Rx REMDESIVIR

COVIFOR

100 mg Lyophilized powder for solution for infusion (IV)
Antiviral

Formulation:
Each vial contains:
Remdesivir .....100 mg/mL

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.

INDICATIONS AND USAGE
Remdesivir for injection is indicated for adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization. Remdesivir for injection should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care.

CLINICAL PHARMACOLOGY
1. CLINICAL PHARMACOLOGY
1.1 Mechanism of Action
Remdesivir is an antiviral drug with activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) *(see Microbiology (1.4))*.

1.2 Pharmacodynamics
Remdesivir and metabolites exposure-response relationships and the time course of pharmacodynamics response are unknown.

1.3 Pharmacokinetics
The pharmacokinetic (PK) properties of remdesivir and metabolites are provided in Table 1. The multiple dose PK parameters of remdesivir and metabolites in healthy adults are provided in Table 2.

Table 1 Pharmacokinetic Properties of Remdesivir and Metabolites (GS-441524 and GS- 704277)

	Remdesivir	GS-441524	GS-704277
Absorption			
Tmax (h)[a]	0.67-0.68	1.51-2.00	0.75-0.75
Distribution			
% bound to human plasma proteins	88-93.6[b]	2	1
Blood-to-plasma ratio	0.68-1.0	1.19	0.56
Elimination			
t1/2 (h)[c]	1	27	1.3
Metabolism			
Metabolic pathway(s)	CES1 (80%) Cathepsin A (10%) CYP3A (10%)	Not significantly metabolized	HINT1
Excretion			
Major route of elimination	Metabolism	Glomerular filtration and active tubular secretion	Metabolism
% of dose excreted in urined	10	49	2.9
% of dose excreted in fecesd	ND	0.5	ND

ND = not detected
a. Remdesivir administered as a 30-minute IV infusion (Study GS-US-399-5505); range of median observed on Day 1 and Day 5 or 10.
b. Range of protein binding for remdesivir from 2 independent experiments show no evidence of concentration-dependent protein binding for remdesivir.
c. Median (Study GS-US-399-4231).
d. Mean (Study GS-US-399-4231).

Table 2 Multiple Dose PK Parameters[a] of Remdesivir and Metabolites (GS-441524 and GS- 704277) Following IV Administration of Remdesivir for injection 100 mg to Healthy Adults

Parameter Mean (CV%)	Remdesivir	GS-441524	GS-704277
C_{max} (nanogram per mL)	2229 (19.2)	145 (19.3)	246 (33.9)
AUC_{tau} (nanogram•h per mL)	1585 (16.6)	2229 (18.4)	462 (31.4)
C_{trough} (nanogram per mL)	ND	69.2 (18.2)	ND

CV = Coefficient of Variation; ND = Not detectable (at 24 hours post-dose)
a. Remdesivir administered as a 30-minute IV infusion (Study GS-US-399-5505).

Specific Populations
Pharmacokinetic differences based on sex, race, age, renal function, and hepatic function on the exposures of remdesivir have not been evaluated.

Pediatric Patients
The pharmacokinetics of Remdesivir in pediatric patients have not been evaluated.

Using modeling and simulation, the recommended dosing regimen is expected to result in comparable steady-state plasma exposures of remdesivir and metabolites in patients 12 years of age and older and weighing at least 40 kg as observed in healthy adults *(see Use in Specific Populations (10.3))*.

Drug Interaction Studies
Clinical drug-drug interaction studies have not been performed with Remdesivir In vitro, remdesivir is a substrate for drug metabolizing enzyme 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, and MATE1. GS-704277 is a substrate for OATP1B1 and OATP1B3. The clinical relevance of these in vitro assessments has not been established.

Remdesivir is not a substrate for CYP1A1, 1A2, 2B6, 2C9, 2C19, or OATP1B3. GS-704277 and GS- 441524 are not substrates for CYP1A1, 1A2, 2B6, 2C8, 2C9, 2D6, or 3A5. GS-441524 is also not a substrate for CYP2C19 or 3A4. GS-704277 and GS-441524 are not substrates for OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2k. GS-441524 is also not a substrate for OATP1B1 or OATP1B3.

1.4 Microbiology
Mechanism of Action
Remdesivir is an inhibitor of the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), which is essential for viral replication. Remdesivir is an adenosine nucleotide prodrug that distributes into cells where it is metabolized to a nucleoside monophosphate intermediate by carboxyesterase 1 and/or cathepsin A, depending upon the cell type. The nucleoside monophosphate is subsequently phosphorylated by cellular kinases to form the pharmacologically active nucleoside triphosphate metabolite (GS-443902). Remdesivir triphosphate (RDV-TP) acts as an analog of adenosine triphosphate (ATP) and competes with high selectivity (3.65-fold) over 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 (position i + 3) during replication of the viral RNA. In a biochemical assay assessing RDV-TP incorporation by the MERS-CoV RdRp complex, RDV-TP inhibited RNA synthesis with an IC50 value of 0.032 µM. RDV-TP can also inhibit viral RNA synthesis following its incorporation into the template viral RNA as a result of read-through by the viral polymerase that may occur at higher nucleotide concentrations. When remdesivir nucleotide is present in the viral RNA template, the efficiency of incorporation of the complementary natural nucleotide is compromised, thereby inhibiting viral RNA synthesis. Remdesivir triphosphate is a weak inhibitor of mammalian DNA and RNA polymerases, including human mitochondrial RNA polymerase.

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 (EC50) of 9.9 nM after 48 hours of treatment. Remdesivir inhibited the replication of SARS-CoV-2 in the continuous human lung epithelial cell line Calu-3 with an EC50 value of 280 nM after 72 hours of 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. The combination of these two substitutions conferred a 5.6-fold reduction in 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 reduction in susceptibility to remdesivir in cell culture and attenuated SARS-CoV pathogenesis in a mouse model.

2. NONCLINICAL TOXICOLOGY
2.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis and Mutagenesis
Given the short-term administration of Remdesivir for the treatment of COVID-19, long-term animal studies to evaluate the carcinogenic potential of remdesivir were not conducted.

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 daily intravenous administration 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.

2.2 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.

Kidney-related effects in rats and monkeys were observed at exposures of the predominant circulating metabolite (GS-441524) that are lower than the exposure in humans at the RHD.

3. CLINICAL STUDIES
NIAID ACTT-1 Study in Subjects with Mild/Moderate and Severe COVID-19
A randomized, double-blind, placebo-controlled clinical trial (ACTT-1, NCT04280705) of hospitalized adult subjects with confirmed SARS-CoV-2 infection and mild, moderate, or severe COVID-19 compared treatment with Remdesivir for 10 days (n = 541) with placebo (n = 521). Mild/moderate disease was defined as SpO_2 > 94% and respiratory rate < 24 breaths/minute without supplemental oxygen; severe disease was defined as an SpO2 ≤ 94% on room air, a respiratory rate ≥ 24 breaths/minute, an oxygen requirement, or a requirement for mechanical ventilation. Subjects had to have at least one of the following to be enrolled in the trial: radiographic infiltrates by imaging, SpO2 ≤ 94% on room air, a requirement for supplemental oxygen, or a requirement for mechanical ventilation. Subjects treated with Remdesivir received 200 mg on Day 1 and 100 mg once daily on subsequent days, for 10 days of treatment via intravenous infusion. Treatment with Remdesivir was stopped in subjects who were discharged from the hospital prior to the completion of 10 days of treatment.

At baseline, mean age was 59 years (with 36% of subjects aged 65 or older); 64% of subjects were male, 53% were White, 21% were Black, and 13% were Asian; 24% were Hispanic or Latino; 105 subjects had mild/moderate disease (10% in both treatment groups); 957 subjects had severe disease (90% in both treatment groups). A total of 285 subjects (27%) (n = 131 received Remdesivir were on invasive mechanical ventilation or ECMO. The most common comorbidities were hypertension (51%), obesity (45%), and type 2 diabetes mellitus (31%); the distribution of comorbidities was similar between the two treatment groups.

The primary clinical endpoint was time to recovery within 29 days after randomization. Recovery was defined as discharged from the hospital without limitations on activities, discharged from the hospital with limitations on activities and/or requiring home oxygen, or hospitalized but not requiring supplemental oxygen and no longer requiring ongoing medical care. The median time to recovery was 10 days in the Remdesivir group compared to 15 days in the placebo group (recovery rate ratio 1.29 [95% CI 1.12 to 1.49], p < 0.001). Among subjects with mild/moderate disease at enrolment (n = 105), the median time to recovery was 5 days in both the Remdesivir and placebo groups (recovery rate ratio 1.22 [95% CI 0.82 to 1.81]). Among subjects with severe disease at enrolment (n = 957), the median time to recovery was 11 days in the Remdesivir group compared to 18 days in the placebo group (recovery rate ratio 1.31 [95% CI 1.12 to 1.52]).

A key secondary endpoint was clinical status on Day 15 assessed on an 8-point ordinal scale consisting of the following categories:
1. not hospitalized, no limitations on activities;
2. not hospitalized, limitation on activities and/or requiring home oxygen;
3. hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;
4. hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);
5. hospitalized, requiring supplemental oxygen;
6. hospitalized, on noninvasive ventilation or high-flow oxygen devices;
7. hospitalized, on invasive mechanical ventilation or ECMO; and
8. death.

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 1.54 [95% CI 1.25 to 1.91]).

Overall, 29-day mortality was 11% for the Remdesivir group vs 15% for the placebo group (hazard ratio 0.73 [95% CI 0.52 to 1.03]).

Study GS-US-540-5773 in Subjects with Severe COVID-19
A randomized, open-label multi-center clinical trial (Study 5773, NCT04292899) in adult subjects with confirmed SARS-CoV-2 infection, an SpO2 of ≤ 94% on room air, and radiological evidence of pneumonia compared 200 subjects who received Remdesivir for 5 days with 197 subjects who received Remdesivir for 10 days. Treatment with Remdesivir was stopped in subjects who were discharged from the hospital prior to completion of their protocol-defined duration of treatment.

Subjects 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 via intravenous infusion, plus standard of care.

At baseline, the median age of subjects was 61 years (range, 20 to 98 years); 64% were male, 75% were White, 12% were Black, and 12% were Asian; 22% were Hispanic or Latino. More subjects in the 10-day group than the 5-day group required invasive mechanical ventilation or ECMO (5% vs 2%), or high-flow oxygen support (30% vs 25%), at baseline. Median duration of symptoms and hospitalization prior to first dose of Remdesivir were similar across treatment groups.

The primary endpoint was clinical status on Day 14 assessed on a 7-point ordinal scale consisting of the following categories:
1. death;
2. hospitalized, receiving invasive mechanical ventilation or ECMO;
3. hospitalized, receiving noninvasive ventilation or high-flow oxygen devices;
4. hospitalized, requiring low-flow supplemental oxygen;
5. hospitalized, not requiring supplemental oxygen but receiving ongoing medical care (related or not related to COVID-19);
6. hospitalized, requiring neither supplemental oxygen nor ongoing medical care (other than that specified in the protocol for remdesivir administration); and
7. not hospitalized.

Overall, after adjusting for between-group differences at baseline, subjects receiving a 5-day course of Remdesivir had similar clinical status at Day 14 as those receiving a 10-day course (odds ratio for improvement 0.75 [95% CI 0.51 to 1.12]). There were no statistically significant differences in recovery rates or mortality rates in the 5-day and 10-day groups once adjusted for between-group differences at baseline. All-cause mortality at Day 28 was 12% vs 14% in the 5- and 10-day treatment groups, respectively.

Study GS-US-540-5774 in Subjects with Moderate COVID-19
A randomized, open-label multi-center clinical trial (Study 5774, NCT04292730) of hospitalized adult subjects with confirmed SARS-CoV-2 infection, SpO2 > 94% and radiological evidence of pneumonia compared treatment with Remdesivir for 5 days (n = 191) and treatment with Remdesivir for 10 days (n = 193) with standard of care (n = 200). Treatment with Remdesivir was stopped in subjects who were discharged from the hospital prior to completion of their protocol-defined duration of treatment.

Subjects treated with Remdesivir received 200 mg on Day 1 and 100 mg once daily on subsequent days via intravenous infusion.

At baseline, the median age of subjects was 57 years (range, 12 to 95 years); 61% were male, 61% were White, 19% were Black, and 19% were Asian; 18% were Hispanic or Latino. Baseline clinical status, oxygen support status, and median duration of symptoms and hospitalization prior to first dose of Remdesivir were similar across treatment groups.

The primary endpoint was clinical status on Day 11 assessed on a 7-point ordinal scale consisting of the following categories:
1. death;
2. hospitalized, receiving invasive mechanical ventilation or ECMO;
3. hospitalized, receiving noninvasive ventilation or high-flow oxygen devices;
4. hospitalized, requiring low-flow supplemental oxygen;
5. hospitalized, not requiring supplemental oxygen but receiving ongoing medical care (related or not related to COVID-19);
6. hospitalized, requiring neither supplemental oxygen nor ongoing medical care (other than that specified in the protocol for remdesivir administration); and
7. not hospitalized.

Overall, the odds of improvement in the ordinal scale were higher in the 5-day REMDESIVIR group at Day 11 when compared to those receiving only standard of care (odds ratio 1.65 [95% CI 1.09 to 2.48], p = 0.017). The odds of improvement in clinical status with the 10-day treatment group when compared to those receiving only standard of care were not statistically significant (odds ratio 1.31 [95% CI 0.88 to 1.95]). All-cause mortality at Day 28 was ≤ 2% in all treatment groups.

4. DOSAGE AND ADMINISTRATION
4.1 Testing Before Initiating and During Treatment with Remdesivir for Injection
Determine eGFR in all patients before starting Remdesivir for injection and monitor while receiving Remdesivir for injection as clinically appropriate *(see Dosage and Administration (4.3) and Use in Specific Populations (10.4, 10.5))*.

Perform hepatic laboratory testing in all patients before starting Remdesivir and while receiving Remdesivir for injection as clinically appropriate *(see Warnings and Precautions (7.2) and Use in Specific Populations (10.6))*.

Determine prothrombin time in all patients before starting Remdesivir for injection and monitor while receiving Remdesivir for injection as clinically appropriate *(see Adverse Reactions (8.1))*.

4.2 Recommended Dosage in Adults and Pediatric Patients 12 Years of Age and Older and Weighing at Least 40 kg
The recommended dosage for adults and pediatric patients 12 years of age and older and weighing at least 40 kg is a single loading dose of Remdesivir for injection 200 mg on Day 1 via intravenous infusion followed by once-daily maintenance doses of Remdesivir for injection 100 mg from Day 2 via intravenous infusion.
- The recommended treatment duration for patients not requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO) is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days for a total treatment duration of up to 10 days.
- Remdesivir for injection must be diluted prior to intravenous infusion. Refer to Dosage and Administration (2.4) for detailed preparation and administration instructions.

4.3 Renal Impairment
Remdesivir for injection is not recommended in patients with eGFR less than 30 mL per minute *(see Dosage and Administration (4.1) and Use in Specific Populations (10.5))*.

4.4 Dose Preparation and Administration
- Remdesivir for injection must be prepared and administered under the supervision of a healthcare provider.
- Remdesivir for injection must be administered via intravenous infusion only. Do not administer by any other route.
- Remdesivir for injection is available in two dosage forms:
- Remdesivir for injection for injection (supplied as 100 mg lyophilized powder in vial) needs to be reconstituted with Sterile Water for Injection prior to diluting in a 100 mL or 250 mL 0.9% sodium chloride infusion bag.
- Remdesivir for injection (supplied as 100 mg/20 mL [5 mg/mL] solution in vial) must be diluted in a 250 mL 0.9% sodium chloride infusion bag.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard the vial if the lyophilized powder or solution is discolored or contains particulate matter. Prior to dilution in a 0.9% sodium chloride infusion bag, reconstituted Remdesivir for injection and Remdesivir for injection solution should be a clear, colorless to yellow solution, free of visible particles.
- Prepare diluted solution under aseptic conditions and on same day as administration.

Remdesivir for injection for Injection (Supplied as 100 mg Lyophilized Powder in Vial)

Reconstitution Instructions
Remove the required number of single-dose vial(s) from storage. For each vial:
- Aseptically reconstitute Remdesivir for injection lyophilized powder by adding 19 mL of Sterile Water for Injection using a suitably sized syringe and needle per vial.
- Only use Sterile Water for Injection to reconstitute Remdesivir for injection lyophilized powder.
- 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. Discard the vial if the contents are not completely dissolved.
- Following reconstitution, each vial contains 100 mg/20 mL (5 mg/mL) of remdesivir solution.
- Use reconstituted product immediately to prepare the diluted drug product *(see Dosage and Administration (4.5))*.

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 intravenous medication immediately after preparation when possible.
- Reconstituted Remdesivir for injection, containing 100 mg/20 mL remdesivir solution, must be further diluted in either a 100 mL or 250 mL 0.9% sodium chloride infusion bag. Refer to Table 3 for instructions.

Table 3 Recommended Dilution Instructions—Reconstituted Remdesivir for Injection Lyophilized Powder

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

- Withdraw and discard the required volume of 0.9% sodium chloride from the bag following instructions in Table 1, using an appropriately sized syringe and needle.
- Withdraw the required volume of reconstituted Remdesivir for injection from the Remdesivir for injection vial following instructions in Table 1, using an appropriately sized syringe. Discard any unused portion remaining in the reconstituted vial.
- Transfer the required volume of reconstituted Remdesivir for injection to the elected infusion bag.
- Gently invert the bag 20 times to mix the solution in the bag. Do not shake.
- The prepared infusion solution is stable for 24 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

Administration Instructions
Do not administer the prepared diluted solution simultaneously with any other medication. The compatibility of Remdesivir injection with intravenous solutions and medications other than 0.9% sodium chloride injection, USP is not known. Administer Remdesivir for injection via intravenous infusion over 30 to 120 minutes.

Administer the diluted solution with the infusion rate described in Table 4.

Table 4 Recommended Rate of Infusion—Diluted Remdesivir for Injection Lyophilized Powder in Adults and Pediatric Patients 12 Years of Age and Older and Weighing 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

Remdesivir Injection (Supplied as 100 mg/20 mL [5 mg/mL] Solution in Vial)

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 intravenous medication immediately after preparation when possible.
- Remove the required number of single-dose vial(s) from storage. Each vial contains 100 mg/20 mL of remdesivir. For each vial:
- Equilibrate to room temperature (20°C to 25°C [68°F to 77°F]). Sealed vials can be stored up to 12 hours at room temperature prior to dilution.
- Inspect the vial to ensure the container closure is free from defects and the solution is free of particulate matter.
- Remdesivir injection must be diluted in an infusion bag containing 250 mL of 0.9% sodium chloride only. Refer to Table 5 for instructions.

Table 5 Recommended Dilution Instructions— Remdesivir Injection (Supplied as Solution in Vial)

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

- Withdraw and discard the required volume of 0.9% sodium chloride from the bag following instructions in Table 3, using an appropriately sized syringe and needle.
- Withdraw the required volume of Remdesivir injection from the Remdesivir vial following instructions in Table 3, using an appropriately sized syringe.
- Pull the syringe plunger rod back to fill the syringe with approximately 10 mL of air.
- Inject the air into the Remdesivir injection vial above the level of the solution.
- Invert the vial and withdraw the required volume of Remdesivir injection solution into the syringe. The last 5 mL of solution requires more force to withdraw.
- Transfer the required volume of Remdesivir injection to the infusion bag.

Leaflet size: 220 x 420 mm
Printing Colour: **BLACK**
Die cut:

- Gently invert the bag 20 times to mix the solution in the bag. Do not shake.
- The prepared infusion solution is stable for 24 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

Administration Instructions

Do not administer the prepared diluted solution simultaneously with any other medication. The compatibility of Remdesivir injection with intravenous solutions and medications other than 0.9% sodium chloride injection, USP is not known. Administer Remdesivir via intravenous infusion over 30 to 120 minutes.

Administer the diluted solution with the infusion rate described in Table 6.

Table 6 Recommended Rate of Infusion—Diluted Remdesivir Injection Solution in Adults and Pediatric Patients 12 Years of Age and Older and Weighing 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

4.5 Storage of Prepared Dosages

Remdesivir for Injection (Supplied as Lyophilized Powder in Vial)

After reconstitution, use vials immediately to prepare diluted solution. The diluted Remdesivir solution in the infusion bags can be stored up to 24 hours at room temperature (20°C to 25°C [68°F to 77°F]) prior to administration or 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

Remdesivir Injection (Supplied as Solution in Vial)

Store Remdesivir injection after dilution in the infusion bags up to 24 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 48 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.

5 DOSAGE FORMS AND STRENGTHS

- Remdesivir for injection, 100 mg, available as a sterile, preservative-free white to off-white to yellow lyophilized powder in single-dose vial for reconstitution.
- Remdesivir injection, 100 mg/20 mL (5 mg/mL), available as a clear, colorless to yellow solution, free of visible particles in single-dose vial.

6 CONTRAINDICATIONS

Remdesivir is contraindicated in patients with a history of clinically significant hypersensitivity reactions to Remdesivir or any components of the product *(see Warnings and Precautions (7.1))*.

7 WARNINGS AND PRECAUTIONS

7.1 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, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, 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. Monitor patients under close medical supervision for hypersensitivity reactions during and following administration of Remdesivir. 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 or any components of the product *(see Contraindications (6))*.

7.2 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 up to 10 days; the transaminase elevations were mild (Grade 1) to moderate (Grade 2) in severity and resolved upon discontinuation of Remdesivir. Transaminase elevations have also been reported in patients with COVID-19 who received Remdesivir *(see Adverse Reactions (8.1))*. Because transaminase elevations have been reported as a clinical feature of COVID-19, and the incidence was similar in patients receiving placebo versus Remdesivir in clinical trials of Remdesivir, discerning the contribution of Remdesivir to transaminase elevations in patients with COVID-19 can be challenging.

Perform hepatic laboratory testing in all patients before starting Remdesivir and while receiving Remdesivir as clinically appropriate *(see Dosage and Administration (4.1) and Use in Specific Populations (10.6))*.

Consider discontinuing Remdesivir if ALT levels increase to greater than 10 times the upper limit of normal.

Discontinue Remdesivir if ALT elevation is accompanied by signs or symptoms of liver inflammation.

7.3 Risk of Reduced Antiviral Activity When Coadministered with Chloroquine Phosphate or Hydroxychloroquine Sulfate

Coadministration of Remdesivir and chloroquine phosphate or hydroxychloroquine sulfate is not recommended based on cell culture data demonstrating an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of Remdesivir *(see Drug Interactions (9) and Microbiology (1.4))*.

8 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Hypersensitivity Including Infusion-related and Anaphylactic Reactions *(see Warnings and Precautions (7.1))*
- Increased Risk of Transaminase Elevations *(see Warnings and Precautions (7.2))*

8.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of Remdesivir is based on data from three Phase 3 studies in 1,313 hospitalized adult subjects with COVID-19, from four Phase 1 studies in 131 healthy adults, and from patients with COVID-19 who received Remdesivir under the Emergency Use Authorization or in a compassionate use program.

Clinical Trials Experience in Subjects with COVID-19

NIAID ACTT-1 was a randomized, double-blind, placebo-controlled clinical trial in hospitalized subjects with mild, moderate, and severe COVID-19 treated with Remdesivir (n = 532) or placebo (n = 516) for up to 10 days. Subjects treated with Remdesivir received 200 mg on Day 1 and 100 mg once daily on subsequent days *(see Clinical Studies (3))*. The collection of adverse event data in this trial was limited to severe (Grade 3) or potentially life-threatening (Grade 4) adverse events, serious adverse events, adverse events leading to study drug discontinuation, and moderate (Grade 2) severity or higher hypersensitivity reactions. Rates of adverse reactions (≥ Grade 3), serious adverse reactions, and adverse reactions leading to treatment discontinuation are presented in Table 7.

Table 7 Summary of Adverse Reaction Rates in Subjects with Mild, Moderate, or Severe COVID-19 in NIAID ACTT-1

Types of Adverse Reactions	REMDESIVIR N = 532 n (%)	Placebo N = 516 n (%)
Adverse reactions, Grades ≥ 3	41 (8%)	46 (9%)
Serious adverse reactions	2 (0.4%)[a]	3 (0.6%)
Adverse reactions leading to treatment discontinuation	11 (2%)b	15 (3%)

a. Seizure (n = 1), infusion-related reaction (n = 1).

b. Seizure (n = 1), infusion-related reaction (n = 1), transaminases increased (n = 3), ALT increased and AST increased (n = 1), GFR decreased (n = 2), acute kidney injury (n = 3).

Study GS-US-540-5773 was a randomized, open-label clinical trial in hospitalized subjects with severe COVID-19 treated with Remdesivir for injection 200 mg on Day 1 and 100 mg once daily for 5 (n = 200) or 10 days (n = 197). Adverse reactions were reported in 33 (17%) subjects in the 5-day group and 40 (20%) subjects in the 10-day group *(see Clinical Studies (3))*. The most common adverse reactions occurring in at least 5% of subjects in either the Remdesivir 5-day or 10-day group, respectively, were nausea (5% vs 3%), AST increased (3% vs 6%), and ALT increased (2% vs 7%). Rates of anyadverse reactions, serious adverse reactions, and adverse reactions leading to treatment discontinuation are presented in Table 8.

Table 8 Summary of Adverse Reaction Rates in Subjects with Severe COVID-19 in Study 5773

Types of Adverse Reactions	Remdesivir 5 Days N = 200 n (%)	Remdesivir 10 Days N = 197 n (%)
Any adverse reaction, all Grades	33 (17%)	40 (20%)
Serious adverse reactions	3 (2%)[a]	4 (2%)[a]
Adverse reactions leading to treatment discontinuation	5 (3%)[b]	9 (5%)[b]

[a] Transaminases increased (n = 5), hepatic enzyme increased (n = 1), hypertransaminasaemia (n = 1).

[b]. Transaminases increased (n = 4), hepatic enzyme increased (n = 2), LFT increased (n = 2), hypertransaminasaemia (n = 1), ALT increased (n = 1), ALT increased and AST increased (n = 2), injection site erythema (n = 1), rash (n = 1).

Study GS-US-540-5774 was a randomized, open-label clinical trial in hospitalized subjects with moderate COVID-19 treated with REMDESIVIR 200 mg on Day 1 and 100 mg daily for 5 (n = 191) or 10 days (n = 193), or standard of care (SOC) only (n = 200) *(see Clinical Studies (3))*. Adverse reactions were reported in 36 (19%) subjects in the 5-day group and 25 (13%) subjects in the 10-day group. The most common adverse reaction occurring in at least 5% of subjects in the Remdesivir groups was nausea (7% in the 5-day group, 4% in the 10-day group). Rates of any adverse reactions, serious adverse reactions, and adverse reactions leading to treatment discontinuation are presented in Table 9.

Table 9 Summary of Adverse Reaction[a] Rates in Subjects with Moderate COVID-19 in Study 5774

Types of Adverse Reactions	Remdesivir 5 Days N = 191 n (%)	Remdesivir 10 Days N = 193 n (%)
Any adverse reaction, all Grades	36 (19%)	25 (20%)
Serious adverse reactions	1 (1%)[b]	0
Adverse reactions leading to treatment discontinuation	4(2%)c	4 (2%)c

[a] Attribution of events to study drug was not performed for the SOC group.

[b] Heart rate decreased.

[c] ALT increased (n = 2), ALT increased and AST increased (n = 1), hypertransaminasaemia (n = 1), blood alkaline phosphatase increased (n = 1), rash (n = 2), heart rate decreased (n = 1).

Less Common Adverse Reactions

Clinically significant adverse reactions that were reported in < 2% of subjects exposed to Remdesivir in clinical trials are listed below:

- Hypersensitivity reactions *(see Warnings and Precautions (7.1))*.
- Generalized seizure
- Rash

Emergency Use Authorization Experience in Patients with COVID-19

The following adverse reactions have been identified during use of Remdesivir under Emergency Use Authorization:

- General disorders and administration site conditions: Administration site extravasation
- Skin and subcutaneous tissue disorders: Rash
- Immune system disorders: Anaphylaxis, angioedema, infusion-related reactions, hypersensitivity
- Investigations: Transaminase elevations

Laboratory Abnormalities

Study GS-US-399-5505 was a Phase 1, randomized, blinded, placebo-controlled clinical trial in healthy volunteers administered Remdesivir 200 mg on Day 1 and 100 mg for either 4 days or 9 days. Mild (Grade 1, n = 8) to moderate (Grade 2, n = 1) elevations in ALT were observed in 9 of 20 subjects receiving 10 days of Remdesivir; the elevations in ALT resolved upon discontinuation of Remdesivir. No subjects (0 of 9) who received 5 days of Remdesivir had graded increases in ALT.

The frequencies of laboratory abnormalities (Grades 3-4) occurring in at least 3% of subjects with COVID-19 receiving Remdesivir in Trials NIAID ACTT-1, 5773, and 5774 are presented in Table 10, Table 11, and Table 12, respectively.

Table 10 Laboratory Abnormalities (Grades 3-4) Reported in 3% of Subjects Receiving Remdesivir in NIAID ACTT-1

Laboratory Parameter Abnormality[a]	Remdesivir 10 Days N = 532	Placebo N = 516
ALT increased	3%	6%
AST increased	6%	8%
Bilirubin increased	2%	5%
Creatinine clearance decreased[b]	18%	20%
Creatinine increased	15%	16%
eGFR decreased	18%	24%
Glucose increased	12%	13%
Hemoglobin decreased	15%	22%
Lymphocytes decreased	11%	18%
Prothrombin time increased	9%	4%

a. Frequencies are based on treatment-emergent laboratory abnormalities. Graded per Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017.

b. Based on the Cockcroft-Gault formula.

Table 11 Laboratory Abnormalities (Grades 3-4) Reported in 3% of Subjects Receiving Remdesivir in Trial 5773

Laboratory Parameter Abnormality[a]	Remdesivir 5 Days N = 200	Remdesivir 10 Days N = 197
ALT increased	6%	8%
AST increased	7%	6%
Creatinine clearance decreased[b]	10%	19%
Creatinine increased	5%	15%
Glucose increased	11%	8%
Hemoglobin decreased	6%	8%

a. Frequencies are based on treatment-emergent laboratory abnormalities. Graded per Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017.

b. Based on the Cockcroft-Gault formula.

Table 12 Laboratory Abnormalities (Grades 3-4) Reported in 3% of Subjects Receiving Remdesivir in Trial 5774

Laboratory Parameter Abnormality[a]	Remdesivir 5 Days N = 191	Remdesivir 10 Days N = 193	SOC N = 200
ALT increased	2%	3%	8%
Creatinine clearance decreased[b]	2%	5%	8%
Glucose increased	4%	3%	2%
Hemoglobin decreased	3%	1%	6%

SOC = Standard of care.

a. Frequencies are based on treatment-emergent laboratory abnormalities. Graded per Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017.

b. Based on the Cockcroft-Gault formula.

9. DRUG INTERACTIONS

Due to antagonism observed in cell culture, concomitant use of Remdesivir with chloroquine phosphate or hydroxychloroquine sulfate is not recommended *(see Warnings and Precautions (7.3) and Microbiology (1.4))*.

Drug-drug interaction trials of Remdesivir and other concomitant medications have not been conducted in humans. Remdesivir and its metabolites are in vitro substrates and/or inhibitors of certain drug metabolizing enzymes and transporters. The clinical relevance of these in vitro assessments has not been established *(see Clinical Pharmacology (1))*.

10.USE IN SPECIFIC POPULATIONS

10.1 Pregnancy

Risk Summary

Available data from published case reports and compassionate use of remdesivir in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. 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) *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo-fetal risk

Pregnant women hospitalized with COVID-19 are at risk for serious morbidity and mortality.

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 times higher (rats and rabbits) 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.

10.2 Lactation

Risk Summary

There are no available data on 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 *(see Data)*. 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. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

Data

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 rats from Gestation Day 6 to Lactation Day 20. Exposures in nursing pups were approximately 1% that of maternal exposure on Lactation Day 10.

10.3 Pediatric Use

The safety and effectiveness of Remdesivir for the treatment of COVID-19 have been established in pediatric patients 12 years and older and weighing at least 40 kg. Use in this age group is based on extrapolation of pediatric efficacy from adequate and well-controlled studies in adults *(see Clinical Pharmacology (1.3) and Clinical Studies (3))*.

Clinical trials of Remdesivir included 30 adult subjects weighing 40-50 kg. The safety in this weight group was comparable to adult subjects weighing greater than 50 kg. Thirty-nine pediatric patients 12 years and older and weighing at least 40 kg received Remdesivir in a compassionate use program; the available clinical data from these patients are limited.

All pediatric patients 12 years of age and older and weighing at least 40 kg must have eGFR determined before starting Remdesivir and while receiving Remdesivir as clinically appropriate *(see Dosage and Administration (4.1, 4.3))*.

The safety and effectiveness of Remdesivir have not been established in pediatric patients younger than 12 years of age or weighing less than 40 kg.

10.4 Geriatric Use

Reported clinical experience has not identified differences in responses between the elderly and younger patients *(see Clinical Studies (3))*. No dosage adjustment is required in patients over the age of 65 years. 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.

10.5 Renal Impairment

The pharmacokinetics of Remdesivir have not been evaluated in patients with renal impairment. Patients with eGFR greater than or equal to 30 mL per minute have received Remdesivir for treatment of COVID-19 with no dose adjustment of Remdesivir *(see Clinical Studies (3))*. All patients must have an eGFR determined before starting Remdesivir and while receiving Remdesivir as clinically appropriate. Because the excipient betadex sulfobutyl ether sodium is renally cleared and accumulates in patients with decreased renal function, administration of drugs formulated with betadex sulfobutyl ether sodium (such as Remdesivir) is not recommended in patients with eGFR less than 30 mL per minute *(see Dosage and Administration (4.1, 4.3))*.

10.6 Hepatic Impairment

The pharmacokinetics of Remdesivir have not been evaluated in patients with hepatic impairment.

Perform hepatic laboratory testing in all patients before starting Remdesivir and while receiving Remdesivir as clinically appropriate *(see Dosage and Administration (4.1) and Warnings and Precautions (7.2))*.

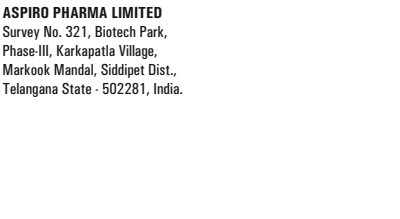
11 OVERDOSAGE

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.

PRODUCT DESCRIPTION

White to off white to yellow lyophilized cake powder Remdesivir is a nucleoside ribonucleic acid (RNA) polymerase inhibitor.

Remdesivir contains remdesivir, a SARS-CoV-2 nucleotide analog 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:



Remdesivir for injection contains 100 mg of remdesivir as a sterile, preservative-free lyophilized white to off-white to yellow powder in a single-dose clear glass vial. It requires reconstitution and then further dilution prior to administration by intravenous infusion *(see Dosage and Administration (4.4))*. The inactive ingredients are 3 g betadex sulfobutyl ether sodium and may include hydrochloric acid and/or sodium hydroxide for pH adjustment.

Remdesivir injection contains 100 mg/20 mL (5 mg/mL) of remdesivir as a sterile, preservative-free, clear, colorless to yellow solution in a single-dose clear glass vial. It requires dilution prior to administration by intravenous infusion *(see Dosage and Administration (4.4))*. The inactive ingredients are 6 g betadex sulfobutyl ether sodium, Water for Injection, USP, and may include hydrochloric acid and/or sodium hydroxide for pH adjustment.

12 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

Remdesivir for injection: 100 mg (NDC 61958-2901-2), is supplied as a single-dose vial containing a sterile, preservative-free white to off-white to yellow lyophilized powder. It requires reconstitution and further dilution prior to administration by intravenous infusion *(see Dosage and Administration (4.4))*. Discard unused portion. The container closure is not made with natural rubber latex.

Storage and Handling

Do not reuse or save reconstituted or diluted Remdesivir for future use. These products contain no preservative; therefore, partially used vials should be discarded *(see Dosage and Administration (4.5))*.

Remdesivir for Injection

Store Remdesivir for injection, 100 mg vials below 30°C (below 86°F) until required for use.

After reconstitution, use vials immediately to prepare diluted solution. Dilute the reconstituted solution in 0.9% sodium chloride injection, USP within the same day as administration. The diluted Remdesivir solution in the infusion bags 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]).

PACK STYLE:

USP Type I clear and colorless glass vial with gray rubber stopper and violet flip-off seal (Box of 1 x 6's).

Storage Condition:

Store at temperatures not exceeding 30°C until time of use.

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

ADR REPORTING STATEMENT:

For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph

Please seek medical attention immediately at the first sign of any adverse drug reaction

Keep out of reach of children

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

Registration Number: DR-XY47634

Date of First Authorization: December 2021

Date of Revision of Package Insert:

Manufactured for:

HETERO LABS LIMITED
#7-2-A2, Hetero Corporate, Industrial Estate,
Sanathnagar, Hyderabad-500018, Telangana State, India.

Imported and Distributed by:

CAMBER PHARMACEUTICALS, INC.
Unit 503-A ITC Bldg., 337 Sen.
Gil Puyat Avenue, Bel-Air, Makati City,
Philippines.

Manufactured by:

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