Remdesivir for injection 100 mg/Vial

For use in hospital/ institutional set up only

PRESCRIBING INFORMATION

1. GENERIC NAME
Remdesivir for injection 100 mg/Vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Remdesivir for Injection (Lyophilized powder), 100 mg:
Each Vial contains
Remdesivir ……100 mg
Each single-dose vial of remdesivir for injection, 100 mg, contains a sterile, preservative-free white to off-white to yellow lyophilized powder that is to be reconstituted with 19 mL of Sterile Water for Injection and diluted into 0.9% sodium chloride prior to administration by intravenous (IV) infusion. Following reconstitution, each vial contains 5 mg/mL remdesivir re-concentrated solution with sufficient volume to allow withdrawal of 20 mL of 5 mg/mL solution containing 100 mg of remdesivir.

3. DOSAGE FORM AND STRENGTH
Remdesivir for injection (lyophilized powder), 100 mg

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications
Remdesivir is indicated for treatment of suspected or laboratory confirmed corona virus disease 2019 (COVID-19) in adults and children hospitalised with severe disease.

4.2 Posology and Method of Administration
Important Testing Prior to and During Treatment and Route of Administration
- Adult and pediatric patients (>28 days old) must have an estimated glomerular filtration rate (eGFR) determined, and full-term neonates (at least7 days to ≤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 Lyophilized Powder for Injection Only	5 mg/kg	2.5 mg/kg
40 kg and higher	Remdesivir Lyophilized Powder 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 (≥7 days to ≤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) × (weight in kg) / 72 × (serum creatinine in mg/dL);
- eGFR, Female: (140 – age in years) × (weight in kg) × 0.85 / 72 × (serum creatinine in mg/dL)

Pediatric patients (greater than 28 days old to less than 1 year of age)
- eGFR: 0.45 × (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 x (height or length)/Scr) if height/length is expressed in centimeters OR 41.3 x (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 (≥7 days and ≤28 days old) with serum creatinine clearance ≥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 (≥7 days to ≤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 ≥40 kg) Remdesivir for Injection (Lyophilized Powder), 100 mg

Reconstitution Instructions
Remove the required number of single-dose vial(s) from storage. For each vial:
- Aseptically reconstitute remdesivir for injection (lyophilized powder) by addition of 19 mL of Sterile Water for Injection using a suitably sized syringe and needle per vial.
- Discard the vial if a vacuum does not pull the Sterile Water for Injection into the vial.
- 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.
- Following reconstitution, each vial contains 100 mg/20 mL (5 mg/mL) of remdesivir solution.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
- After reconstitution, the total storage time before administration should not exceed 4 hours at room temperature or 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

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.
- The reconstituted remdesivir lyophilized powder for injection, containing 100 mg/20 mL remdesivir solution, 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 (Lyophilized Powder) in Adults and Pediatric Patients Weighing ≥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 × 20 mL)
	100 mL	40 mL	40 ml (2 × 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 bag 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 (lyophilized powder) infusion solution as per the infusion rate described in Table 3.

Table 3: Recommended Rate of Infusion—Diluted Remdesivir for Injection (Lyophilized Powder) in Adults and Pediatric Patients Weighing ≥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 (Lyophilized Powder), 100 mg

For pediatric patients weighing 3.5 kg to <40 kg, use remdesivir for injection (lyophilized powder), 100 mg, only.

Reconstitution Instructions
Remove the required number of single-dose vial(s) from storage. For each vial:
- Aseptically reconstitute remdesivir for injection (lyophilized powder) by addition of 19 mL of Sterile Water for Injection using a suitably sized syringe and needle per vial.
- Discard the vial if a vacuum does not pull the Sterile Water for Injection into the vial.
- 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.
- Following reconstitution, each vial contains 100 mg/20 mL (5 mg/mL) of remdesivir solution.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
- After reconstitution, the total storage time before administration should not exceed 4 hours at room temperature or 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

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.

Following reconstitution as instructed above, each vial will contain a 100 mg/20 mL (5 mg/mL) remdesivir concentrated solution. 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) reconstituted 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 infusion fluids).

ADMINISTRATION INSTRUCTIONS
The prepared diluted solution should not be administered simultaneously with any other medication. The compatibility of remdesivir injection with 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 (Lyophilized Powder) Infusion Solution 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

[a] Note: Rate of infusion may be adjusted based on total volume to be infused.

Storage of Prepared Dosages

Lyophilized Powder
After reconstitution, vials can be stored up to 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) prior to administration or 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]). Dilute within the same day as administration.

Diluted Infusion Solutions
Store diluted remdesivir (lyophilized powder and injection solution) 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, lyophilized powder, 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, diaphoresis, 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 ≥5 times the upper limit of normal at baseline.
- Remdesivir should be discontinued in patients who develop:
- ALT ≥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, concomitant 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 (OAPT1B1) and P-glycoprotein (P-gp) transporters. *In vitro*, remdesivir is an inhibitor of CYP3A4, OATP1B1, OATP1B3, BSEP, MRP4, and NTCP. 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 drug in breastfeeding infants, the developmental and health benefits of breastfeeding should be considered along with the mother'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, lyophilized powder only.

Pediatric patients (>28 days) must have eGFR determined and full-term neonates (≥7 days to ≤28 days) must have serum creatinine determined before dosing and daily while receiving remdesivir. Pediatric patients should be monitored for renal function and consideration given 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 (≥7 days and ≤28 days old) with serum creatinine clearance ≥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 (≥7 days to ≤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 (≥7 days and ≤28 days old) with serum creatinine clearance ≥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 (≥7 days to ≤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 ≥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 ≥3 non-serious adverse events in the remdesivir treatment arm are shown in Table 5.

Table 5: Most Common Grade ≥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 ≥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 increased (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 ≥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 8.

Table 8: Hepatic Laboratory Abnormalities—Study GS-US-540-5773

n/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	0	1/190 (1)	1/383 (<1)

Compassionate-Use Experience

Experience in Patients With COVID -19

In the compassionate-use program in patients with severe or critical illness with COVID- 19, liver function test abnormalities were reported in 11.7% (19/163) of patients. Time to onset from first dose ranged from 1 to 16 days. Of these patients, 4 discontinued remdesivir treatment with elevated transaminases occurring on day 5 of remdesivir treatment as per protocol.

Seven cases of serious liver-related laboratory abnormality were identified. There was one serious adverse event of blood bilirubin increased in a critically ill patient with septic shock and multi-organ failure. None of the other cases had reported adverse events suggestive of hyperbilirubinemia or symptoms of hepatitis.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/ to report a side effect. You can also report side effects directly via the National Pharmacovigilance Programme of India by calling on **1800 180 3024** or you can report to MSN Labs on **+918458305295**. By reporting side effects, you can help provide more information on the safety of this product.

4.9 Overdose

There is no human experience of acute overdosage with remdesivir. Treatment of overdose with remdesivir should consist of general supportive measures, including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with remdesivir.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Mechanism of Action

Remdesivir is an adenosine nucleotide prodrug that distributes into cells where it is metabolized to form the pharmacologically active nucleoside triphosphate metabolite. Metabolism of remdesivir to remdesivir triphosphate has been demonstrated in multiple cell types. Remdesivir triphosphate acts as an analog of adenosine triphosphate (ATP) and competes with the natural ATP substrate for incorporation into nascent RNA chains by the SARS-CoV-2 RNA-dependent RNA polymerase, which results in delayed chain termination during replication of the viral RNA. Remdesivir triphosphate is a weak inhibitor of mammalian DNA and RNA polymerases with low potential for mitochondrial toxicity.

Pharmacodynamic Properties

Microbiology/Resistance Information

Antiviral Activity

Remdesivir exhibited cell culture antiviral activity against a clinical isolate of SARS-CoV- 2 in primary human airway epithelial (HAE) cells with a 50% effective concentration (EC_{50}) of 9.9 nM after 48 hours of treatment. The EC_{50} values of Remdesivir against SARS-CoV- 2 *in Vero* cells was 137 nM at 24 hours and 750 nM at 48 hours post-treatment. The antiviral activity of remdesivir was antagonized by chloroquine phosphate in a dose-dependent manner when the two drugs were co-incubated at clinically relevant concentrations in Hep 2 cells infected with respiratory syncytial virus (RSV). Higher remdesivir EC50 values were observed with increasing concentrations of chloroquine phosphate. Increasing concentrations of chloroquine phosphate reduced formation of remdesivir triphosphate in normal human bronchial epithelial cells.

Resistance

No clinical data are available on the development of SARS-CoV-2 resistance to remdesivir. The cell culture development of SARS-CoV-2 resistance to remdesivir has not been assessed to date.

Cell culture resistance profiling of remdesivir using the rodent CoV murine hepatitis virus identified two substitutions (F476L and V553L) in the viral RNA-dependent RNA polymerase at residues conserved across CoVs that conferred a 5.6-fold reduced susceptibility to remdesivir. The mutant viruses showed reduced viral fitness in cell culture and introduction of the corresponding substitutions (F480L and V557L) into SARS-CoV resulted in 6-fold reduced susceptibility to remdesivir in cell culture and attenuated SARS- CoV pathogenesis in a mouse model.

Clinical Trial Results

Remdesivir is an unapproved antiviral drug with available data from two randomized clinical trials and a compassionate-use program in patients with COVID-19

Compassionate-Use Program In Patients With COVID -19

Remdesivir has been provided through a compassionate–use, multicenter, open-label program to over 1,200 adult patients with PCR-confirmed SARS-CoV-2 infection and manifestations of severe disease. In addition, remdesivir has been provided to 76 pediatric patients <18 years of age and 96 pregnant women through the compassionate- use program.

Patients were treated with remdesivir 200 mg once daily followed by remdesivir 100 mg for 9 days by the IV route, plus standard of care, for a total of up to 10 days of therapy.

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.

Clinical Trials in Subjects with COVID-19

NIAID ACTT-1 STUDY TRIAL IN SUBJECTS WITH MILD/MODERATE AND SEVERE COVID-19

A randomized, double-blind, placebo-controlled clinical trial evaluated remdesivir 200 mg once daily for 1 day followed by remdesivir 100 mg once daily for 9 days (for a total of up to 10 days of intravenously administered therapy) in hospitalized adult subjects with COVID-19 with evidence of lower respiratory tract involvement. The trial enrolled 1,063 subjects: 120 [11.3%] subjects with mild/moderate disease and 943 [88.7%] subjects with severe disease. A total of 272 subjects (25.6%) (n=125 received remdesivir) were on mechanical ventilation/ECMO. Subjects were randomized in a 1:1 manner, stratified by disease severity at enrollment, to receive remdesivir (n=541) or placebo (n=522), plus standard of care. The primary clinical endpoint was time to recovery within 28 days after randomization, defined as either discharged from the hospital or hospitalized but not requiring supplemental oxygen and no longer requiring ongoing medical care. In a preliminary analysis of the primary endpoint performed after 607 recoveries were attained (n=1,059; 538 remdesivir, 521 placebo), the median time to recovery was 11 days in the remdesivir group compared to 15 days in the placebo group (recovery rate ratio 1.32; 95% CI 1.12 to 1.55, p<0.001); 14-day mortality was 7.1% for the remdesivir group versus 11.9% for the placebo group (hazard ratio 0.70 [95% CI 0.47, 1.04], p=0.07). Among subjects with mild/moderate disease at enrollment (n=119), the median time to recovery was 5 days in both the remdesivir and placebo groups (recovery rate ratio 1.09; [95% CI 0.73 to 1.62]). Among subjects with severe disease at enrollment (n=940), the median time to recovery was 12 days in the remdesivir group compared to 18 days in the placebo group (recovery rate ratio, 1.37; [95% CI, 1.15 to 1.63]; p<0.001; n=940) and 14-day mortality was 7.7% and 13%, respectively (hazard ratio, 0.71; [95% CI, 0.48 to 1.05]).

STUDY GS-US-540-5773 IN SUBJECTS WITH SEVERE COVID-19

A randomized, open-label multi-center clinical trial (Study GS-US-540-5773) of hospitalized subjects at least 12 years of age with confirmed SARS-CoV-2 infection, oxygen saturation of ≤94% on room air, and radiological evidence of pneumonia compared 197 subjects who received IV remdesivir for 5 days with 200 subjects who received IV remdesivir for 10 days. Patients on mechanical ventilation at screening were excluded. All subjects received 200 mg of remdesivir on Day 1 and 100 mg once daily on subsequent days, plus standard of care. The primary endpoint was clinical status on Day 14 assessed on a 7-point ordinal scale ranging from hospital discharge to increasing levels of oxygen and ventilatory support to death. After adjusting for between-group differences at baseline, patients receiving a 10-day course of remdesivir had similar clinical status at Day 14 as those receiving a 5-day course (odds ratio for improvement: 0.75; [95% CI 0.51 to 1.12]).

Clinical improvement was defined as an improvement of two or more points from baseline on the 7-point ordinal scale. Subjects achieved clinical recovery if they no longer required oxygen support or were discharged from the hospital. At Day 14, observed rates between the 5- and 10-day treatment groups were 65% vs 54% for clinical improvement, 70% vs 59% for clinical recovery, and 8% vs 11% for mortality.

5.2 Pharmacokinetic Properties

Pharmacokinetic Properties

The pharmacokinetics of remdesivir has been evaluated in adults in several Phase 1 trials.

The pharmacokinetics of remdesivir and metabolites have not been in evaluated in patients with COVID-19.

- Following single-dose, 2-hour IV administration of remdesivir solution formulation at doses ranging from 3 to 225 mg, remdesivir exhibited a linear pharmacokinetic profile.
- Following single-dose, 2-hour IV administration of remdesivir at doses of 75 and 150 mg, both the lyophilized powder and injection solution formulations provided comparable pharmacokinetic parameters (AUC_{inf}, AUC_{last}, and C_{max}), indicating similar formulation performance.
- Remdesivir 75 mg lyophilized formulation administered by the IV route over 30 minutes provided similar peripheral blood mononuclear cell (PBMC) exposure of the active triphosphate metabolite GS-443902 as remdesivir 150 mg lyophilized formulation administered by the IV route over 2 hours.
- Following a single 150 mg IV dose of [^{14}C]-remdesivir, mean total recovery of the dose was greater than 92%, consisting of approximately 74% and 18% recovered in urine and feces, respectively. The majority of remdesivir dose recovered in urine was the metabolite GS-441524 (49%), while 10% was recovered as remdesivir.

Special Populations

Sex, Race and Age

Pharmacokinetic differences based on sex, race, and age have not been evaluated.

Pediatric Patients

The pharmacokinetics of remdesivir in pediatric patients has not been evaluated. PBPK modeling of pharmacokinetic data from healthy adults was used to derive pediatric doses. PBPK modeling incorporated in vitro data for remdesivir and other similar compounds along with age-dependent changes in physiology (e.g., organ volume/function, blood flow), metabolism, distribution, and elimination of remdesivir. 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.

Patients with Renal Impairment

Because the excipient 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 adult and pediatric patients (>28 days old) with eGFR<30 mL per minute or in full-term neonates (≥7 days and ≤28 days old) with serum creatinine clearance ≥1 mg/dL unless the potential benefit outweighs the potential risk.

6. NONCLINICAL PROPERTIES

Nonclinical Toxicology

Carcinogenesis: Given the short-term administration of remdesivir for the treatment of COVID-19, long- term animal studies to evaluate the carcinogenic potential of remdesivir are not required.

Mutagenesis: Remdesivir was not genotoxic in a battery of assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes, and *in vivo* rat micronucleus assays.

Impairment of Fertility: Nonclinical toxicity studies in rats demonstrated no adverse effect on male fertility at exposures of the predominant circulating metabolite (GS-441524) approximately 2 times the exposure in humans at the RHD.

Reproductive toxicity, including decreases in corpora lutea, numbers of implantation sites and viable embryos, was seen when remdesivir was administered by the IV route daily at a systemically toxic dose (10 mg/kg) in female rats 14 days prior to mating and during conception; exposures of the predominant circulating metabolite (GS-441524) were 1.3 times the exposure in humans at the RHD.

Animal Toxicology and/or Pharmacology: IV administration (slow bolus) of remdesivir to male rhesus monkeys at dosage levels of 5, 10 and 20 mg/kg/day for 7 days resulted, at all dose levels, in increased mean urea nitrogen and increased mean creatinine, renal tubular atrophy, and basophilia and casts.

IV administration (slow bolus) of remdesivir to rats at dosage levels of ≥3 mg/kg/day for up to 4 weeks resulted in findings indicative of kidney injury and/or dysfunction.

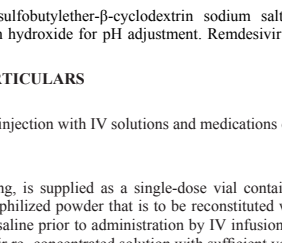
Animal Pharmacologic and Efficacy Data: It is unknown, at present, how the observed antiviral activity of remdesivir in animal models of SARS-CoV-2 infection will translate into clinical efficacy in patients with symptomatic disease. Key attributes of the remdesivir nonclinical profile supporting its development for the treatment of COVID-19 are provided below:

- Remdesivir showed cell culture antiviral activity against a clinical isolate of SARS-CoV-2 in primary HAE cells (EC50 value = 9.9 nM). The EC_{50} values of remdesivir against SARS-CoV-2 in Vero cells has been reported to be 137 nM at 24 hours and 750 nM at 48 hours post-treatment.
- Remdesivir showed antiviral activity in SARS-CoV-2-infected rhesus monkeys. Administration of remdesivir at 10/5 mg/kg (10 mg/kg first dose, followed by 5 mg/kg once daily thereafter) using IV bolus injection initiated 12 hours post-inoculation with SARS-CoV-2 resulted in a reduction in clinical signs of respiratory disease, lung pathology and gross lung lesions, and lung viral RNA levels compared with vehicle-treated animals

7. DESCRIPTION

Chemical name for remdesivir: 2-ethylbutyl N-{(S)-[2-C-(4 aminopyrrolo [2,1- f][1,2,4]triazin-7-yl)-2,5-anhydro-d-altrononitril-6-O-yl] phenoxyphosphoryl}-L-alaninate.

Its structural formula is as below:



Molecular formula: $C_{27}H_{35}N_6O_8P$ Molecular weight: 602.6 g/mol

Physical Appearance

Lyophilized Powder

Remdesivir for injection, 100 mg, is a sterile, preservative-free lyophilized powder that is to be reconstituted with 19 mL of Sterile Water for Injection and further diluted into 0.9% sodium chloride infusion bag prior to administration by intravenous infusion. Remdesivir for injection, 100 mg, is supplied in a single-dose clear glass vial.

The appearance of the lyophilized powder is white to off-white to yellow.

Inactive Ingredients

The inactive ingredients are sulfobutylether-β-cyclodextrin sodium salt (SBECD), and may include hydrochloric acid and/or sodium hydroxide for pH adjustment. Remdesivir for injection, 100 mg, contains 3 g SBECD.

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

The compatibility of remdesivir injection with IV solutions and medications other than saline is not known.

8.2 Packing Information

Lyophilized Powder

Remdesivir for injection, 100 mg, is supplied as a single-dose vial containing a sterile, preservative-free white to off-white to yellow lyophilized powder that is to be reconstituted with 19 mL of Sterile Water for Injection and diluted into 0.9% saline prior to administration by IV infusion. Following reconstitution, each vial contains 5 mg/mL remdesivir re- concentrated solution with sufficient volume to allow withdrawal of 20 mL of 5 mg/mL solution containing 100 mg of remdesivir.

Discard any unused portion.

The container closure is not made with natural rubber latex.

8.3 Storage and Handling Instructions

Do not reuse or save unused remdesivir for injection (lyophilized powder), remdesivir injection solution, or diluted solutions for infusion for future use. This product contains no preservatives.

Lyophilized Powder

Store remdesivir for injection (lyophilized powder), 100 mg, vials below 30°C (below 86°F) until required for use. Do not use after the expiration date.

After reconstitution, vials can be stored up to 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) prior to administration or 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]). Dilute within the same day as administration.

9. PATIENT COUNSELLING INFORMATION

You are being given a medicine called remdesivir for the treatment of coronavirus disease 2019 (COVID-19). This fact sheet contains information to help you understand the risks and benefits of taking remdesivir, which you have received or may receive.

Receiving remdesivir may benefit certain people in the hospital with COVID-19. Read this fact sheet for information about remdesivir. Talk to your healthcare provider if you have questions.

10. DETAILS OF MANUFACTURER

MSN Laboratories Private Limited
(Formulations Division), Plot No. 42, Anrich Industrial Estate, Bollaram,
Sangareddy District - 502 325, Telangana, INDIA.

11. DETAILS OF MANUFACTURING LICENCE NUMBER

38/MD/AP/2007/F/CC

12. DATE OF REVISION

June 2020.

B32658-00