Remdesivir is authorized for treatment of COVID-19 in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplement oxygen. Health care providers must submit a report on all adverse events related to remdesivir.

Remdesivir for Injection 100 mg/vial DESREM™

Lyophilized Powder for Injection for IV Infusion

1. INDICATION

For the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen.

2. DOSAGE AND ADMINISTRATION

2.1 General Information

- The optimal dosing and duration of treatment is unknown. The suggested dose and duration may be updated as data from clinical trials becomes available.
- All patients must have an eGFR determined before dosing of 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.

2.2 Posology

- The dose of the drug for patients should be a single dose of 200 mg infused intravenously over 30-120 minutes on day 1 followed by once daily maintenance dose of 100 mg, infused intravenously over 30-120 minutes from day 2.
- Remdesivir is to be administered via intravenous infusion in a total volume of up to 250 mL 0.9% saline over 30 to 120 minutes *[see Dosage and Administration (2.6)]*.
- The total duration of treatment should be at least 5 days and not more than 10 days.

All patients must have creatinine clearance determined before dosing *[see Dosage and Administration (2.4)]*.

Hepatic laboratory testing should be performed in all patients prior to starting remdesivir and daily while receiving remdesivir dosing *[see Dosage and Administration (2.5)]*.

2.3 Pregnancy

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

2.4 Renal Impairment

Use in patients with renal impairment are 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.

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 patients with eGFR less than 30 mL per minute.

2.5 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 *[see Warnings and Precautions (5.2)].*

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

2.6 Dose Preparation and Administration 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.

- Using Table 1, determine the volume of 0.9% saline to withdraw from the infusion bag.

Table 1: Recommended Dilution Instructions— Remdesivir for Injection Lyophilized Powder in Adults and Adolescents Patients (aged 12 years and older with body weight at least 40 kg)

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	2 × 20 mL
	100 mL	40 mL	2 × 20 mL
100 mg (1 vial)	250 mL	20 mL	20 mL
	100 mL	20 mL	20 mL

- Withdraw the required volume of saline from the bag using an appropriately sized syringe and needle. Discard the saline that was withdrawn from the bag.
- 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 medication. The compatibility of remdesivir injection with IV solutions and medications other than saline is not known. Administer the diluted solution with the infusion rate described in Table 2.

Table 2: Recommended Rate of Infusion — Diluted Remdesivir for Injection Lyophilized Powder in Adults and Adolescents Patients (aged 12 years and older with body weight at least 40 kg)

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

2.7 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.

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.

3. 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 or lumps or solid that is to be reconstituted with 19 mL of Sterile Water for Injection and diluted into 0.9% saline prior to administration by intravenous infusion. Following reconstitution, each vial contains 5 mg/mL remdesivir reconcentrated solution with sufficient volume to allow withdrawal of 20 mL of 5 mg/mL solution containing 100 mg of remdesivir.

4. CONTRAINDICATIONS

Remdesivir is contraindicated in patients with known hypersensitivity to any ingredient of remdesivir *[see Product Description (11)].*

5. 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.

5.1 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 [see Contraindications (4)].

5.2 Increased Risk of Transaminase Elevations

Transaminase elevations have been observed in the remdesivir clinical development program, including in healthy volunteers and patients with COVID19. As transaminase elevations have been reported as a component of COVID-19 in some patients, 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 INR

5.3 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 [see Drug Interactions (8)].

6. 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.

6.1 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.

NIAID ACTT-1 Trial

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 3.

Table 3: 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%)	47(9%)
Acute kidney injury, decreased eGFR or creatinine renal clearance, or increased blood creatinine	40(7%)	38(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 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.

6.2 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 Patients 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 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 4.

Table 4: 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 1-16 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 1 serious adverse event (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.

7. 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. The following laboratory tests should be performed daily while receiving remdesivir: serum chemistries, hematology, ALT, AST, bilirubin, and alkaline phosphatase; renal function tests (creatinine and creatinine clearance).

8. 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 [see Warnings and Precautions (5.3)].

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 (Pgp) 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.

9. USE IN SPECIFIC POPULATIONS

9.1 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).

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.

9.2 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.

9.3 Pediatric Use

The safety and effectiveness of remdesivir for treatment of COVID-19 have not been assessed in pediatric patients. Dosing instructions for pediatric patients were derived based on pharmacokinetic data from adult healthy volunteers and *in vitro* data for remdesivir and other similar compounds, as part of the PBPK modeling and simulation approach which accounts for age-dependent changes in metabolism, distribution, and elimination of remdesivir.

9.4 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.

9.5 Renal Impairment

Use in patients with renal impairment are 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. 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.

9.6 Hepatic Impairment

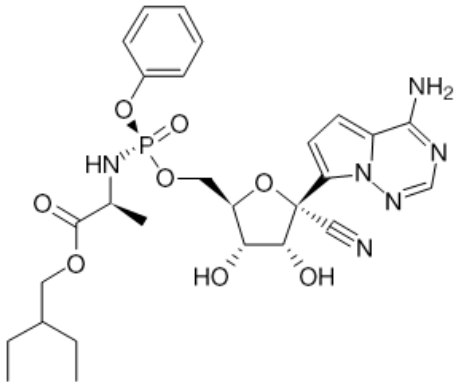
The pharmacokinetics of remdesivir have not been evaluated in patients with hepatic impairment. It is not known if dosage adjustment is needed in patients with hepatic impairment and remdesivir should only be used in patients with hepatic impairment if the potential benefit outweighs the potential risk *[see Warnings and Precautions (5.2)].*
Hepatic laboratory testing should be performed in all patients prior to starting remdesivir and daily while receiving remdesivir.

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

11. PRODUCT DESCRIPTION

Remdesivir is a nucleoside ribonucleic acid (RNA) polymerase inhibitor.
The chemical name for remdesivir is 2-ethylbutyl *N*-{(*S*)-[2-*C*-(4aminopyrrolo[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:



11.1 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 diluted into 0.9% saline 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 lyophilized powder or lumps or solid.

11.2 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.

12. CLINICAL PHARMACOLOGY

12.1 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.

12.2 Pharmacokinetics

The pharmacokinetics (PK) of remdesivir have been evaluated in adults in several Phase 1 trials.

- 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 greater than 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. Physiologically-based pharmacokinetic models were developed to estimate remdesivir and GS-441524 exposure and predict pediatric patient exposure based on age-dependent physiologic changes (e.g., organ volume/function, blood flow). These simulations do not account for the impact of infection on the pharmacokinetics of remdesivir and GS-441524, which is currently unknown.

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 patients with eGFR less than 30 mL per minute.

13. 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.

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 RNAdependent 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.

14. 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.

15. 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.

16. CLINICAL TRIAL RESULTS

Remdesivir is an unapproved antiviral drug with available data from two randomized clinical trials and clinical trials in healthy volunteers.

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-control 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 patients with COVID-19 with evidence of lower respiratory tract involvement. The trial enrolled 1063 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) 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 adult patients

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 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.

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-US399-5505). In these studies, transient graded elevations in ALT and AST were observed at repeated once-daily doses of remdesivir.

17. 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 or lumps or solid that is to be reconstituted with 19 mL of Sterile Water for Injection and diluted into 0.9% saline prior to administration by intravenous infusion. Following reconstitution, each vial contains 5 mg/mL remdesivir reconcentrated solution with sufficient volume to allow withdrawal of 20 mL of 5 mg/mL solution containing 100 mg of remdesivir.

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,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.

For further information write to: ProductSafety@mylan.com

Mylan

Manufactured by:

Mylan Laboratories Limited [Specialty Formulation Facility], No.19-A, Plot No. 284-B/1, Bommasandra - Jigani Link Road, Industrial Area, Anekal Taluk, Bangalore - 560 105.
Mfg. Lic. No.: KTK/28/384/2009
TM - Trade Mark under registration

Gland Pharma Limited (Unit-II)
Sangareddy District – 502307, Telangana, Republic of India

Aurobindo Pharma Limited
Sangareddy District – 502307, Telangana, Republic of India

DESREM is manufactured under a license from Gilead Sciences, Inc.
Market Authorization Holder: Viatris Pharmaceuticals (Thailand) Limited. Bangkok, THAILAND.
Market Authorization Number: 1C 45/63 (NG)
Date of Authorization: 31 July 2020