REMDESIVIR

INDICATION AND USAGE

REMDESIVIR 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 should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care.

DOSAGE AND ADMINISTRATION

#Testing Before Initiating and During Treatment with REMDESIVIR

- Determine Renal function test in all patients before starting REMDESIVIR and monitor while receiving REMDESIVIR as Clinically appropriate
- Perform hepatic laboratory testing in all patients before starting REMDESIVIR and while receiving REMDESIVIR as clinically appropriate
- Determine prothrombin time in all patients before starting REMDESIVIR and monitor while receiving REMDESIVIR as clinically appropriate

Recommended Dosage in Adults and Pediatric Patients 12 Years of Age and Older and Weighing at Least 40 kg

Single loading dose of 200 mg on Day 1 via intravenous infusion followed by once-daily maintenance doses of 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.
- The recommended total treatment duration for patients requiring invasive mechanical ventilation And/or ECMO is 10 days.
- REMDESIVIR must be diluted prior to intravenous infusion.

Renal impairment

REMDESIVIR is not recommended in patients with eGFR less than 30 mL per minute

#Dose preparation and administration

- REMDESIVIR must be prepared and administered under the supervision of a healthcare provider.
- REMDESIVIR must be administered via intravenous infusion only. Do not administer by any other means.

Dosage forms

REMDESIVIR is available as

- REMDESIVIR 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
- REMDESIVIR 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 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 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

Reconstitution instructions

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

- Aseptically reconstitute REMDESIVIR 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 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.

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.
- 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) .

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.

#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 tthere 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 uviato 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.
- 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.

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]). bags can be stored up to 24 hours at room temperature (20°C to 25°C [68°F to 77°F]

PHARMACOLOGY

Mechanism of action

REMDESIVIR is an antiviral drug with activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

#Pharmacodynamics

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

Pharmacokinetics

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 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.

Drug interactions

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.

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 corporation into the template viral RNA as a result of readthrough 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.

CONTRAINDICATIONS

REMDESIVIR is contraindicated in patients with a history of clinically significant hypersensitivity reactions to REMDESIVIR or any components of the product .

WARNINGS AND PRECAUTIONS

#Hypersensitivity reactions including infusion related and anaphylactic

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.

Increased risk of transaminase reactions

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 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.

•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.

Reduced antiviral activity when coadministered with chloroquine phosphate or Hydroxychloroquine sulphate

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

ADVERSE REACTIONS

- Hypersensitivity Including Infusion-related and Anaphylactic Reactions
- Increased Risk of Transaminase Elevation.

Clinical trial 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 *].*

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 5. and adverse reactions leading to treatment discontinuation are presented in Table 5.

Table 5 Summary of Adverse Reaction Rates in Subjects with Mild, Moderate, or Severe COVID-19 in NIAID ACTT-1

Types of Adverse Reactions	VEKLURY 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 VEKLURY 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 (14)]*. The most common adverse reactions occurring in at least 5% of subjects in either the VEKLURY 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 any

Table 6 Summary of Adverse Reaction Rates in Subjects with Severe COVID-19 in Study 5773

Types of Adverse Reactions	VEKLURY 5 Days N=200 n (%)	VEKLURY 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 VEKLURY 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 (14)]*. 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 VEKLURY 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 7.

Table 7 Summary of Adverse Reaction[a] Rates in Subjects with Moderate COVID-19 in Study 5774

Types of Adverse Reactions	VEKLURY 5 Days N=191 n (%)	VEKLURY 10 Days N=193 n (%)
Any adverse reaction, all Grades	36 (19%)	25 (13%)
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 VEKLURY in clinical trials are listed below:

- Hypersensitivity reactions .
- 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 8, Table 9, and Table 10, respectively.

Table 8 Laboratory Abnormalities (Grades 3-4) Reported in ≥3% of Subjects Receiving VEKLURY in NIAID ACTT-1

Laboratory Parameter Abnormality[a]	VEKLURY 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 9 Laboratory Abnormalities (Grades 3-4) Reported in ≥3% of Subjects Receiving VEKLURY in Trial 5773

Laboratory Parameter Abnormality[a]	VEKLURY 5 Days N=200	VEKLURY 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 10 Laboratory Abnormalities (Grades 3-4) Reported in ≥3% of Subjects Receiving VEKLURY in Trial 5774

Laboratory Parameter Abnormality[a]	VEKLURY 5 Days N=191	VEKLURY 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.

#DRUG INTERACTIONS

Due to antagonism observed in cell culture, concomitant use of REMDESIVIR with chloroquine phosphate or hydroxychloroquine sulfate is not recommended

Drug-drug interaction trials of REMDESIVIR and other concomitant medications have not been conducted in humans

#USE IN SPECIFIC POPULATIONS

#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.

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)

#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.

developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for REMDESIVIR and any potential adverse effects on the breastfed child from remdesivir or from the underlying maternal condition.

#Pediatric Use

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.

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 VEKLURY as clinically appropriate.

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

#Geriatric Use

Reported clinical experience has not identified differences in responses between the elderly and younger patients. 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.

#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 treatment of COVID-19 with no dose adjustment of REMDESIVIR.

#Hepatic Impairment 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.

*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.

*DESCRIPTION

REMDESIVIR

*A SARS-CoV-2 nucleotide analog RNA polymerase inhibitor.

*chemical name for remdesivir is 2-ethylbutyl N-{(S)-[2-C-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7yl)2,5anhydro-d-altrononitril-6-O-yl]phenoxyphosphoryl}-L-alaninate. It has a molecular formula of C27H35N6O8P and a molecular weight of 602.6 g/mol.

* Injection contains 100 mg of remdesivir as a sterile, preservative-free lyophilized white to offwhite to yellow powder in a single-dose clear glass vial. It requires reconstitution and then further dilution prior to administration by intravenous infusion.

The inactive ingredients are 3 g betadex sulfobutyl ether sodium and may include hydrochloric acid and/or sodium hydroxide for pH adjustment.

NONCLINICAL TOXICOLOGY

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.

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.

HOW SUPPLIED/STORAGE AND HANDLING

#How Supplied

REMDESIVIR for injection: 100 mg, is supplied as a single-dose vial containing a Sterile, preservativefree white to off-white to yellow lyophilized powder. It requires reconstitution and

further dilution prior to administration by intravenous infusion .Discard unused portion. The container closure is not made with natural rubber latex.

REMDESIVIR injection: 100 mg/20 mL (5 mg/mL) , is supplied as a single-dose vial containing a sterile, preservative-free, clear, colorless to yellow aqueous-based solution. It requires Dilution prior to administration by intravenous infusion. 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

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 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

Store REMDESIVIR injection vials at refrigerated temperature (2°C to 8°C [36°F to 46°F]) until required for use.

Dilute within the same day as administration. Prior to dilution, equilibrate REMDESIVIR injection 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. Store REMDESIVIR injection after dilution in the infusion bags for no more than 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]).

PATIENT COUNSELING INFORMATION

#Hypersensitivity Reactions

Inform patients that hypersensitivity reactions have been seen in patients receiving REMDESIVIR during and after infusion. Advise patients to inform their healthcare provider if they experience any of the following: changes in heart rate; fever; shortness of breath, wheezing; swelling of the lips, face, or throat; rash; nausea; sweating; or shivering .

#Increased Risk of Transaminase Elevations

Inform patients that REMDESIVIR may increase the risk of hepatic laboratory abnormalities. Advise patients to alert their healthcare provider immediately if they experience any symptoms of liver inflammation.

#Drug Interactions

Inform patients that REMDESIVIR may interact with other drugs. Advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including chloroquine phosphate or hydroxychloroquine sulfate.

#Pregnancy

Inform patients to notify their healthcare provider immediately in the event of a pregnancy [see Use in specific Populations .

#Lactation

Inform mothers that it is not known whether REMDESIVIR can pass into their breast milk

CURRENT STATUS

 # Indications by ICMR

EUA/Off label use (based on limited available evidence and only in specific circumstances):

Remdesivir (EUA) may be considered ONLY in patients with

- Moderate to severe disease (requiring SUPPLEMENTAL OXYGEN), AND
- No renal or hepatic dysfunction (eGFR <30 ml/min/m2; AST/ALT >5 times ULN (Not an
- Absolute contradiction), AND
- Who are within 10 days of onset of symptom/s.

❖ **Recommended dose**: 200 mg IV on day 1 f/b 100 mg IV OD for next 4 days.

Not to be used in patients who are NOT on oxygen support or in home settings

#ISSUES

Efiicacy

Remdesivir was originally developed to treat hepatitis C but was given emergency use authorisation (EUA) by FDA after initial trials.Still the efficacy of drug is still in question. On one hand therebare trials like NIAD ACTT-1 trials, which showed that the drug led to a "fiveday faster recovery in hospitalized patients overall, and a seven-day faster recovery in people who required oxygen support at baseline, compared with placebo."

On other hand WHO noted "There is currently no evidence that Remdesivir improves survival and other outcomes in these patients," citing detailed studies it sponsored. "The evidence suggested no important effect on mortality, need for mechanical ventilation, time to clinical improvement, and other patient-important outcomes."

So there are possibilities to drop the drug from COVID treatment recommendations if its costeffectiveness ratio doesn't meet the required standards.

Pricing

With increasing demand of drug the prices began to hike and the government had to stepped in to slash down remdesivir prices. Alll district officials were directed to ensure that every injection is used judiciously and cap the prices to check illegal hoarding.

The revised price rate in India are as follow:-

S.No.	Name of the Company	Brand Name	Earlier MRP (Rs.)	Revised MRP (Rs.)
1.	Cadila Healthcare Ltd	REMDAC	2,800/-	899/-
2.	Syngene International Ltd (Biocon Biologics India)	RemWin	3,950/-	2,450/-
3.	Dr. Reddy's Laboratories Ltd	REDYX	5,400/-	2,700/-
4.	Cipla Ltd	CIPREMI	4,000/-	3,000/-
5.	Mylan Pharmaceuticals Pvt Ltd	DESREM	4,800/-	3,400/-
6.	Jubilant Generics Ltd	JUBI-R	4,700/-	3,400/-
7.	Hetero Healthcare Ltd	COVIFOR	5,400/-	3,490/-

REFERENCE

Remdesivir – US Food and Drug Administration by JOHN J FARLEY, 22-Oct-2020

https://www.google.co.in/url?sa=t&source=web&rct=j&url=https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214787Orig1s000lbl.pdf&ved=2ahUKEwjUiK7hqfvwAhVFxzgGHbnAAU8Q6sMDMAB6BAgJEAc&usg=AOvVaw0tJuQ60K1OLGU9dHiw8DASe