℞ **COVIFOR**

Remdesivir for Injection 100 mg

Each vial contains: 100 mg of Remdesivir

DRUG DESCRIPTION

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.

CLINICAL PHARMACOLOGY

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.

Pharmacokinetics

The pharmacokinetics (PK) of remdesivir have 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 PK profile.
- Following single-dose, 2-hour IV administration of remdesivir at doses of 75 and 150 mg, both the lyophilized and solution formulations provided comparable PK parameters (AUC_{inf}, AUC_{last}, and C_{max}), indicating similar formulation performance.
- Remdesivir 75 mg lyophilized formulation administered IV 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 IV over 2 hours.
- Following a single 150 mg intravenous dose of [^{14}C]-remdesivir, mean total recovery of the dose was > 92%, consisting of approximately 74% and 18% recovered in urine and feces, respectively. The majority of remdesivir dose recovered in urine was metabolite GS-441524 (49%), while 10% was recovered as remdesivir.

Specific 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.

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 (greater than 28 days old) with eGFR less than 30 mL/min per minute or in full-term neonates (at least 7 days and less than or equal to 28 days old) with serum creatinine greater than or equal to 1 mg/dL unless the potential benefit outweighs the potential risk.

DOSAGE FORMS AND STRENGTHS

- Remdesivir for injection, 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 further diluted into 0.9% sodium chloride infusion bag prior to administration by intravenous infusion. Following reconstitution, each vial contains 100 mg/20 mL (5 mg/mL)remdesivir reconcentrated solution.

Contraindications

Remdesivir is contraindicated in patients with known hypersensitivity to any ingredient of remdesivir.

Authorized Use

Remdesivir is authorized for use under an EUA (Emergency Use Authorization) for treatment of patients hospitalized with suspected or laboratory confirmed SARS-CoV-2 infection and severe disease. Severe disease is defined as patients with an oxygen saturation (SpO2) ≤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 intravenous (IV) agent is clinicallyappropriate.

DOSAGE AND ADMINISTRATION

Important Testing Prior to and During Treatment and Route of Administration

- 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 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 intravenous (IV) infusion only. Do not administer as an intramuscular (IM) injection.

Recommended Dosage in 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 infusion.
- For patients requiring invasive mechanical ventilation and / or ECMO, total treatment duration is 10 days.
- For patients not requiring invasive mechanical ventilation and/or ECMO, total treatment duration is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days (i.e., up to a total of 10 days).
- Administer remdesivir via IV infusion in a total volume of up to 250 mL 0.9% sodium chloride over 30 to 120 minutes.

Recommended Dosage in 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:

- **For pediatric patients weighing 3.5 kg to less than 40 kg, use remdesivir for injection, 100 mg, lyophilized powder only**. Do not use remdesivir injection, 100 mg/20 mL (5 mg/mL), for pediatric patients weighing 3.5 kg to less than 40 kg due to the higher amount of SBECD present and resulting higher tonicity of the solution concentrate compared to the lyophilized formulation.
- 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

- For pediatric patients requiring invasive mechanical ventilation and/or ECMO, total treatment duration is 10 days.
- For pediatric patients not requiring invasive mechanical ventilation and/or ECMO, total treatment duration Is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days (i.e., up to a total of 10 days).

Pregnancy

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

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 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 (greater than 28 days old) with eGFR less than 30 mL per minute or in full-term neonates (at least 7 days and less than or equal to 28 days old)] with serum creatinine clearance greater than or equal to 1 mg/dL unless the potential benefit outweighs the potential risk.

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.

Adult Dose Preparation and Administration, Adults and Pediatric Patients Weighing 40 kg and Higher

Remdesivir for Injection, 100 mg, Lyophilized Powder

Reconstitution Instructions

Remove the required number of single-dose vial(s) from storage. For each vial:

- Aseptically reconstitute remdesivir 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% sodium chloride to withdraw from the infusion bag.

Table 2: Recommended Dilution Instructions Using Reconstituted Remdesivir for Injection Lyophilized Powder in Adults and Pediatric Patients Weighing ≥ 40 kg and Higher

Remdesivir dose	0.9% saline infusion bag volume to be used	Volume of saline to be withdrawn and discarded from 0.9% saline infusion bag	Required volume of reconstituted remdesivir for injection
200 mg (2 vials)	250 mL	40 mL	40 mL (2 × 20 mL)
	100 mL	40 mL	40 mL (2 × 20 mL)
100 mg (1 vial)	250 mL	20 mL	20 mL
	100 mL	20 mL	20 mL

- Withdraw and discard the required volume of 0.9% sodium chloride from the bag 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 2. 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 with IV solutions and medications other than 0.9% sodium chloride is not known.

Administer the diluted solution with 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 and Higher

Infusion bag volume	Infusion time	Rate of infusion
250 mL	30 min	8.33 mL/min
	60 min	4.17 mL/min
	120 min	2.08 mL/min
100 mL	30 min	3.33 mL/min
	60 min	1.67 mL/min
	120 min	0.83 mL/min

Dose Preparation and Administration, Pediatric Patients Weighing 3.5 kg to Less Than 40 kg

For pediatric patients weighing 3.5 kg to less than 40 kg, use remdesivir for injection, 100 mg, lyophilized powder only. Remdesivir injection, 100 mg/20 mL (5 mg/mL), should not be used for pediatric patients weighing 3.5 kg to less than 40 kg due to the higher amount of SBECD present and resulting higher tonicity of the solution concentrate compared to the lyophilized formulation.

Remdesivir for Injection, 100 mg, Lyophilized Powder

Reconstitution Instructions

Remove the required number of single-dose vial(s) from storage. For each vial:

- Aseptically reconstitute remdesivir 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 with the infusion rate described in Table 4.

Table 4: Recommended Rate of Infusion—Diluted Remdesivir for Injection Lyophilized Powder for Pediatric Patients Weighing 3.5 kg to Less Than 40 kg

Infusion bag volume	Infusion time	Rate of infusion[a]
100 mL	30 min	3.33 mL/min
	60 min	1.67 mL/min
	120 min	0.83 mL/min
50 mL	30 min	1.67 mL/min
	60 min	0.83 mL/min
	120 min	0.42 mL/min
25 mL	30 min	0.83 mL/min
	60 min	0.42 mL/min
	120 min	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 Solution

Store diluted remdesivir solution for infusion 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.

CONTRAINDICATIONS

Remdesivir is contraindicated in patients with known hypersensitivity to any ingredient of remdesivir.

WARNINGS AND PRECAUTIONS

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 hypersensitivity 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 greater than or equal to 5 times the upper limit of normal at baseline
- Remdesivir should be discontinued in patients who develop:
  - ALT greater than or equal to 5 times the upper limit of normal during treatment with remdesivir. Remdesivir may be restarted when ALT is less than 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 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.

Serious Side Effects

An adverse reaction associated with remdesivir in clinical trials in healthy adult subjects was increased liver transaminases. Additional adverse reactions associated with the drug, some of which may be serious, may become apparent with more widespread use.

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,

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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 NTCP. The clinical relevance of these in vitro assessments has not been established.

OVERALL SAFETY SUMMARY

In healthy subjects and hospitalized patients with PCR-confirmed SARS-CoV-2 infection, graded elevations in ALT and AST have been observed with a loading dose of remdesivir 200 mg administered intravenously on Day 1 followed by 100 mg administered intravenously 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

Study GS-US-540-5773

In a randomized, open-label clinical trial (Study GS-US-540-5773) of remdesivir in 397 hospitalized 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, SAEs were reported in 21% and 35% of subjects, respectively, and Grade ≥ 3 adverse events were reported in 30% 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

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 Subjects with COVID-19

NIAID ACTT-1 trial

Grade ≥ 3 non-serious adverse events of increased aminotransferase levels including ALT, AST, or both were reported in 4% of subjects receiving remdesivir compared with 6% receiving placebo.

Study GS-US-540-5773

Grade ≥ 3 hepatic laboratory abnormalities reported in subjects treated with remdesivir for 5 (n = 200) or 10 days (n = 197) are shown in Table 5.

Table 5: 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 Increased	Grade 3	1/193 (1%)	3/190 (2%)	4/383 (1%)
	Grade 4	0	1/190 (1%)	1/383 (< 1%)

Compassionate Use Experience

In the compassionate use program in patients with severe or critical illness with COVID-19, liver function test abnormalities were reported in 12% (19/163) of patients. Time to onset from first dose ranged from 1-16 days. Four of these patients 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 SAE of blood bilirubin increased in a critically ill patient with septic shock and multiorgan failure. None of the other cases had reported adverse events suggestive of hyperbilirubinemia or symptoms of hepatitis.

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.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

No adequate and well-controlled studies of remdesivir use in pregnant women have been conducted. 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 embryofetal 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) (*see Data*).

Animal Data

Remdesivir was administered via intravenous injection to pregnant rats and rabbits (up to 20 mg/kg/day) on Gestation Days 6 through 17, and 7 through 20, respectively, and also to rats from Gestation Day 6 to Lactation/Post-partum Day 20. No adverse effects on embryo-fetal (rats and rabbits) or pre/postnatal (rats) development were observed in rats and rabbits at nontoxic doses in pregnant animals. During organogenesis, exposures to the predominant circulating metabolite (GS-441524) were 4 (rats and rabbits) times higher than the exposure in humans at the RHD. In a pre/postnatal development study, exposures to the predominant circulating metabolite of remdesivir (GS-441524) were similar to the human exposures at the RHD.

Nursing Mothers

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.

Animal Data

Remdesivir and its metabolites were detected in the plasma of nursing rat pups, likely due to the presence of remdesivir and/or its metabolites in milk, following daily intravenous administration of remdesivir to pregnant mothers from Gestation Day 6 to Lactation Day 20. Exposures in nursing pups were approximately 1% that of maternal exposure on lactation day 10.

Pediatric Use

The safety, effectiveness, or pharmacokinetics of remdesivir for 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 with weighing 3.5 kg to less than40 kg, use remdesivir for injection, 100 mg, lyophilized powder only. Remdesivir injection, 100/20 mL (5 mg/mL), should not be used for pediatric patients weighing 3.5 kg to less than 40 kg due to the higher amount of SBECD present and resulting higher tonicity of the solution concentrate compared to the lyophilized formulation.

Pediatric patients (older than 28 days) must have eGFR determined and full-term neonates (at least 7 days to less than or equal 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 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 (older than 28 days old) with eGFR less than 30 mL/min or in full-term neonates at least 7 days and less than or equal to 28 days old) with serum creatinine clearance greater than or equal to 1 mg/dL unless the potential benefit outweighs the potential risk.

Geriatric Use

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.

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 (at least 28 days old) with eGFR less than 30 mL/min or in full-term neonates (at least 7 days and less than or equal to 28 days old) with serum creatinine greater than or equal to 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.

Hepatic Impairment

The pharmacokinetics of remdesivir have 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.

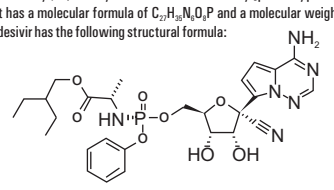
OVERDOSAGE

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 patient. There is no specific antidote for overdose with remdesivir.

PRODUCT DESCRIPTION

Remdesivir is a nucleoside ribonucleic acid (RNA) polymerase inhibitor.

The chemical name for remdesivir is 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. It has a molecular formula of $C_{27}H_{35}N_6O_8P$ and a molecular weight of 602.6 g/mol. Remdesivir has the following structural formula:



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), Water for Injection, USP, and may include hydrochloric acid and/or sodium hydroxide for pH adjustment. Remdesivir for injection, 100 mg, contains 3 g SBECD.

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 EC_{50} 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 2 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.

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 intravenous 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

Intravenous 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.

Intravenous 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 (EC_{50} 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.

CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

Remdesivir is an unapproved antiviral drug with available data from two randomized clinical trials in patients with COVID-19.

Clinical Trials in Subjects with COVID-19

NIAID ACTT-1 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]).

Overall, the odds of improvement in the ordinal scale were higher in the remdesivir group at Day 15 when compared to the placebo group (odds ratio, 1.50; [95% CI, 1.18 to 1.91], p = 0.001; n = 844).

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.

HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

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 further diluted into 0.9% sodium chloride infusion bag prior to administration by intravenous infusion. Following reconstitution, each vial contains 100 mg/20 mL (5 mg/mL) remdesivir reconcentrated solution.

Discard unused portion.

The container closure is not made with natural rubber latex.

Storage and Handling

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

Lyophilized Powder

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

COVIFOR is manufactured under a license from Gilead Sciences, Inc.

Manufactured by:
HETERO LABS LIMITED
Hyderabad, India.

Manufactured at:
ASPIRO PHARMA LIMITED
Survey No. 321, Biotech Park,
Phase-III, Karkapatla Village,
Markook Mandal, Siddipet Dist.,
Telangana State - 502281, India.

To be distributed and used only in the licensed countries identified below:

Afghanistan	Guyana	South Sudan
Algeria	Haiti	Sri Lanka
Angola	Honduras	St. Kitts and Nevis
Anguilla	India	St. Lucia
Antigua & Barbuda	Indonesia	St. Vincent and the Grenadines
Armenia	Jamaica	Sudan
Aruba	Kazakhstan	Suriname
Azerbaijan	Kenya	Tajikistan
Bahamas	Kiribati	Tanzania
Bangladesh	Korea, Dem. People's Rep.	Thailand
Barbados	(North Korea)	Timor-Leste
Belarus	Kyrgyzstan	Togo
Belize	Lao DR (Laos)	Tonga
Benin	Lesotho	Trinidad & Tobago
Bermuda	Liberia	Tunisia
Bhutan	Libya	Turkmenistan
Botswana	Madagascar	Turks & Caicos
British Virgin Islands	Malawi	Tuvalu
Burkina Faso	Maldives	Uganda
Burundi	Mali	Ukraine
Cambodia	Marshall Islands	Uzbekistan
Cameroon	Mauritania	Vanuatu
Cape Verde	Mauritius	Vietnam
Cayman Island	Micronesia, Fed. Sts.	Zambia
Central Af R.	Moldova	Zimbabwe
Chad	Mongolia	
Comoros	Montserrat	
Congo Rep.	Morocco	
Cook Islands	Mozambique	
Costa Rica	Myanmar	
Cote d'Ivoire	Namibia	
Cuba	Nauru	
Curacao	Nepal	
Djibouti	Nicaragua	
Dominica	Niger	
Dominican Republic	Nigeria	
Egypt	Pakistan	
El Salvador	Palau	
Equatorial Guinea	Panama	
Eritrea	Papua New Guinea	
Eswatini (Swaziland)	Philippines	
Ethiopia	Rwanda	
Fiji	Samoa	
Gabon	Sao Tome and Principe	
Gambia, The	Senegal	
Georgia	Seychelles	
Ghana	Sierra Leone	
Grenada	Sint Maarten (Dutch part)	
Guatemala	Solomon Islands	
Guinea	Somalia	2058671
Guinea Bis	South Africa	21000991