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Remdesivir for Injection 100 mg/vial

DESREM™

Lyophilized Powder for Injection for IV Infusion

1. INDICATION

For treatment of suspected or laboratory confirmed corona virus disease 2019 (COVID-19) in adults and children hospitalised with severe disease.

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.
- Adult and pediatric patients (>28 days old) must have an eGFR determined and full-term neonates (≥7 days to ≤28 days old) must have serum creatinine 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 Adult Patients

- The dose of the drug for adults 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 for 4 days.
- 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 (2.7)]*.
- Extension of administration of drug beyond 5 days to 10 days is not recommended.

All adult patients must have creatinine clearance determined before dosing *[see Dosage and Administration (2.5)]*.

Hepatic laboratory testing should be performed in all patients prior to starting remdesivir and daily while receiving remdesivir dosing *[see Dosage and Administration (2.6)]*.

2.3 Pediatric Patients

Dosing in pediatric patients is based upon physiologically based (PBPK) modeling and simulation of pharmacokinetic data from healthy adult subjects.

The recommended pediatric dose for pediatric patients weighing between 3.5 kg and <40 kg should be calculated using the mg/kg dose according to the patient's weight *[see Dosage and Administration (2.8)]*:

- The dose of the drug for paediatric patients weighing more than 40 kg should be a single dose of 200mg infused intravenously over 30-120 minutes on day 1 followed by once daily maintenance dose of 100mg, infused intravenously over 30-120 minutes for 4 days.
- The dose for paediatric patients with body weight between 3.5 kg and less than 40 kg should be a single dose of 5 mg/kg infused intravenously over 30-120 minutes on day 1 followed by once daily maintenance dose of 2.5 mg/kg, infused intravenously over 30-120 minutes for 4 days.
- Extension of administration of drug beyond 5 days to 10 days is not recommended.

Pediatric patients (>28 days old) must have an eGFR determined and full-term neonates (≥7 days to ≤28 days old) must have serum creatinine determined before dosing *[see Dosage and Administration (2.5)]*.

Hepatic laboratory testing should be performed in all patients prior to starting remdesivir and daily while receiving remdesivir dosing *[see Dosage and Administration (2.6)]*.

2.4 Pregnancy

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

2.5 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.

Because the excipient sulfobutylether-β-cyclodextrin sodium salt (SBECD) is renally cleared and accumulates in patients with decreased renal function, administration of drugs formulated with SBECD (such as remdesivir) is not recommended in adults and pediatric patients (>28 days old) with eGFR less than 30 mL per minute or in full-term neonates (≥7 days and ≤28 days old) with serum creatinine clearance ≥1 mg/dL unless the potential benefit outweighs the potential risk.

2.6 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.

2.7 Adult 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 Pediatric Patients Weighing ≥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 Pediatric Patients Weighing ≥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

2.8 Pediatric Dose Preparation and Administration
Remdesivir for Injection, 100 mg, Lyophilized Powder

For pediatric patients with body weight between 3.5 kg and <40 kg, use remdesivir for injection, 100 mg, lyophilized powder only.

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 3 and Table 4, determine the volume of 0.9% saline to withdraw from the infusion bag. Table 3 and Table 4 include the volume requirements for preparing pediatric weight-based dosing regimens at 5 mg/kg and 2.5 mg/kg, respectively.

Table 3: Recommended Remdesivir Loading Dose Dilution Instructions for Pediatric Patients Weighing 3.5 kg to <40 kg

Body weight (kg)	Pediatric loading dose for body weight <40 kg 5 mg/kg (mg)	0.9% saline infusion bag volume to be used (mL)	Volume of saline to be withdrawn and discarded from 0.9% saline infusion bag (mL)	Required volume of reconstituted remdesivir for injection (mL)
3.5	17.5	25	3.5	3.5
4	20		4	4
5	25		5	5
7.5	37.5	50	7.5	7.5
10	50		10	10
15	75	100	15	15
20	100		20	20
25	125[a]		25 (20+5)	25 (20+5)
30	150[a]		30 (20+10)	30 (20+10)
35	175[a]	250	35 (20+15)	35 (20+15)

[a] These doses require the use of 2 vials of remdesivir for Injection.

Table 4: Recommended Remdesivir Maintenance Dose Dilution Instructions for Pediatric Patients Weighing 3.5 kg to <40 kg

Body weight (kg)	Pediatric maintenance dose for body weight <40 kg 2.5 mg/kg (mg)	0.9% saline infusion bag volume to be used (mL)	Volume of saline to be withdrawn and discarded from 0.9% saline infusion bag (mL)	Required volume of reconstituted remdesivir for injection (mL)
3.5	8.8	25	0	1.8
4	10		0	2
5	12.5		2.5	2.5
7.5	18.8	50	3.8	3.8
10	25		5	5
15	37.5		7.5	7.5
20	50		10	10
25	62.5	100	12.5	12.5
30	75		15	15
35	87.5		17.5	17.5

- 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 3 or 4. 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) (including any time before dilution into intravenous infusion fluids).

Administration Instructions

The prepared diluted solution should not be administered simultaneously with any other medication. The compatibility of remdesivir injection with IV solutions and medications other than saline is not known.

Administer the diluted solution with the infusion rate described in Table 5.

Table 5: Recommended Rate of Infusion for Pediatric Patients Weighing 3.5 kg to <40 kg

Infusion bag volume	Infusion time	Rate of infusion[a]
100 mL	30 min	3.33 mL/min
	60 min	1.67 mL/min
	120 min	0.83 mL/min
50 mL	30 min	1.67 mL/min
	60 min	0.83 mL/min
	120 min	0.42 mL/min
25 mL	30 min	0.83 mL/min
	60 min	0.42 mL/min
	120 min	0.21 mL/min

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

2.9 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 Infusion-Related Reactions

Infusion-related reactions have been observed during, and/or been temporally associated with, administration of remdesivir. Signs and symptoms may include hypotension, nausea, vomiting, diaphoresis, and shivering. If signs and symptoms of a clinically significant infusion reaction occur, immediately discontinue administration of remdesivir and initiate appropriate treatment. The use of remdesivir is contraindicated in patients with known hypersensitivity to remdesivir.

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. In healthy volunteers who received up to 150 mg daily for 14 days, alanine aminotransferase (ALT) elevations were observed in the majority of patients, including elevations to up to 10 times baseline values in one subject without evidence of clinical hepatitis; no ≥ Grade 3 adverse events were observed. Transaminase elevations have also been reported in patients with COVID-19 who received remdesivir, including one patient with ALT elevation up to 20 times the upper limit of normal. 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:
  - o 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
  - o ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR
- Risk of Reduced Antiviral Activity When Coadministered with Chloroquine or Hydroxychloroquine Coadministration of remdesivir and chloroquine phosphate or hydroxychloroquine sulfate is not recommended based on in vitro data demonstrating an antagonistic effect of chloroquine on the intracellular.

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

In a randomized, open-label clinical trial (Study GS-US-540-5773) of remdesivir in 397 subjects with severe COVID-19 treated with remdesivir for 5 (n=200) or 10 days (n=197), adverse events were reported in 71% and 74% of subjects, respectively, serious adverse events were reported in 21% and 35% of subjects, respectively, and Grade ≥3 adverse events were reported in 31% and 43% of subjects, respectively. Nine (5%) 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

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 6.

Table 6: 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)

Experience in Patients with Ebola Virus Disease

In the PALM study, 175 subjects with Ebola virus disease were randomized to receive remdesivir. No SAEs of transaminase elevations or hepatic events were reported.

Twenty subjects received remdesivir in a double-blinded, randomized, viral persistence study in the semen of Ebola survivors. Preliminary results indicated there were no SAEs for transaminase elevations.

FRONT SIDE

ARTWORK DETAIL LABEL

Product	**DESREM - Remdesivir for Injection 100 mg/vial**				
Buyer/Country	Mylan / ROW (General Export)	Component	Pack Insert		
Dimension	**420 x 290 mm**			Pack	--
New Item Code	**1xxxxxx**	Old Item Code	NA		
Colour Shades	Black			No. of Colours	1

Change Control No.	NA
Design/Style	Front & Back Printing. To be supplied in folded size of 55 x 35 mm. Brand name facing front after final folding.
Substrate	40/45 GSM Paper.
Special Instructions	Printing clarity to be clear & sharp.
Autocartonator Requirements	NA

Caution to the printer: Before processing, please ensure that the ARTWORK received for printing is exactly in line with APPROVED ARTWORK provided to you. In case of any FONTS/DESIGN are Mis-matching with the APPROVED ARTWORK, please inform PDC for further action. **DO NOT MAKE ANY CHANGE TO THE ARTWORK WITHOUT WRITTEN INSTRUCTIONS FROM PDC.**

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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. 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.

For pediatric patients with body weight between 3.5 kg to <40 kg, use remdesivir for injection, 100 mg, lyophilized powder only *[see Dosage and Administration (2.3 and 2.8)]*.

Pediatric patients (>28 days) must have creatinine clearance determined and fullterm neonates (≥7 days to ≤28 days) must have serum creatinine determined before dosing. Pediatric patients should be monitored for renal function and consideration given for stopping therapy in the setting of substantial decline. The use of remdesivir is not recommended in pediatric patients (>28 days old) with eGFR <30 mL/min and in full-term neonates (≥7 days and ≤28 days old) with serum creatinine clearance ≥1 mg/dL unless the potential benefit outweighs the potential risk.

Because the excipient sulfobutylether-β-cyclodextrin sodium salt (SBECD) is renally cleared and accumulates in patients with decreased renal function, administration of drugs formulated with SBECD (such as remdesivir) is not recommended in adults and pediatric patients (>28 days old) with eGFR less than 30 mL per minute or in full-term neonates (≥7 days and ≤28 days old) with serum creatinine clearance ≥1 mg/dL unless the potential benefit outweighs the potential risk.

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.

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.

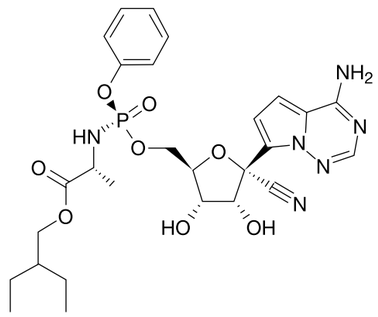
10. OVERDOSAGE

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.

- The pharmacokinetics of remdesivir and metabolites have not been in evaluated in patients with COVID-19
- Following single-dose, 2-hour IV administration of remdesivir solution formulation at doses ranging from 3 to 225 mg, remdesivir exhibited a linear PK profile.
- Following single-dose, 2-hour IV administration of remdesivir at doses of 75 and 150 mg, both the lyophilized and solution formulations provided comparable PK parameters (AUC_{inf}, AUC_{last}, and C_{max}), indicating similar formulation performance.
- Remdesivir 75 mg lyophilized formulation administered IV over 30 minutes provided similar peripheral blood mononuclear cell (PBMC) exposure of the active triphosphate metabolite GS-443902 as remdesivir 150 mg lyophilized formulation administered IV over 2 hours.
- Following a single 150 mg intravenous dose of [^{14}C]-remdesivir, mean total recovery of the dose was 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 adult and pediatric patients (>28 days old) with eGFR less than 30 mL per minute or in full-term neonates (≥7 days and ≤28 days old) with serum creatinine clearance ≥1 mg/dL unless the potential benefit outweighs the potential risk.

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

The nonclinical toxicology profile of remdesivir has been characterized through the conduct of repeat-dose studies in rats and cynomolgus monkeys with once daily dosing up to 4 weeks in duration, studies to evaluate the genotoxic potential of the compound, a battery of reproduction and developmental studies (fertility in rats, embryofetal development in rats and rabbits, and a pre- and postdevelopmental study in rats), and a hemolysis/blood compatibility study. Following repeated dosing in rats and monkeys, the kidney was identified as the target organ. In both species, clinical chemistry, urinalysis, and/or urinary biomarkers were early predictors of the observed kidney changes.

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 a compassionate use program in patients with COVID-19, and from clinical trials in healthy volunteers and subjects with Ebola virus disease.

Clinical Trials in Subjects with COVID-19

NIAID ACTT-1 Study

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. The trial enrolled 1063 hospitalized patients in a 1:1 manner to receive remdesivir or placebo. The primary clinical endpoint was time to recovery within 28 days after randomization. In a preliminary analysis of the primary endpoint performed after 606 recoveries were attained, the median time to recovery was 11 days in the remdesivir group compared to 15 days in the placebo group (hazard ratio 1.31; 95% CI 1.12 to 1.54, p<0.001). Mortality was 8.0% for the remdesivir group versus 11.6% for the placebo group (p=0.059).

Study GS-US-540-5773

A randomized, open-label multi-center clinical trial (Study GS-US-540-5773) of patients with severe COVID-19 compared 197 adult patients who received remdesivir 200 mg once daily followed by remdesivir 100 mg once daily for 9 days (for a total of 10 days of intravenously administered therapy) with 200 adult patients who received remdesivir 200 mg once daily followed by remdesivir 100 mg for 4 days (for a total of 5 days of intravenously administered therapy), plus standard of care. The primary clinical endpoint was clinical status assessed by a 7-point ordinal scale at Day 14 after randomization. The study suggested that patients receiving a 10-day treatment course of remdesivir had similar improvement in clinical status compared with those receiving a 5-day treatment course (10-to-5 day odds ratio: 0.76; 95% confidence interval [CI] 0.51 to 1.13] on Day 14).

Clinical improvement was defined as an improvement of two or more points from baseline on a predefined 7-point scale, ranging from hospital discharge to increasing levels of oxygen support to death. Patients achieved clinical recovery if they no longer required oxygen support or were discharged from the hospital.

The time to clinical improvement for 50% of patients was 10 days in the 5-day treatment group and 11 days in the 10-day treatment group. 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.

Compassionate Use Program in Patients with COVID-19

Remdesivir has been provided through a compassionate use multi-center, openlabel program to over 1,200 adult patients with confirmed SARS-CoV-2 infection by polymerase chain reaction (PCR) and manifestations of severe disease. In addition, remdesivir has been provided to 76 pediatric patients <18 years of age and 96 pregnant women through the compassionate use program.

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

Clinical Studies in Healthy Adults

Remdesivir was evaluated in four Phase 1 studies in 138 healthy adult volunteers

(Studies GS-US-399-1812, GS-US-399-1954, GS-US-399-4231, and GS-US399-5505). In these studies, transient graded elevations in ALT and AST were observed at repeated once-daily doses of remdesivir.

Clinical Study in Subjects with Ebola Virus Disease

Supportive safety data are provided from the PALM study, a Phase 2/3, openlabel, randomized, parallel group study to assess the safety and efficacy of investigational treatments, including remdesivir, in patients with Ebola virus disease. 175 patients were randomized to receive remdesivir. A total of 9 SAEs judged by the site investigator as not related to underlying Ebola virus disease were reported for participants receiving remdesivir. Of these, an event of hypotension, which occurred during administration of the loading dose and led to fatal cardiac arrest, was considered related to remdesivir. The independent pharmacovigilance committee noted that the death could not be readily distinguished from underlying fulminant Ebola virus disease.

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.

POM | Schedule 2 **PP**

For further information write to:
ProductSafety@mylan.com

Mylan

Manufactured by:
Mylan Laboratories Limited
[Specialty Formulation Facility],
Bangalore - 560 105, India.

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BACK SIDE

ARTWORK DETAIL LABEL

Product	**DESREM - Remdesivir for Injection 100 mg/vial**				
Buyer/Country	Mylan / ROW (General Export)	Component	Pack Insert		
Dimension	**420 x 290 mm**			Pack	--
New Item Code	**1xxxxxx**	Old Item Code	NA		
Colour Shades	Black			No. of Colours	1

Change Control No.	NA
Design/Style	Front & Back Printing. To be supplied in folded size of 55 x 35 mm. Brand name facing front after final folding.
Substrate	40/45 GSM Paper.
Special Instructions	Printing clarity to be clear & sharp.
Autocartonator Requirements	NA
Caution to the printer: Before processing, please ensure that the ARTWORK received for printing is exactly in line with APPROVED ARTWORK provided to you. In case of any FONTS/DESIGN are Mis-matching with the APPROVED ARTWORK, please inform PDC for further action. **DO NOT MAKE ANY CHANGE TO THE ARTWORK WITHOUT WRITTEN INSTRUCTIONS FROM PDC.**	

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