For use in Hospital/Institutional set up only

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Remdesivir for Injection Lyophilized

RemWin™ रेमविन

Rx
Remdesivir FOR INJECTION 100 mg
(Lyophilized)

1. NAME OF THE MEDICINAL PRODUCT
Remdesivir for Injection 100mg (Lyophilized)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each Vial Contains: Remdesivir ... 100 mg
Excipients q.s.

3. DOSAGE FORM AND STRENGTH
Lyophilized Powder for concentrate for solution for infusion - 100 mg

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
For the treatment of suspected or laboratory confirmed corona virus disease 2019 (COVID-19) in adults and children hospitalized with severe disease.

4.2 Posology and method of administration
Adult dose:
- The recommended dosage in adults requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO) is single loading dose of Remdesivir 200 mg on Day 1 followed by once-daily maintenance dose of Remdesivir 100 mg for 9 days.
- The recommended dosage in adults not requiring invasive mechanical ventilation and/or ECMO is a single dose of Remdesivir 200 mg on Day 1 followed by once-daily maintenance dose of Remdesivir 100 mg for 4 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days (i.e. up to a total of 10 day.)
- 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.
- The dose of the drug for adult and paediatric patients weighing more than 40 kg should be a single dose of 200 mg infused intravenously over 30 to 120 min on day 1 followed by once daily maintenance dose of 100 mg, infused intravenously over 30 to 120 min for 4 days.

Paediatric dose:
- The dose for paediatric patients with body weight between 3.5 Kg and less than 40 Kg should be single loading dose of Remdesivir 5mg/Kg IV infused over 30 to 120 mins on Day 1 followed by Remdesivir 2.5 mg/Kg IV infused over 30 to 120 min once daily for 4 days. Extension of administration of drug beyond 5 days to 10 days is not recommended.

USE IN SPECIAL POPULATION
Hepatic Impairment
Use of drug in patient 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. Hepatic laboratory testing should be performed in all patients prior to starting Remdesivir and daily while receiving Remdesivir.

Renal Impairment
The pharmacokinetics of Remdesivir has not been evaluated in patients with renal impairmant. 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 with eGFR<30mL/min.
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. Remdesivir is not recommended in adult and paediatric patients (>28 days old) with eGFR less than 30 mL/min or in full-term neonates (≥7 days to ≤28 days old) with serum creatinine greater than or equal to 1 mg/dL unless the potential benefit outweighs the potential risk.

Geriatric patients
The pharmacokinetics of Remdesivir has not bean evaluated in patients aged >65 year. 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.

Method of administration
Intravenous use
Remdesivir should be administered as an intravenous infusion adminisitered over a 30 to 120 minutes period.

If an anaphylactic reaction occurs, the infusion should be discontinued, appropriate medical therapies should be administered and treatment with Remdesivir should be discontinued.

Reconstitution Instructions
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.
- 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 discolouration 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 concentrate for solution for infusion

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	2x20 ml
	100 ml	40 ml	2x20 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 madications 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 Adult 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

4.3 Contraindications
Remdesivir is contraindicated in patients with known hypersensitivity to any ingredient of Remdesivir.

4.4 Special warnings and precautions for use
There are limited clinical data available for Remdesivir. Serious and unexpected adverse events may occur that have not been previously reported with Remdesivir use.

Infusion-Related Reactions
Infusion reactions have been observed during, and/or been temporary association with, administration of Remdesivir. Signs and symptoms may include hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, 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.

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 patents, Including elevations to up to 10 times baseline values in one subject without evidence of clinical hepatitis. 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 limits 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.
Liver Function Tests should be performed in all patients prior to starting Remdesivir and periodically thereafter while receiving Remdesivir.

- Remdesivir should not be initiated in patients with ALT ≥ it 5 times the upper limit of normal (ULN) at baseline
- Remdesivir should be discontinued in patients who develop:
  - ALT ≥ 5 times the ULN during treatment with Remdesivir
    It may be restarted when ALT is < 5 times the ULN.
    OR
  - ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalised ratio (INR)

4.5 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. 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 (P-gp) 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.

4.6 Pregnancy and lactation
Pregnancy
No adequate and well-controlled studies of Remdesivir use in pregnant woman have been conducted. Remdesivir should be used during pregnancy only if time 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.

Nursing Mothers
There is no information regarding the presence of Remdesivir in human milk, the effects on the breastfeed 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 breast feeding infants, the developmental and health benefits of breastfeeding should be considered along with the other's clinical need for Remdesivir and any potential adverse effects on the breast feeding child from Remdesivir or from the underlying maternal condition.

Paediatric Use
The safety and effectiveness of remdesivir for treatment of COVID-19 have not been assured in paediatric patients. Dosing instructions for paediatric 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 modelling and simulation approach which accounts for age dependent changes in metabolism, distribution and elimination of remdesivir.

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Paediatric patients (> 28 days) must have creatinine clearance determined and full-term neonates (≥ 7 days to ≤ 28 days) must have serum creatinine determined before dosing. Paediatric patients should be monitored for renal functions and consideration given for stopping therapy in the setting of substantial decline. The use of remdesivir is not recommended in paediatric patients (> 28 days old) with eGFR <30 mL/min and in full-term neonates (≥ 7 days to ≤ 28 days old) with serum creatinine clearance ≥ 1mg/dL unless the potential benefit outweighs the potential risk.
Because the excipient sulfobutylether-β-cyclodextrin sodium salt (SBECD) is renally cleared and accumulate in patients with decreased renal function, administration of drugs formulated with SBECD (such as remdesivir) is not recommended in adults and paediatric patients (> 28 days old) with eGFR less than 30 mL per minute or in full-term neonates (≥ 7 days to ≤ 28 days) with serum creatinine clearance ≥ 1 mg/dL unless the potential benefit outweighs the potential risk.

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.

4. 7 Effect on ability to drive and use machines
Remdesivir is predicted to have no or negligible influence on these abilities.

4.8 Undesirable effects
The most common adverse reaction in healthy volunteers is increased transaminases. The most common adverse reaction in patients with COVID-19 is nausea. Common adverse reactions include headache and rash. Additional adverse reactions associated with the drug, some of which may be serious, may become apparent with more widespread use.

4.9 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.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

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.

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. The EC50 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 RNA dependent 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.

5.2 Pharmacokinetic properities
The pharmacokinetics (PK) of Remdesivir have been evaluated in adults in several Phase 1 trials.
- Following single-dose, 2-hour IV administration of Remdesivir solution formulation at doses ranging from 3 to 225 mg, Remdesivir exhibited a linear PK profile.
- Following single-dose, 2-hour IV administration of Remdesivir at doses of 75 and 150 mg. both the lyophilized and solution formulations provided comparable PK parameters (AUC_{inf}, AUC_{last}, and Cmax), 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 [14C]-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.

5.3 Preclinical safety data

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. The EC50 values of Remdesivir against SARS-CoV- 2 in Vero cells was 137 nM at 24 hours and 750 nM at 48 hours post-treatment.

6. NON CLINICAL PROPERTIES
Remdesivir inhibits viral RNA polymerases and has broad spectrum activity against members of the filoviruses (eg, EBOV, MARV), CoVs (eg, SARS-CoV, MERS-CoV), and paramyxoviruses (eg, respiratory syncytial virus [RSV), Nipah virus (NiV), and Hendra virus).

In vitro susceptibility of coronaviruses
In HAE cells, Remdesivir efficiently inhibited both MERS-CoV and SARS-CoV replication with IC50 values of 0.074 and 0.069 µM. respectively. In both HAE and Calu-3 cells, no cytotoxicity was observed at 10 µM Remdesivir, the highest concentration tested, demonstrating that Remdesivir has a favorable in vitro selectivity index.

Results from initial in vitro testing showed that Remdesivir has potent antiviral activity against SARS-CoV-2 in Vero cells (EC50 = 0.137 µM; preliminary data). In another study conducted by the Wuhan Institute of Virology, Remdesivir also showed in vitro activity against SARS-CoV-2 in Vero cells (EC50 = 0.77 µM).

The in vitro development of resistance to Remdesivir in CoVs has been assessed by cell culture passaging of MHV in the presence of the Remdesivir nucleoside analog GS-441524. After 23 passages, 2 mutations were selected in the nsp12 polymerase at residues conserved across CoVs: F476L and V553L. Compared with wild-type virus, recombinant MHV containing the F476L mutation showed 2.4-fold reduced susceptibility to Remdesivir, and MHV containing V553L demonstrated 5-fold reduced susceptibility, while the double mutant conferred 5.6-fold reduced susceptibility to Remdesivir in vitro.

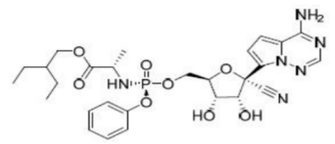
No resistance data have been submitted specific to SARS-Cov-2.
Efficacy in disease models of coronaviruses

Efficacy of Remdesivir Against SARS-CoV (not SARS-CoV-2) in Mice
Mice were inoculated intranasally with 104 pfu/50 µL (prophylactic) or 103 pfu/50 µL (therapeutic) of SARS-CoV, and the effect of subcutaneous administration of Remdesivir on viral load in lung tissue, disease-related clinical signs, lung function assessments, and lung histopathology was assessed on day 4 post-infection
Prophylactic administration of 25 mg/kg Remdesivir subcutaneously twice daily, Initiated 1day prior to virus inoculation, improved pulmonary function (ie, reduced Penh scores), reduced virus titers in the lung, and reduced SARS-CoV-induced weight loss compared to control vehicle-treated animals. Similarly, therapeutic administration of the same Remdesivir dosing regimen initiated 1 day post-infection improved weight loss, viral load in lung and lung function, albeit to a lesser extent than the prophylactic regimen.

Efficacy of Remdesivir against MERS-CoV in Mice
In a prophylactic study, Remdesivir (25 mg/kg, twice daily) was administered subcutaneously1 day prior to intranasal infection in mice with 5 * 104 PFU or 5 * 105 PFU of MERS-CoV. Prophylactic Remdesivir significantly diminished MERS-CoV-induced weight loss compared with control vehicle-treated animals and also prevented mortality in mice administered a lethal dose (ie, 5 *105 PFU) of MERS-CoV. Prophylactic Remdesivir also significantly reduced virus lung titers on Days 4 and 6 post-infection, decreased lung haemorrhage scores, and diminished the pathological features of acute lung injury compared with control vehicle-treated animals. In contrast, a similarly designed study conducted in the same mouse model demonstrated that prophylactic LPV/RTV-IFNb slightly reduced viral loads but did not impact other disease parameters

Prophylactic and Therapeutic Efficacy of 5 mg/kg Remdesivir Against MERS-CoV in Rhesus Monkeys
The prophylactic and therapeutic efficacy of a 5 mg/kg daily dose of Remdesivir was determined in MERS-CoV-infected rhesus monkeys {De Wit 2020}. Vehicle or Remdesivir 5 mg/kg was administered once daily using IV bolus injection beginning 24 hours prior to (prophylactic) or 12 hours after (therapeutic) MERS-CoV inoculation until Day 6 post-inoculation. Animals were inoculated on Day 0 with a target dose of 7*106 tissue culture infectious dose 50 (TCID50) of MERS-CoV via the intranasal, ocular, oral, and intratracheal routes.

7. DESCRIPTION
Remdesivir is a nucleoside ribonucleic acid (RNA) polymerase inhibitor. The chemical name for Remdesivir is 2-ethylbutyl N-{(S)-[2-C-(4- aminopyrrolo[2,1-f][1,2,4]triazin-7- yl)-2,5-anhydro-d-altrononitril-6-Oyl]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 refer Figure 1:
Figure 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.

8. PHARMACEUTICAL PARTICULARS
8.1 List of excipients
Sulfobutylether-β-cyclodextrin for SBECD, Hydrochloric Acid and Sodium Hydroxide.

8.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products.

8.3 Shelf life
Please refer carton / label.

8.4 Packaging Information
USP Type-1 glass vial.

8.5 Storage and handling instruction
Do not store above 30°C.
Keep all medicines out of reach & sight of children.

9. PATIENT COUNSELLING INFORMATION
Ask the patient to Inform the treating physicians in case of any of the below:
Have any allergies
Have kidney or liver problems
Are pregnant or plan to become pregnant
Are breastfeeding or plan to breastfeed
Have any serious illnesses
Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

Manufactured by:
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Marketed by:
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Before administration of the injection to the patient, it is the responsibility of the treating physician /institution to administer informed consent form (ICF) as per prescribed, as per institutional format.

BF/LL/4081/01