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MDESTIV™
(Remdesivir)

Lyophilized Powder for Infusion 100mg

For IV use only

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

QUALITATIVE AND QUANTITATIVE COMPOSITION

MDESTIV™ Lyophilized Powder for Infusion 100mg
Each lyophilized vial contains:
Remdesivir MS..... 100mg

PHARMACEUTICAL FORM

Lyophilized powder for infusion

CLINICAL PARTICULARS

THERAPEUTIC INDICATIONS: MDESTIV™ is indicated for adults and paediatric patients (12 years of age and older and weighing at least 40kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization.
MDESTIV™ should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to in patient hospital care.

POSOLOGY AND METHOD OF ADMINISTRATION:
Testing Before Initiating and During Treatment with MDESTIV™ : Determine eGFR 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 Paediatric Patients 12 Years of Age and Older and Weighing at Least 40kg: The recommended dosage for adults and paediatric patients 12 years of age and older and weighing at least 40kg is a single loading dose of remdesivir 200mg on Day 1 via intravenous infusion followed by once-daily maintenance doses of remdesivir 100mg 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.
Elderly: No dose adjustment of remdesivir is required in patients over the age of 65 years.
Renal impairment: The pharmacokinetics of remdesivir have not been evaluated in patients with renal impairment. Patients with eGFR ≥30mL/min have received remdesivir for treatment of COVID-19 with no dose adjustment. Remdesivir should not be used in patients with eGFR <30mL/min.
Hepatic impairment: The pharmacokinetics of remdesivir have not been evaluated in patients with hepatic impairment. It is not known if dosage adjustment is appropriate in patients with hepatic impairment.
Paediatric population: The safety and efficacy of remdesivir in children under the age of 12 years and weighing <40kg have not yet been established. No data are available.

METHOD OF ADMINISTRATION: For intravenous use. Remdesivir is for administration by intravenous infusion after reconstitution and further dilution. It must not be given as an intramuscular (IM) injection.

Table 1: Recommended rate of infusion-for reconstituted and diluted Remdesivir lyophilized powder for infusion

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

CONTRAINDICATIONS: Remdesivir is contraindicated in patients with a history of clinically significant hypersensitivity reactions to remdesivir or any components of the product.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Hypersensitivity 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, vomiting, diaphoresis, and shivering. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration of remdesivir and initiate appropriate treatment.
Transaminase elevations: Have been observed in the remdesivir clinical trials, including in healthy volunteers and patients with COVID-19. Liver function should be determined in all patients prior to starting remdesivir and should be monitored while receiving it as clinically appropriate.
No clinical studies with remdesivir have been conducted in patients with hepatic impairment. Remdesivir should only be used in patients with hepatic impairment if the potential benefit outweighs the potential risk.
Remdesivir should not be initiated in patients with Alanine Aminotransferase (ALT) ≥5 times the upper limit of normal at baseline.
Remdesivir should be discontinued in patients who develop:
- ALT ≥5 times the upper limit of normal during treatment with remdesivir. It may be restarted when ALT is <5 times the upper limit of normal.

OR

ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalised ratio (INR).
Renal impairment: All patients should have eGFR determined prior to starting remdesivir and while receiving it as clinically appropriate. Remdesivir should not be used in patients with eGFR <30 mL/min.
Risk of reduced antiviral activity when coadministered with chloroquine or hydroxychloroquine: Co administration of remdesivir and chloroquine phosphate or hydroxychloroquine sulphate is not recommended based on in vitro data demonstrating an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of remdesivir.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION:
No clinical interaction studies have been performed with remdesivir. The overall potential for interactions is currently unknown; patients should remain under close observation during the days of remdesivir administration. Due to antagonism observed in vitro, concomitant use of remdesivir with chloroquine phosphate or hydroxychloroquine sulphate is not recommended.
Effects of other medicinal products on remdesivir: Strong inhibitors may result in increased remdesivir exposure. The use of strong inducers (e.g. rifampicin) may decrease plasma concentrations of remdesivir and is not recommended.
Dexamethasone is reported to be a moderate inducer of CYP3A and P-gp. Induction is dose-dependent and occurs after multiple doses. Dexamethasone is unlikely to have a clinically significant effect on remdesivir as remdesivir has a moderate-high hepatic extraction ratio, and is used for a short duration in the treatment of COVID-19.
Effects of remdesivir on other medicinal products: Remdesivir may transiently increase plasma concentrations of medicinal products that are substrates of CYP3A or OATP 1B1/1B3. No data is available, however it can be suggested that medicinal products that are substrates of CYP3A4 or substrates of OATP 1B1/1B3 should be administered at least 2 hours after remdesivir. Remdesivir induced CYP1A2 and potentially CYP3A in vitro. Co-administration of remdesivir with CYP1A2 or CYP3A4 substrates with narrow therapeutic index may lead to loss of their efficacy.
Dexamethasone is a substrate of CYP3A4 and although remdesivir inhibits CYP3A4, due to remdesivir's rapid clearance after I.V administration, remdesivir is unlikely to have a significant effect on dexamethasone exposure.

FERTILITY, PREGNANCY AND LACTATION:
Pregnancy: There are no or limited amount of data from the use of remdesivir in pregnant women. Remdesivir should not be used during pregnancy unless the clinical condition of the women requires treatment with it. Women of child-bearing potential have to use effective contraception during treatment.
Fertility: No human data on the effect of remdesivir on fertility are available.
Breast-feeding: It is unknown whether remdesivir is excreted in human milk or the effects on the breast-fed infant, or the effects on milk production. Because of the potential for viral transmission to SARS-CoV-2-negative infants and adverse reactions from the drug in breast-feeding infants, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from remdesivir therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.
Paediatric Use: The safety and effectiveness of remdesivir for the treatment of COVID-19 have been established in paediatric patients 12 years and older and weighing at least 40kg. Use in this age group is based on extrapolation of paediatric efficacy from adequate and well-controlled studies in adults.
All paediatric patients 12 years of age and older and weighing at least 40kg must have eGFR determined before starting remdesivir and while receiving remdesivir as clinically appropriate. The safety and effectiveness have not been established in paediatric patients younger than 12 years of age or weighing less than 40kg.
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 and monitoring of elderly patients, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy
EFFECTS ON ABILITY TO DRIVE AND USE MACHINES: Remdesivir is predicted to have no or negligible influence on these abilities.

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UNDESIRABLE EFFECTS: The most common adverse reaction in healthy volunteers is increased transaminases (14%). The most common adverse reaction in patients with COVID-19 is nausea (4%). The adverse reactions are listed below

- **Immune system disorder:** Hypersensitivity (rare)
- **Gastrointestinal disorder:** Nausea (common)
- **Skin & subcutaneous tissue disorder:** Rash (common)
- **Nervous system disorder:** Headache (common)
- **Hepatobiliary disorder:** Transaminase increased (very common)
- **Injuries, poisoning and procedural complications:** Infusion related reaction (rare)

OVERDOSE: 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.

PHARMACOLOGICAL PROPERTIES

PHARMACODYNAMIC PROPERTIES: Pharmacotherapeutic group: Antivirals for systemic use, direct acting antivirals, other antivirals.

MECHANISM OF ACTION: Remdesivir is an adenosine nucleotide prodrug that is metabolized within host cells to form the pharmacologically active nucleoside triphosphate metabolite. 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.

Antiviral activity: The antiviral activity of remdesivir was antagonised by chloroquine phosphate in a dose-dependent manner when the two drugs were coincubated 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: The cell culture development of SARS-CoV-2 resistance to remdesivir has not been assessed to date. No clinical data are available on the development of SARS-CoV-2 resistance to remdesivir.

PHARMACOKINETIC PROPERTIES: The pharmacokinetic properties of remdesivir has been investigated in healthy volunteers. No pharmacokinetic data is available from patients with COVID-19.

Absorption: The pharmacokinetic properties of remdesivir and the predominant circulating metabolite GS-441524 have been evaluated in healthy adult subjects. Following intravenous administration of remdesivir adult dosage regimen, peak plasma concentration was observed at end of infusion, regardless of dose level, and declined rapidly thereafter with a half-life of approximately 1 hour. Peak plasma concentrations of GS-441524 were observed at 1.5 to 2.0 hours post start of a 30 minutes infusion.

Distribution: Remdesivir is approximately 88% bound to human plasma proteins. Protein binding of GS-441524 was low (2% bound) in human plasma. After a single 150mg dose of [14C]-remdesivir in healthy subjects, the blood to plasma ratio of 14Cradioactivity was approximately 0.68 at 15 minutes from start of infusion, increased over time reaching ratio of 1.0 at 5 hours, indicating differential distribution of remdesivir and its metabolites to plasma or cellular components of blood.

Biotransformation: Remdesivir is extensively metabolized to the pharmacologically active nucleoside analog triphosphate GS-443902 (formed intracellularly). The metabolic activation pathway involves hydrolysis by esterases, which leads to the formation of the intermediate metabolite, GS-704277. The human mass balance study also indicates presence of a currently unidentified major metabolite (M27) in plasma.

Elimination: Following a single 150mg IV dose of [14C]-remdesivir, mean total recovery of the dose was 92%, consisting of approximately 74% and 18% recovered in urine and feces, respectively. The majority of the remdesivir dose recovered in urine was GS-441524 (49%), while 10% was recovered as remdesivir. These data indicate that renal clearance is the major elimination pathway for GS-441524. The median terminal half-lives of remdesivir and GS-441524 were approximately 1 and 27 hours, respectively.

Other Special Populations:

Gender, race and age: Pharmacokinetic differences for gender, race, and age have not been evaluated.

Paediatric patients: The pharmacokinetics in paediatric patients have not been evaluated.

Renal impairment: The pharmacokinetics of remdesivir and GS-441524 in renal impairment has not been evaluated. Remdesivir is not cleared unchanged in urine to any substantial extent, but its main metabolite GS-441524 is renally cleared and the metabolite levels in plasma may theoretically increase in patients with impaired renal function. Remdesivir should not be used in patients with eGFR <30 mL/min.

Hepatic impairment: The pharmacokinetics of remdesivir and GS-441524 in hepatic impairment has not been evaluated. The role of the liver in the metabolism of remdesivir is unknown.

Special Precautions for Disposal and Other handling: Prepare solution for infusion under aseptic conditions and on the same day as administration. Remdesivir should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Should either be observed, the solution should be discarded and fresh solution prepared.

Remdesivir must be reconstituted with 19mL sterile water for injections and diluted in sodium chloride 9mg/mL (0.9%) solution for injection before being administered via intravenous infusion over 30 to 120 minutes.

Preparation of Remdesivir solution for infusion: ***Reconstitution:***

- Remove the required number of single-use vial(s) from storage. For each vial:
- Aseptically reconstitute remdesivir powder for concentrate for solution for infusion by addition of 19 mL of sterile water for injections using a suitably sized syringe and needle per vial.
- Discard the vial if a vacuum does not pull the sterile water for injections 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.
- Inspect the vial to ensure the container closure is free from defects and the solution is free of particulate matter.
- Dilute immediately after reconstitution.

Dilution:

- Care should be taken 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 medicines immediately after preparation when possible.
- Using below table , determine the volume of sodium chloride 9mg/mL (0.9%) solution for injection to withdraw from the infusion bag.

Table 2: Recommended dilution instructions-Reconstituted Remdesivir lyophilized powder for infusion

Remdesivir Dose	Sodium Chloride 9mg/mL (0.9%) infusion bag volume to be used	Volume to be withdrawn and discarded from sodium chloride 9mg/mL (0.9%) infusion bag	Required Volume of reconstituted Remdesivir
200mg (2 vials)	250mL	40mL	2 x 20mL
	100mL	40mL	2 x 20mL
100mg (1 vial)	250mL	20mL	20mL
	100mL	20mL	20mL

NOTE: 100mL should be reserved for patients with severe fluid restriction, e.g. with ARDS or renal failure.

- Withdraw and discard the required volume of sodium chloride 9mg/ml from the bag using an appropriately sized syringe and needle as per Table 2
- Withdraw the required volume of reconstituted remdesivir powder for concentrate for solution for infusion using an appropriately sized syringe as per Table 2. Discard any unused portion remaining in the remdesivir vial.
- Transfer the required volume of reconstituted remdesivir powder for concentrate for solution for infusion to the selected infusion bag.
- Gently invert the bag 20 times to mix the solution in the bag. Do not shake.
- The prepared solution is stable for 4 hours at room temperature (20°C to 25°C) or 24 hours in the refrigerator (2°C to 8°C) (including any time before dilution into intravenous infusion fluids).
- After infusion is complete, flush with at least 30mL of sodium chloride 9mg/ml.

Disposal: Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

SHELF LIFE:

See expiry on the pack.

AVAILABILITY

MDESTIV™ Lyophilized Powder for Infusion 100mg in a pack of 1 vial + 2x10ml Sterile Water for Injection.

INSTRUCTIONS

Dosage: As advised by the physician.
To be sold on the prescription of registered medical practitioner.
Keep out of reach of children.
Avoid exposure to heat, light and humidity.
Store below 30°C.
Improper storage may deteriorate the medicine.

Manufactured by:
SAMI Pharmaceuticals (Pvt.) Ltd.
F-95, S.I.T.E., Karachi-Pakistan
www.samipharmapk.com
Mfg Lic. No. 000072

ایم ڈیسٹِو™ لائیوفلائیزڈ پاؤڈر برائے
(ریمڈیسیور) انفیوژن ۱۰۰ ملی گرام

خوراک: ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
صرف رجسٹرڈ ڈاکٹر کے نسخے کے مطابق فروخت کریں۔
بچوں کی پہنچ سے دور رکھیں۔
دوا کو دھوپ، گرمی اور نمی سے محفوظ ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر رکھیں
ورنہ دوا خراب ہو جائیگی۔
دوا کو نمی سے محفوظ رکھنے کے لیے اسکی اصل پیکنگ میں رکھیں۔

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