag.
- Gently invert the bag 20 times to mix the solution in the bag. Do not shake.

INFUSION WITH SYRINGE

- Select an appropriately sized syringe equal to or larger than the calculated total infusion volume of 1.25 mg/mL remdesivir solution needed.
- Withdraw the required volume of 100 mg/20 mL (5 mg/mL) remdesivir solution from the vial into the syringe followed by the required volume of 0.9% sodium chloride needed to achieve a 1.25 mg/mL remdesivir solution.
- Mix the syringe by inversion 20 times.
- The prepared diluted solution is stable for 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 24 hours in the refrigerator at 2°C to 8°C (36°F to 46°F) (including any time before dilution into intravenous infusions).

ADMINISTRATION INSTRUCTIONS

The prepared diluted solution should not be administered simultaneously with any other medication. The compatibility of remdesivir injection IV solutions and medications other than 0.9% sodium chloride is not known.

Administer the diluted solution as per the infusion rate described in Table 4.

Table 4: Recommended Rate of Infusion—Diluted Remdesivir for Injection in Pediatric Patients Weighing 3.5 kg to $<$ 40 kg

Infusion bag volume	Infusion time	Rate of infusion ^a
100 mL	30 minutes	3.33 mL/min
	60 minutes	1.67 mL/min
	120 minutes	0.83 mL/min
50 mL	30 minutes	1.67 mL/min
	60 minutes	0.83 mL/min
	120 minutes	0.42 mL/min
25 mL	30 minutes	0.83 mL/min
	60 minutes	0.42 mL/min
	120 minutes	0.21 mL/min

^aNote: Rate of infusion may be adjusted based on total volume to be infused.

Storage of Prepared Dosages

Diluted Infusion Solutions

Store diluted remdesivir infusion solutions up to 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

IMPORTANT:

This product contains no preservative. Any unused portion of a single-dose remdesivir vial should be discarded after a diluted solution is prepared. Maintain adequate records showing receipt, use, and disposition of remdesivir. For unused intact vials, maintain adequate records showing disposition of remdesivir; do not discard unused intact vials.

4.3 Contraindications

Remdesivir is contraindicated in patients with known hypersensitivity to any ingredient of remdesivir for injection and remdesivir injection solution.

4.4 Special Warnings and Precautions for Use

There are limited clinical data available for remdesivir. Serious and unexpected adverse events may occur that have not been previously reported with remdesivir use.

Hypersensitivity Including Infusion-Related and Anaphylactic Reactions

Hypersensitivity reactions including infusion-related and anaphylactic reactions have been observed during and following administration of remdesivir. Signs and symptoms may include hypotension, tachycardia, bradycardia, dyspnea, wheezing, angioedema, rash, nausea, vomiting, diarrhoea, and shivering. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. If signs and symptoms of a clinically significant infusion reaction occur, immediately discontinue administration of remdesivir and initiate appropriate treatment. The use of remdesivir is contraindicated in patients with known hypersensitivity to remdesivir.

Increased Risk of Transaminase Elevations

Transaminase elevations have been observed in healthy volunteers who received 200 mg of remdesivir followed by 100 mg doses for 5-10 days. Transaminase elevations have also been reported in patients with COVID-19 who received remdesivir in clinical trials. As transaminase elevations have been reported as a component of COVID-19, including in patients receiving placebo in clinical trials of remdesivir, discerning the contribution of remdesivir to transaminase elevations in this patient population is challenging.

Hepatic laboratory testing should be performed in all patients prior to starting remdesivir and daily while receiving remdesivir.

- Remdesivir should not be initiated in patients with ALT \geq 5 times the upper limit of normal at baseline.
- Remdesivir should be discontinued in patients who develop:

- ALT \geq 5 times the upper limit of normal during treatment with remdesivir. Remdesivir may be restarted when ALT is $<$ 5 times the upper limit of normal.

- OR
- ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or International Normalized Ratio (INR).

Risk of Reduced Antiviral Activity When Coadministered with Chloroquine or Hydroxychloroquine

Coadministration of remdesivir and chloroquine phosphate or hydroxychloroquine sulfate is not recommended based on *in vitro* data demonstrating an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of remdesivir.

Patient Monitoring Recommendations

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 while receiving remdesivir.

4.5 Drug Interactions

Drug-drug interaction trials of remdesivir and other concomitant medications have not been conducted in humans. Due to antagonism observed *in vitro*, remdesivir use of remdesivir with chloroquine phosphate or hydroxychloroquine sulfate is not recommended.

In vitro, remdesivir is a substrate for drug-metabolizing enzymes, CYP2C8, CYP2D6, and CYP3A4, and is a substrate for organic anion transporting polypeptides 1B1 (OATP1B1) and P-glycoprotein (P-gp) transporters. *In vitro*, remdesivir is an inhibitor of CYP3A4, OATP1B1, OATP1B3, BSEP, MRP4, and NTCIP. The clinical relevance of these *in vitro* assessments has not been established.

4.6 Use in Special Populations

Pregnant Women

Risk Summary

Remdesivir should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the fetus.

In nonclinical reproductive toxicity studies, remdesivir demonstrated no adverse effect on embryo-fetal development when administered to pregnant animals at systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) that were 4 times (rats and rabbits) the exposure in humans at the recommended human dose (RHD).

Lactating Women

Risk Summary

There is no information regarding the presence of remdesivir in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies, remdesivir and metabolites have been detected in the nursing pups of mothers given remdesivir, likely due to the presence of remdesivir in milk. Because of the potential for viral transmission to SARS-CoV-2-negative infants and adverse reactions from the mother in breastfeeding infants, the developmental and health benefits of breast-feeding should be considered along with the drug's clinical need for remdesivir and any potential adverse effects on the breastfed child from remdesivir or from the underlying maternal condition.

Pediatric Patients

Safety and effectiveness of remdesivir for the treatment of COVID-19 have not been assessed in pediatric patients. Physiologically-based pharmacokinetics (PBPK) modeling of pharmacokinetic data from healthy adults was used to derive pediatric doses. Pediatric doses are expected to result in comparable steady-state exposures of remdesivir and metabolites as observed in healthy adults following administration of the recommended dosage regimen.

For pediatric patients weighing 3.5 kg to $<$ 40 kg, use remdesivir for injection, 100 mg/20 mL (5 mg/ml) only.

Pediatric patients ($>$ 28 days) must have eGFR determined and full-term neonates (\geq 7 days to \leq 28 days) must have serum creatinine determined before dosing and daily while receiving remdesivir. Pediatric patients should be monitored for renal function and considered for stopping therapy in the setting of substantial decline.

Because the excipient sulfobutylether- β -cyclodextrin sodium salt (SBECD) is renally cleared and accumulates in patients with decreased renal function, administration of drugs formulated with SBECD (such as remdesivir) is not recommended in adults and pediatric patients ($>$ 28 days old) with eGFR less than 30 mL per minute or in full-term neonates (\geq 7 days and \leq 28 days old) with serum creatinine \geq 1 mg/dL unless the potential benefit outweighs the potential risk.

Geriatric Patients

The pharmacokinetics of remdesivir have not been evaluated in patients $>$ 65 years of age. In general, appropriate caution should be exercised in the administration of remdesivir and monitoring of elderly patients, reflecting the greater frequency of decreased hepatic, renal or cardiac function, and of concomitant disease or other drug therapy.

Remdesivir is not recommended in adult and paediatric patients ($>$ 28 days old) with eGFR less than 30 mL/min or in full-term neonates (\geq 7 days to \leq 28 days old) with serum creatinine greater than or equal to 1 mg/dL unless the potential benefit outweighs the potential risk.

Patients with Renal Impairment

Patients with eGFR greater than or equal to 30 mL/min have received remdesivir for treatment of COVID-19 with no dose adjustment. The safety and efficacy of remdesivir have not been assessed in patients with severe renal impairment or ESRD. The pharmacokinetics of remdesivir have not been evaluated in patients with renal impairment. Remdesivir is not recommended in adults and pediatric patients ($>$ 28 days old) with eGFR less than 30 mL per minute or in full-term neonates (\geq 7 days and \leq 28 days old) with serum creatinine clearance \geq 1 mg/dL unless the potential benefit outweighs the potential risk.

Adult and pediatric patients (greater than 28 days old) must have eGFR determined and full-term neonates (at least 7 days to less than or equal to 28 days old) must have serum creatinine determined before dosing and daily while receiving remdesivir.

Use in patients with renal impairment is based on potential risk and potential benefit considerations. Patients with eGFR greater than or equal to 30 mL/min are reported to have received remdesivir for treatment of COVID-19 with no dose adjustment of remdesivir. All patients must have an eGFR determined before dosing. Remdesivir is not recommended in adult and paediatric patients ($>$ 28 days old) with eGFR less than 30 mL/min or in full-term neonates (\geq 7 days to \leq 28 days old) with serum creatinine greater than or equal to 1 mg/dL unless the potential benefit outweighs the potential risk.

Patients with Hepatic Impairment

The pharmacokinetics of remdesivir has not been evaluated in patients with hepatic impairment. It is not known if dosage adjustment is needed in patients with hepatic impairment and remdesivir should only be used in patients with hepatic impairment if the potential benefit outweighs the potential risk.

Hepatic laboratory testing should be performed in all patients prior to starting remdesivir and daily while receiving remdesivir.

It is not known if dosage adjustment is needed in patients with hepatic impairment and remdesivir should only be used in patients with hepatic impairment if the potential benefit outweighs the potential risk. Hepatic laboratory testing should be performed in all patients prior to starting remdesivir and daily while receiving remdesivir.

4.7 Effects on Ability to Drive and Use Machines

No data is available on the effect of remdesivir on ability to drive and use machines.

4.8 Undesirable Effects

Overall Safety Summary

In healthy subjects and hospitalized patients with polymerase chain reaction (PCR)-confirmed SARS-CoV-2 infection, graded elevations in ALT and AST have been observed with a loading dose of remdesivir 200 mg administered by the IV route on day 1 followed by 100 mg administered by the IV route once daily for up to 9 days. The mechanism of these elevations is unknown.

Patients should have appropriate clinical and laboratory monitoring to aid in early detection of any potential adverse events. The decision to continue or discontinue remdesivir after development of an adverse event should be made based on the clinical risk/benefit assessment for the individual.

Clinical Trials Experience

Clinical Studies in Healthy Adults

Remdesivir was evaluated in four Phase 1 studies in 138 healthy adult volunteers (Studies GS-US-399-1812, GS-US-399-1954, GS-US-399-4231, and GS-US-399-5505). In these studies, transient graded elevations in ALT and AST were observed at repeated once-daily doses of remdesivir.

In a randomized, double-blind, placebo-controlled clinical trial (ACTT-1) of remdesivir in 1,063 hospitalized subjects with COVID-19 treated with remdesivir (n=541) or placebo (n=522) for 10 days, serious adverse events (SAEs) were reported in 21% and 27% of subjects, respectively, and Grade \geq 3 non-serious adverse events were reported in 29% and 33% of subjects, respectively. The most common SAE was respiratory failure reported in 5% of subjects treated with remdesivir and 8% of subjects treated with placebo. The most common Grade \geq 3 non-serious adverse events in the remdesivir treatment arm are shown in Table 5.

Table 5: Most Common Grade \geq 3 Non-Serious Adverse Events in Subjects Receiving Remdesivir—NIAID ACTT-1 Trial

n (%)	Remdesivir N=538	Placebo N=521
Anemia or decreased hemoglobin	43 (8%)	43 (8%)
Acute kidney injury, decreased eGFR or creatinine renal clearance, or increased blood creatinine	40 (7%)	40 (7%)
Pyrexia	27 (5%)	17 (3%)
Hyperglycemia or increased blood glucose	22 (4%)	17 (3%)
Increased transaminases, including ALT and/or AST	22 (4%)	31 (6%)

Study GS-US-540-5773

In a randomized, open-label clinical trial (Study GS-US-540-5773) of remdesivir in 397 subjects with severe COVID-19 treated with remdesivir for 5 (n=200) or 10 days (n=197), adverse events were reported in 70% and 74% of subjects, respectively, serious adverse events were reported in 21% and 35% of subjects, respectively, and Grade \geq 3 adverse events were reported in 31% and 43% of subjects, respectively. The most common adverse events were nausea (10% in the 5-day group vs 9% in the 10-day group), acute respiratory failure (6% vs 11%), ALT increase (6% vs 8%), and constipation (7% in both groups). Nine (4%) subjects in the 5-day group and 20 (10%) subjects in the 10-day group discontinued treatment due to an adverse event. All-cause mortality at Day 28 was 10% vs 13% in the 5- and 10-day treatment groups, respectively.

Hepatic Adverse Reactions

Clinical Trials Experience in Healthy Volunteers

Grade 1 and 2 transaminase elevations were observed in healthy volunteers in Study GS-US-399-5505 (200 mg followed by 100 mg dosing for 5-10 days) and Study GS-US-399-1954 (150 mg daily for 7 or 14 days), which resolved after discontinuation of remdesivir.

Experience in Patients With COVID-19

Grade \geq 3 hepatic laboratory abnormalities reported in Study GS-US-540-5773 of remdesivir in 397 subjects with severe COVID-19 treated with remdesivir for 5 (n=200) or 10 days (n=197) are shown in Table 6.

Table 6: Hepatic Laboratory Abnormalities—Study GS-US-540-5773

n (%)	Remdesivir for 5 days	Remdesivir for 10 days	Total	
ALT	Grade 3	8/194 (4)	11/191 (6)	19/385 (5)
	Grade 4	4/194 (2)	5/191 (3)	9/385 (2)
AST	Grade 3	11/194 (6)	7/190 (4)	18/384 (5)
	Grade 4	3/194 (2)	4/190 (2)	7/384 (2)
Total Bilirubin	Grade 3	1/193 (1)	3/190 (2)	4/383 (1)
	Grade 4			