Abstract:
Remdesivir, a drug originally designed to be used for Ebola virus, has antiviral activity against SARS-CoV-2 and has been included in the COVID-19 treatment regimens. Remdesivir is an adenosine nucleotide analog prodrug that is metabolically activated to a nucleoside triphosphate metabolite (GS-443902). The active nucleoside triphosphate metabolite is incorporated into the SARS-CoV-2 RNA viral chains, preventing its replication. The lack of reported drug development and characterization studies with remdesivir in public domain has created a void where information on the absorption, distribution, metabolism, elimination (ADME) properties, pharmacokinetics (PK), or drug-drug interaction (DDI) is limited. By understanding these properties, clinicians can prevent subtherapeutic and supra-therapeutic levels of Remdesivir and thus avoid further complications in COVID-19 patients. Remdesivir is metabolized by both cytochrome P450 (CYP) and non-CYP enzymes such as carboxylesterase. In this narrative Review, we have evaluated the currently available ADME, PK, and DDI information about remdesivir and have discussed the potential of DDIs between remdesivir and different COVID-19 drug regimens and agents used for comorbidities.

Keywords:
Remdesivir, COVID-19, Pandemic, therapeutic uses, pharmacokinetics study.

INTRODUCTION:
In December 2019, the novel Corona virus Disease 2019 (COVID-19) was first identified as a new emerging infectious disease in China. It has rapidly spread across the globe, and was declared a global health emergency by the World Health Organization (WHO) on 30th January 2020. To date, many countries are still struggling to contain the spread of this virus. As of 2nd November 2020, there are among 218 countries affected, 46.8 million infections and over 1.2 million deaths reported worldwide. These numbers continue to rise daily. [16,20] Remdesivir is indicated for the treatment of adult and paediatric patients aged 12 years and over weighing at least 40 kg for coronavirus disease 2019 (COVID-19) infection requiring hospitalization. Under this
indication, remdesivir should only be administered in a hospital or other healthcare setting capable of providing acute care comparable to an inpatient hospital setting.\cite{1,2,17}
Remdesivir was originally granted FDA Emergency Use Authorization (EUA)\cite{15} on May 1, 2020, for use in adults and children with suspected or confirmed COVID-19 in a hospital setting with an SpO2 $\leq$ 94\%. Following FDA approval, this EUA was revised to cover hospitalized patients between 3.5 and 40 kg, as well as those under 12 years of age that weigh at least 3.5 kg, with suspected or laboratory-confirmed COVID-19.\cite{1,10,21}
Under both the on-label and EUA indications, patients not needing invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO) should be treated for 5 days (including the loading dose on day 1) and may be extended up to 10 days if they do not show improvement. Patients requiring invasive mechanical ventilation or ECMO should be treated for 10 days.\cite{1,5,6,7}

1. Structure

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{remdesivir_structure.png}
\caption{Structure of Remdesivir\cite{25,27}}
\end{figure}

2. IUPAC Name

2-ethylbutyl (2S)-2-[[S]-[[(2R,3S,4R,5R)-5-\{4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl\}-5-cyano-3,4-dihydroxyoxolan-2-yl]methoxy]phenoxy]phosphoryl]amino]propanoate \cite{25}

3. Molecular weight

602.6 g/mole \cite{25,26,27}

4. Chemical Formula

C$_{27}$H$_{35}$N$_{6}$O$_{8}$P \cite{25,26,27}

5. Synonyms

- Remdesivir
- Remdésvir
- Remdesivirum \cite{26}

6. Chemical Taxonomy

- Description
This compound belongs to the class of organic compounds known as alpha amino acid esters. These are ester derivatives of alpha amino acids.
Kingdom - Organic compounds
Super Class - Organic acids and derivatives
Class - Carboxylic acids and derivatives
Sub Class - Amino acids, peptides, and analogues
Direct Parent - Alpha amino acid esters

Pharmacodynamics
Remdesivir is a nucleoside analog used to inhibit the action of RNA polymerase. The duration of action is moderate, as it is given once daily. Due to much higher selectivity of mammalian DNA and RNA polymerases, including human mitochondrial RNA polymerase, for ATP over remdesivir triphosphate, remdesivir is not a significant inhibitor of these enzymes, which contributes to its overall tolerability and safety profile. Despite this, remdesivir carries risks for hypersensitivity reactions, including anaphylaxis and other infusion-related reactions, elevated transaminase levels, and potential decreased efficacy when combined with hydroxychloroquine or chloroquine.

Mechanism of action
COVID-19 is caused by the positive-sense RNA virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Replication of the viral genome is a key step in the infectious cycle of RNA viruses, including those of the Filoviridae, Paramyxoviridae, Pneumoviridae, and Coronaviridae families, and is carried out by viral RNA-dependent RNA polymerase (RdRp) enzymes or enzyme complexes. For both SARS-CoV and SARS-CoV-2, the RdRp comprises nsp7, nsp8, and nsp12 subunits under physiological conditions, although functional RdRp complexes can be reassembled in vitro that incorporate only the nsp8 and nsp12 subunits, similar to the Middle East respiratory syndrome coronavirus (MERS-CoV).

Remdesivir is a phosphoramidite prodrug of a 1'-cyano-substituted adenosine nucleotide analogue that competes with ATP for incorporation into newly synthesized viral RNA by the corresponding RdRp complex. Remdesivir enters cells before being cleaved to its monophosphate form through the action of either carboxylesterase 1 or cathepsin A; it is subsequently phosphorylated by undescribed kinases to yield its active triphosphate form remdesivir triphosphate (RDV-TP or GS-443902). RDV-TP is efficiently incorporated by the SARS-CoV-2 RdRp complex, with a 3.65-fold selectivity for RDV-TP over endogenous ATP. Unlike some nucleoside analogues, remdesivir provides a free 3'-hydroxyl group that allows for continued chain elongation. However, modelling and in vitro experiments suggest that at i+4 (corresponding to the position for the incorporation of the fourth nucleotide following RDV-TP incorporation), the 1'-cyano group of remdesivir sterically clashes with Ser-861 of the RdRp, preventing further enzyme translocation and terminating replication at position i+3. This mechanism was essentially identical between SARS-CoV, SARS-CoV-2, and MERS-CoV, and genomic comparisons reveal that Ser-861 is conserved across alpha-, beta-, and delta coronaviruses, suggesting remdesivir may possess broad antiviral activity.
Considerations for the use of nucleotide analogues like remdesivir include the possible accumulation of resistance mutations. Excision of analogues through the 3’-5’ exonuclease (ExoN) activity of replication complexes, mediated in SARS-CoV by the nsp14 subunit, is of possible concern. Murine hepatitis viruses (MHVs) engineered to lack ExoN activity are approximately 4-fold more susceptible to remdesivir, supporting the proposed mechanism of action. However, the relatively mild benefit of ExoN activity to remdesivir resistance is proposed to involve its delayed chain termination mechanism, whereby additional endogenous nucleotides are incorporated following RDV-TP. In addition, serial passage of MHV in increasing concentrations of the remdesivir parent molecule GS-441524 led to the development of resistance mutations F476L and V553L, which maintain activity when transferred to SARS-CoV. However, these mutant viruses are less fit than wild-type in both competition assays and in vivo in the absence of selective pressure. To date, no clinical data on SARS-CoV-2 resistance to remdesivir have been described. [1,11,13,20,29]

- **Absorption**

Remdesivir is absorbed quickly; maximal plasma concentrations following a single 30-minute intravenous infusion are reached within 0.67-0.68 hours (Tmax). Repeated dosing yields a Cmax (coefficient of variation as a percent) of 2229 (19.2) ng/mL and an AUCtau of 1585 (16.6) ng*h/mL. A 10mg/kg intravenous dose given to cynomolgus monkeys distributes to the testes, epididymis, eyes, and brain within 4h. [26,29]

- **Volume of distribution**

Data regarding the volume of distribution of remdesivir is not readily available. [25,26]

- **Protein binding**

Remdesivir is 88-93.6% bound to human plasma proteins while its metabolites GS-441524 and GS-704277 are 2% and 1% bound, respectively. [9,10,26]

- **Metabolism**

Remdesivir is a phosphoramidate prodrug that must be metabolized within host cells to its triphosphate metabolite to be therapeutically active. Upon cell entry, remdesivir is presumed to undergo first esterase-mediated hydrolysis to a carboxylate form followed by cyclization to eject the phenoxide moiety and finally hydrolysis of the cyclic anhydride to yield the detectable alanine metabolite (GS-704277). The alanine metabolite is subsequently hydrolyzed to yield the monophosphate form of remdesivir, which is either hydrolyzed again to yield the bare nucleoside metabolite GS-441524 or phosphorylated by cellular kinases to
yield the active triphosphate form. metabolite GS-441524, and 10% is recovered as the unmetabolized parent compound. A small amount (0.5%) of the GS-441524 metabolite is found in feces. [1,16,25,27]

➢ **Route of elimination**
Remdesivir is 74% eliminated in the urine and 18% eliminated in the feces. 49% of the recovered dose is in the form of the metabolite GS-441524, and 10% is recovered as the unmetabolized parent compound. A small amount (0.5%) of the GS-441524 metabolite is found in feces. [26]

➢ **Half-life**
Remdesivir has an elimination half-life of 1 hour following a single 30-minute intravenous infusion. Under the same conditions, the elimination half-lives of the remdesivir metabolites GS-441524 and GS-704277 are 27 hours and 1.3 hours, respectively. A 10mg/kg intravenous dose in non-human primates has a plasma half-life of 0.39h. The nucleoside triphosphate metabolite has a half-life of 14h in non-human primates. The nucleoside triphosphate metabolite has a half-life of approximately 20 hours in humans. [25,26,27,29]

➢ **Drug Standard Dose**

1. **Generic Name**
Remdesiv for Injection 100mg/vial (Lyophilized powder) [13,24,26]

2. **Qualitative and quantitative composition**
Each lyophilized vial Remdesiv contains;

<table>
<thead>
<tr>
<th>Remdesivir</th>
<th>100 mg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excipients</td>
<td>q. s. [26]</td>
</tr>
</tbody>
</table>

3. **Dosage form and strength**
Lyophilized powder for injection. 100 mg/vial.

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 that is to be reconstituted with 19 mL of Sterile Water for Injection and further diluted into 0.9% sodium chloride infusion bag prior to administration by intravenous infusion. Following reconstitution, each vial contains 100 mg/20 mL (5mg/mL) remdesivir reconcentrated solution. [13]

4. **Clinical particulars**

4.1 **Therapeutic indication**
For treatment of suspected or laboratory confirmed corona virus disease 2019 (COVID-19) in adults and children hospitalised with severe disease. [26]

4.2 **Posology and method of administration**
Important Testing Prior to and During Treatment and Route of Administration Adult and paediatric patients (greater than 28 days old (must have an eGFR determined and full-term neonates (at least 7 days to less than or equal to 28 day old) must have serum creatinine determined before dosing of remdesivir and daily while
receiving remdesivir Hepatic laboratory testing should be performed in all patients prior to starting remdesivir and daily while receiving remdesivir. Remdesivir should be administered via IV infusion only (using 21G or above needle only). Do not administer as an intramuscular (IM) injection.\cite{13,14,26}

**Recommended Dosage in Adult Patients**

The recommended dosage in adults is a single loading dose of remdesivir 200 mg on Day 1 followed by once-daily maintenance doses of remdesivir 100 mg from Day 2-5 via IV infusion. Administer remdesivir via IV infusion in a total volume of up to 250 mL 0.9% sodium chloride over 30 to 120 minutes.

Recommended Dosage in Paediatric Patients For paediatric patients weighing 3.5 kg to less than 40 kg. the dose should be calculated using the mg/kg dose according to the patient's weight as follows:

Extension of administration of drug beyond 5 days to 10 days is not recommended.

**Pregnancy**

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

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>Recommended Dosage Form</th>
<th>Loading Dose (On Day 1)</th>
<th>Maintenance Dose (From Day 2-5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5 kg to less than 40 kg</td>
<td>Remdesivir lyophilized powder for injection only</td>
<td>5 mg/kg</td>
<td>2.5 mg/kg</td>
</tr>
<tr>
<td>40 kg and higher</td>
<td>Remdesivir lyophilized powder for injection or Remdesivir injection</td>
<td>200 mg</td>
<td>100 mg</td>
</tr>
</tbody>
</table>

**Renal Impairment**

Adult and paediatric patients (greater than 28 days old) must have an eGFR determined and full-term neonates (at least 7 days to less than or equal to 28 days old) must have serum creatinine determined before dosing and daily while receiving remdesivir. Patients with eGFR greater than or equal to 30 mU/min have received remdesivir for treatment of COVID-19 with no dose adjustment. Remdesivir is not recommended in adults and paediatric patients (at least 28 days old) with eGFR less than 30 mL/min or in full-term neonates (at least 7 days and less than or equal to 28 days old) with serum creatinine greater than or equal to 1 mg/dL unless the potential benefit outweighs the potential risk Adults.

eGFR, Male: \((140 \text{- age in years}) \times \text{(weight in kg)}/72 \text{ (serum creatinine in mg/dL)}\);
eGFR, Female: \((140 \text{- age in years}) \times \text{(weight in kg)} \times 0.85/72 \text{ (serum creatinine in mg/dL)}\).
eGFR: 0.45 (height in cm) / serum creatinine in mg/dL creatinine in mg/dL) Paediatric patients (at least 1 year of age to less than 18 years of age).

\[
eGFR = 0.413 \times \left( \frac{\text{height or length}}{\text{Scr}} \right)
\]

if height/length is expressed in centimetres OR 41.3 \times \left( \frac{\text{height or length}}{\text{Scr}} \right)

if height/length is expressed in meters.\[^{[8,29]}\]

4.3 Contraindication

Remdesivir contraindicated in patients with known hypersensitivity to any ingredient of remdesivir

- **Cardiovascular**: Hypotension, arrhythmias, and cardiac arrest.
- **Pulmonary**: Dyspnea, Acute respiratory failure, acute respiratory distress, pneumothorax, pulmonary embolism
- **Hematological**: Anemia, lymphopenia
- **Endocrine**: Hyperglycemia
- **Infectious**: Pneumonia, septic shock
- **Gastrointestinal**: Elevated lipase, nausea, vomiting, diarrhea, constipation, poor appetite, gastroparesis, and lower GI bleeding
- **Hepatic**: Hepatic manifestation characterized by Grade 1-4 increase in serum transaminases (ALT and/or AST) are the most common adverse effects seen in patients treated with remdesivir. Other abnormalities include hyperbilirubinemia
- **Renal and Metabolic**: Acute kidney injury or worsening of underlying chronic kidney disease, hypernatremia, hypokalemia
- **Neurological**: Headache, lightheadedness
- **Skin**: Rash, contact dermatitis, pruritus
- **Psychiatric**: Delirium
- **Other adverse effects**: Pyrexia, insomnia, multi-organ dysfunction, DVT, and hypersensitivity/anaphylactic reactions related to the infusion.\[^{[4,8,13,22]}\]

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

- **Hypersensitivity including Infusion-Related and Anaphylactic Reactions**

Hypersensitivity reactions including infusion-related and anaphylactic reactions have been observed during and following administration of remdesivir. Signs and symptoms may include hypotension, tachycardia, bradycardia, dyspnoea, 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. The use of remdesivir is contraindicated in patients with known hypersensitivity to remdesivir.\[^{[3,13]}\]

- **Increased Risk of Transaminase Elevations**

Transaminase elevations have been observed in healthy volunteers who received 200 mg of remdesivir followed by 100 mg doses for 5-10 days Transaminase elevations have also been reported in patients with
COVID-19 who received remdesivir in clinical trials. As transaminase elevations have been reported as a component of COVID-19, including in patients receiving placebo in clinical trials of remdesivir, 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 greater than or equal to 5 times the upper limit of normal at baseline. [26]

- **Remdesivir should be discontinued in patients who develop:**
  ALT greater than or equal to 5 times the upper limit of normal during treatment with remdesivir. Remdesivir may be restarted when ALT is less than 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 INR.

Risk of Reduced Antiviral Activity When Coadministered with Chloroquine or Hydroxychloroquine. [7]

Go administration 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 metabolic activation and antiviral activity of remdesivir.

4.5 Drugs interactions

Drug-drug interaction trials of remdesivir and other concomitant medications have not been conducted in humans. Due to antagonism observed in vitro, concomitant use of remdesivir with chloroquine phosphate or hydroxychloroquine sulfate is not recommended. In vitro, remdesivir is a substrate for drug metabolizing enzymes CYP2C8, CYP2D6, and CYP3A4. and is a substrate for Organic Anion Transporting Polypeptides 181 (OATP1B1 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. [2,8,13]

4.6 Use in special populations

(Such pregnant women, lactating women, paediatric patients, geriatric patients etc.)

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 Summar 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 that were 4 times (rats and rabbits) he 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 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.

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.\[13,16,19,20,21,26\]

4.7 Undesirable effects
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. Most Common Grade 2 Non-Serious Adverse Events in Subjects Receiving Remdesivir include: Anemia or decreased haemoglobin, Acute kidney injury, decreased eGFR or creatinine renal clearance, or increased blood creatinine, Pyrexia, Hyperglycaemia or increased blood glucose, Increased transaminases, including ALT and/or AST.

In the compassionate use program in patients with severe or critical illness with COVID-19, liver function test abnormalities were reported in 12% (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 one 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.\[2,7,13\]
4.8 Overdose

There is no human experience of acute over dosage 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. [25,26,27]

5. Pharmacological properties

5.1 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. [25]

5.2 Pharmacodynamics properties

• 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 mM at 24 hours and 750 nM at 48 hours post-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 redise 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. [8,19,22,30]

• 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. [26,30]
5.3 Pharmacokinetic properties
The pharmacokinetics (PK) of remdesivir have been evaluated in adults in several Phase 1 trials-

- The pharmacokinetics of remdesivir and metabolites have not been evaluated in patients with COVID-19.
- Following single-dose, 2-hour IV administration of remdesivir solution formulation 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 at doses the lyophilized and solution formulations provided comparable PK parameters (AUCinf, AUClast, 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 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. [25,26,27]

6. Nonclinical properties
6.1 Animal Toxicology or Pharmacology
- 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
Non-clinical 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 intravenously 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 all dose novels, 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 23 mg/kg/day for up to 4 weeks resulted in findings indicative of kidney injury and/or dysfunction. [26]
7. Description

Remdesivir is a nucleoside ribonucleic acid (RNA) polymerase inhibitor. The chemical name for remdesivir is 2-ethylbutyl N-(S)-12-C-(4-aminopyrrolo[2, 1-f][1,2,4]triazin-7-yl)-2,5-anhydro-d-altronionitril-6-0-ylphenoxyphosphoryl)-L-alaninate. It has a molecular formula of C_{27}H_{35}N_{6}O_{8}P and a molecular weight of 602.6 g/mol.\[16,26\]

8. Pharmaceutical particulars

8.1 Incompatibilities Infusion

Solution should not be mixed with any other medicine.\[26\]

8.2 Packaging information

Remdesivir for injection, 100 mg is supplied as a single-dose vial containing a sterile, preservative free lyophilized powder that is to be reconstituted with 19 ml of Sterile Water for Injection and further diluted into 0.9% sodium chloride infusion bag prior to administration by intravenous infusion following reconstitution, each vial contains 100 mg/20 mL (5 mg/mL) remdesivir reconcentrated solution.\[26\]

8.3 Storage and handing instructions

Slow below 30°C. After reconstitution, vials can be stored up to 4 hours at room temperature prior to administration or 24 hours at refrigerated temperature. Dilute within the same day as ad instructions.\[26\]

➢ Safety Outcomes

In the as-treated population, serious adverse events occurred in 131 of 532 patients (24.6%) in the remdesivir group and in 163 of 516 patients (31.6%) in the placebo group. There were 47 serious respiratory failure adverse events in the remdesivir group (8.8% of patients), including acute respiratory failure and the need for endotracheal intubation, and 80 in the placebo group (15.5% of patients). No deaths were considered by the investigators to be related to treatment assignment.\[2,8,14,30\]

Grade 3 or 4 adverse events occurred on or before day 29 in 273 patients (51.3%) in the remdesivir group and in 295 (57.2%) in the placebo group; 41 events were judged by the investigators to be related to remdesivir and 47 events to placebo. The most common no serious adverse events occurring in at least 5% of all patients included decreased glomerular filtration rate, decreased haemoglobin level, decreased lymphocyte count, respiratory failure, anemia, pyrexia, hyperglycaemia, increased blood creatinine level, and increased blood glucose level. The incidence of these adverse events was generally similar in the remdesivir and placebo groups.\[19,20,29\]

➢ Remdesivir as an anti-viral agent: in vitro and in vivo studies

Remdesivir, also named as GS-5734 is an adenosine analogue with a broad-spectrum antiviral activity against RNA viruses. It is a produg that requires metabolism by the host cell to its active form, GS-441524, that interferes with viral RNA-dependent RNA polymerase (RdRp) enzyme causing a delay in chain termination, arresting RNA synthesis and viral replication. In vitro, remdesivir has been shown to inhibit viral replication in both MERS-CoV and SARS-CoV. Sheaha ne tall measured intracellular genomic and sub-genomic viral RNA via quantitative reverse transcriptase polymerase chain reaction in remdesivir-treated human airway epithelial cell line. A dose dependent reduction for both SARS-CoV and MERS-CoV was demonstrated, which is consistent with titer reduction.\[13,16,17\]
Similarly, in mouse models of SARS-CoV infection, prophylactic or early administration of remdesivir lowered viral load and reduced SAR-CoV-associated pulmonary pathology of denuding bronchiolitis, perivascular inflammatory infiltrates and intra-alveolar edema, and prevented deterioration in pulmonary function. Interestingly, therapeutic remdesivir treatment in SARS-CoV after virus replication and lung epithelial cell damage had peaked did not alter disease severity or mortality, despite a significant reduction in SARS-CoV lung viral titre. These findings are consistent with studies on non-human primates (rhesus macaque model). A reduction in lung viral load was observed in both prophylactic and therapeutic treatment groups. [14,16,22]

Respiratory rate of animals treated prophylactically with remdesivir remained normal throughout the study; however, 83% of those treated therapeutically developed increased heart rate. Pulmonary pathology was absent in the prophylactic treated group. Gross lung lesions were observed in 83% of the animals treated therapeutically with remdesivir, the total lung area affected was, however, significantly smaller than that compared to control animals. Evidence from the above in vitro and in vivo studies of SARS-CoV and MERS-CoV suggest that prophylactic treatment with remdesivir inhibit viral replication, prevent clinical disease and changes in pulmonary pathology. [2,8,14,30]

**CONCLUSION**

In depth understanding of the emerging data related to COVID-19 is crucial to curb this pandemic. Among the candidate therapies, remdesivir has demonstrated efficacy in both in vitro and in vivo models against coronaviruses. Recently, through a compassionate use indication, remdesivir has supportive evidence for yielding some clinical improvement in COVID-19 patients. In addition, an interim analysis of the Adaptive COVID-19 Treatment Trial supports improvement in the primary endpoint for patients receiving remdesivir, compared to control, with a 31% faster time to recovery. At present, remdesivir remains an investigational drug for the treatment of COVID-19. Although it is associated with shorter hospital length of stay, and a more rapid clinical improvement, no mortality benefit has been demonstrated. It has been suggested that remdesivir is unlikely to achieve adequate concentration in lung tissues through intravenous infusion alone because of its low tissue distribution and poor lung penetration. A proposed combination of pulmonary and intravenous administration of remdesivir has been suggested for a more effective strategy for the treatment of COVID-19.

Remdesivir appears to have optimal safety profile although its efficacy in the treatment of COVID-19 appears to have a mixed outcome at the moment. Jury is still out and future trials should further enlighten its cost-effectiveness, in particular when the results of head-to-head trial with other low-cost repurposed drugs is available.

Remdesivir has shown much potential to combat SARS-CoV-2 infection, however, this treatment option currently lacks patient-friendly dosage forms, sufficient toxicity, and Drug interaction data. In addition to the currently available parental dosage forms, a major Opportunity for improvement is the development of inhaled dosage forms for localized Absorption and distribution. The current dose regimen of remdesivir may yield a Concentration in inhibiting COVID-19 in the lungs, which is the primary site of attack SARS-CoV-2. The
inhaled administration would allow the medication to be absorbed into the lungs in therapeutic concentrations to effectively treat and kill SARS-CoV-2.

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