# SUMMARY OF PRODUCT CHARACTERISTICS

## 1 NAME OF THE MEDICINAL PRODUCT

Veklury 100 mg powder for concentrate for solution for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg of remdesivir. After reconstitution, each vial contains 5 mg/mL of remdesivir solution.

Excipients with known effect

Each vial contains 3 g betadex sulfobutyl ether sodium.

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).
White to off-white to yellow powder.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg):

- with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment).
- who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

(see section 5.1).

### 4.2 Posology and method of administration

Patients should be monitored when receiving remdesivir (see section 4.4).

Patients receiving remdesivir in an outpatient setting should be monitored according to local medical practice. Use under conditions where treatment of severe hypersensitivity reactions, including anaphylaxis, is possible.

Posology

**Table 1: Recommended dose in adults and paediatric patients**

| | **Given by intravenous infusion** | | |
|---|---|---|---|
| | **Adults** | **Paediatric patients (weighing at least 40 kg)** | **Paediatric patients at least 4 weeks old (weighing at least 3 kg but less than 40 kg)** |
| **Day 1 (single loading dose)** | 200 mg | 200 mg | 5 mg/kg |
| **Day 2 and onwards (once daily)** | 100 mg | 100 mg | 2.5 mg/kg |

**Table 2: Treatment duration**

| | **Adults** | **Paediatric patients (weighing at least 40 kg)** | **Paediatric patients at least 4 weeks old (weighing at least 3 kg but less than 40 kg)** |
|---|---|---|---|
| Patients with **pneumonia and requiring supplemental oxygen** | Daily for **at least 5 days and not more than 10 days.** | Daily for **at least 5 days** and **not more than 10 days**. | Daily for up to a **total of 10 days**. |
| Patients who **do not require supplemental oxygen and are at increased risk for progressing to severe COVID-19** | Daily for **3 days**, starting as soon as possible after diagnosis of COVID-19 and within 7 days of the onset of symptoms. | Daily for **3 days**, starting as soon as possible after diagnosis of COVID-19 and within 7 days of the onset of symptoms. | Daily for **3 days**, starting as soon as possible after diagnosis of COVID-19 and within 7 days of the onset of symptoms. |

Special populations

*Elderly*
No dose adjustment of remdesivir is required in patients over the age of 65 years (see sections 5.1 and 5.2).

*Renal impairment*
No dose adjustment of remdesivir is required in patients with renal impairment, including those on dialysis. However, safety data in patients with severe renal impairment and end stage renal disease (ESRD) are limited (see section 4.4) and based on a 5-day treatment duration. The timing of administration of remdesivir is without regard to dialysis (see section 5.2).
*Hepatic impairment*
No dose adjustment of remdesivir is required in patients with mild, moderate and severe hepatic impairment (Child-Pugh Class A, B, C) (see section 5.2). However, safety data in patients with severe hepatic impairment are limited and only based on a single 100 mg dose administration.

*Paediatric population*
The safety and efficacy of remdesivir in children less than 4 weeks of age and weighing less than 3 kg have not yet been established (see section 5.1).

*Immunocompromised population*
The safety and efficacy of remdesivir in immunocompromised patients have not yet been established. Only limited data are available (see section 4.4).

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.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

**Table 3: Recommended rate of infusion – for reconstituted and diluted remdesivir powder for concentrate for solution for infusion in adults and paediatric patients weighing at least 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 |

**Table 4: Recommended rate of infusion – for reconstituted and diluted remdesivir powder for concentrate for solution for infusion in paediatric patients at least 4 weeks of age and weighing at least 3 kg but less than 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 Rate of infusion may be adjusted based on total volume to be infused.

## 4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

## 4.4 Special warnings and precautions for 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, hypertension, tachycardia, bradycardia, hypoxia, fever, 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. Monitor patients for hypersensitivity reactions during and following administration of remdesivir as clinically appropriate. Patients receiving remdesivir in an outpatient setting should be monitored after administration according to local medical practice. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration of remdesivir and initiate appropriate treatment.

Renal impairment

As clinically appropriate, patients should have eGFR determined prior to starting remdesivir and while receiving it. Safety data from patients with severe renal impairment and ESRD reported during Study GS-US-540-5912 were comparable to the known safety profile of remdesivir  However, there are limited safety data in this patient population. Therefore, taking the significant higher exposure of the metabolite GS-441524 into account, patients with severe renal impairment and ESRD should be closely monitored for adverse events during treatment with remdesivir (see section 5.2).

Risk of reduced antiviral activity when coadministered with chloroquine or hydroxychloroquine

Coadministration 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 (see sections 4.5 and 5.1)

Immunocompromised patients:

It is unclear if the treatment duration of three days is sufficient to clear the virus in immunocompromised patients, in whom prolonged viral shedding occurs. There is a potential risk of resistance development. Only limited data are available.

Excipients

This medicinal product contains 212 mg sodium per 100 mg dose, equivalent to 10.6% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

## 4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Due to antagonism observed *in vitro*, concomitant use of remdesivir with chloroquine phosphate or hydroxychloroquine sulphate is not recommended.

Pharmacokinetic interactions

*Effects of other medicinal products on remdesivir*
*In vitro*, remdesivir is a substrate for esterases in plasma and tissue, drug metabolizing enzyme CYP3A4 and is a substrate for Organic Anion Transporting Polypeptides 1B1 (OATP1B1) and P-glycoprotein (P-gp) transporters. GS-704277 (a metabolite of remdesivir) is a substrate for OATP1B1 and OATP1B3.

A drug-drug interaction study was conducted with remdesivir. Table 5 summarises the pharmacokinetic effects of studied drugs on remdesivir and metabolites GS-704277 and GS-441524.

**Table 5: Effect of other drugs on remdesivir and metabolites GS-704277 and GS-441524**

| **Co-administered Drug Dose (mg)** | **Interaction Geometric mean change (%)** | **Recommendation concerning co-administration** |
|---|---|---|
| Cyclosporin 400 single dose | remdesivir: $C_{max}$ ↑49%<br>$AUC_{inf}$ ↑89%<br>GS-704277: $C_{max}$ ↑151%<br>$AUC_{inf}$ ↑197%<br>GS-441524: $C_{max}$ ↑17%<br>$AUC_{inf}$ ↔<br>No interactions are expected when co-administering remdesivir with inhibitors of OATP1B1/1B3 and/or P-gp. | No dose adjustment of remdesivir is required when it is co-administered with inhibitors of OATP1B1 and OATP1B3. |
| Carbamazepine 300 twice daily | remdesivir: $C_{max}$ ↓13%<br>$AUC_{inf}$ ↓8%<br>GS-704277: $C_{max}$ ↔<br>$AUC_{inf}$ ↔<br>GS-441524: $C_{max}$ ↔<br>$AUC_{inf}$ ↓17%<br>No interactions are expected when co-administering remdesivir with strong CYP3A4 inducers or CYP3A4 inhibitors. | No dose adjustment of remdesivir is required when it is co-administered with strong CYP3A4 and/or P-gp inducers. |

NOTE: Interaction study conducted in healthy volunteers.

*Effects of remdesivir on other medicinal products*
Remdesivir is not a clinically relevant inhibitor of CYP3A4, OATP1B1, and OATP1B3. *In vitro*, remdesivir is an inhibitor of UGT1A1, MATE1, OAT3, and OCT1; however no clinically significant drug interactions are expected with remdesivir and substrates of these enzymes or transporters.

Remdesivir is not a clinically relevant inducer of CYP3A4. Remdesivir induced CYP1A2 *in vitro*; however no clinically significant drug interaction is expected with remdesivir and CYP1A2 substrates.

Drug-drug interaction studies were conducted with remdesivir. Table 6 summarises the effect of remdesivir on the pharmacokinetics of studied drugs.

**Table 6: Effect of remdesivir on other drugs**

| Co-administered Drug Dose (mg) | Remdesivir Dose (mg) | Interaction Geometric mean change (%) | Recommendation concerning co-administration |
|---|---|---|---|
| Midazolam 2.5 single dose | 200 single dose | $C_{max}$ ↑29% [a]<br>$AUC_{inf}$ ↑20% [a]<br>No inhibition is expected when co-administering remdesivir with substrate of CYP3A | No dose adjustment of remdesivir is required when it is co-administered with substrate of CYP3A |
| Midazolam 2.5 single dose | 200 single dose followed by 100 once daily (10 doses)[b] | $C_{max}$ ↑45%[c]<br>$AUC_{inf}$ ↑30%[c]<br>No induction is expected when co-administering remdesivir with substrate of CYP3A | |
| Pitavastatin 2 single dose | 200 single dose | $C_{max}$ ↑5% [a]<br>$AUC_{inf}$ ↑17% [a]<br>No inhibition is expected when co-administering remdesivir with substrate of OATP1B1/OATP1B3 | No dose adjustment of remdesivir is required when it is co-administered with substrate of OATP1B1/OATP1B3 |

NOTE: Interaction study conducted in healthy volunteers.

a. No effect = 1.00 (0.80-1.25).
b. Midazolam administered with last dose of remdesivir.
c. No effect = 1.00 (0.70-1.43)

## 4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of remdesivir in pregnant women (less than 300 pregnancy outcomes). Most of the exposures occurred in the second, third or an unknown trimester and available data do not indicate any risk.

Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity at exposures of the major metabolite of remdesivir that were around human therapeutic exposures (see section 5.3).

Due to very limited experience, remdesivir should not be used during first trimester in pregnancy unless the clinical condition of the woman requires treatment with it. Use in the second and third trimester of pregnancy may be considered.

Use of effective contraception during treatment should be considered in women of child-bearing potential.

Breast-feeding

Remdesivir and its major metabolite are excreted into breast milk in very small amounts after intravenous administration. No clinical effect on the infant is expected due to low breast milk transfer and poor oral bioavailability.

As the clinical experience is limited, a decision about breast-feeding during treatment should be made after a careful individual benefit-risk assessment.

Fertility

No human data on the effect of remdesivir on fertility are available. In male rats, there was no effect on mating or fertility with remdesivir treatment. In female rats, however, an impairment of fertility was observed (see section 5.3). The relevance for humans is unknown.

## 4.7 Effects on ability to drive and use machines

Remdesivir is predicted to have no or negligible influence on these abilities.

## 4.8 Undesirable effects

Summary of the safety profile

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%).

Tabulated summary of adverse reactions

The adverse reactions in Table 7 are listed below by system organ class and frequency. Frequencies are defined as follows: Very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); not known (cannot be estimated from the available data).

**Table 7: Tabulated list of adverse reactions**

| **Frequency** | **Adverse reaction** |
|---|---|
| *Immune system disorders* | |
| Rare | hypersensitivity |
| Not known | anaphylactic reaction, anaphylactic shock |
| *Nervous system disorders* | |
| Common | headache |
| *Cardiac disorders* | |
| Not known | sinus bradycardia* |
| *Gastrointestinal disorders* | |
| Common | nausea |
| *Hepatobiliary disorders* | |
| Very common | transaminases increased |
| *Skin and subcutaneous tissue disorders* | |
| Common | rash |
| *Investigations* | |
| Very common | prothrombin time prolonged |
| *Injury, poisoning and procedural complications* | |
| Rare | infusion-related reaction |

*Reported in post-marketing, usually normalised within 4 days following last remdesivir administration without additional intervention

Description of selected adverse reactions

*Transaminases increased*
In healthy volunteer studies, increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST) or both in subjects who received remdesivir were 1.25 to 2.5 times the upper limit of normal (ULN) (10%) or 2.5 to 5 times ULN (4%). In clinical studies of patients with COVID-19, the incidence of increased transaminases was similar in patients treated with remdesivir compared to placebo or standard of care.

*Prothrombin time prolonged*
In a clinical study (NIAID ACTT-1) of patients with COVID-19, the incidence of prolonged prothrombin time or INR (predominantly less than 2 times ULN) was higher in subjects who received remdesivir compared to placebo, with no difference observed in the incidence of bleeding events between the two groups. In Study GS-US-540-9012, the incidence of increased prothrombin time or INR was similar in patients treated with remdesivir compared to placebo.

*Patients with renal impairment*
In Study GS-US-540-5912, 163 hospitalised patients with confirmed COVID-19 and acute kidney injury, chronic kidney disease or ESRD on haemodialysis received remdesivir for up to 5 days (see sections 4.4 and 5.2). Safety data from these patients were comparable to the known safety profile of remdesivir. In this same study, the incidence of increased prothrombin time or INR was higher in patients treated with remdesivir compared to placebo, with no difference observed in the incidence of bleeding events between the two groups (see section 5.1).

*Paediatric population*
The safety assessment of remdesivir in children 4 weeks of age and older and weighing at least 3 kg with COVID-19 is based on data from a Phase 2/3, open-label clinical trial (Study GS-US-540-5823) in patients who were treated with remdesivir (see Section 5.1). The adverse reactions observed were consistent with those observed in clinical trials of remdesivir in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via *the dedicated COVID-19 Yellow Card reporting site at coronavirus-yellowcard.mhra.gov.uk.*

## 4.9 Overdose

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. In one clinical pharmacology trial, remdesivir 600 mg as a single dose over 30 minutes, equivalent to 3 times the therapeutic loading dose of 200 mg, was administered to 60 healthy subjects. Nausea and/or vomiting (Grades 1-2) was reported for 33 (55%) subjects. One subject (2%) had increased AST and ALT (Grade 4) without elevation of bilirubin.

# 5 PHARMACOLOGICAL PROPERTIES

## 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals for systemic use, direct acting antivirals, ATC code: J05AB16

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. As an additional mechanism, remdesivir triphosphate can also inhibit viral RNA synthesis following its incorporation into the template viral RNA as a result of read-through by the viral polymerase that may occur in the presence of higher nucleotide concentrations. When remdesivir nucleotide is present in the viral RNA template, the efficiency of incorporation of the complementary natural nucleotide is compromised, thereby inhibiting viral RNA synthesis.

Antiviral activity

Remdesivir exhibited *in vitro* activity against a clinical isolate of SARS-CoV-2 in primary human airway epithelial cells with a 50% effective concentration ($EC_{50}$) of 9.9 nM after 48 hours of treatment. Remdesivir inhibited the replication of SARS-CoV-2 in the continuous human lung epithelial cell lines Calu-3 and A549-hACE2 with $EC_{50}$ values of 280 nM after 72 hours of treatment and 115 nM after 48 hours of treatment, respectively. The $EC_{50}$ values of remdesivir against SARS-CoV-2 in Vero cells were 137 nM at 24 hours and 750 nM at 48 hours post-treatment.

The antiviral activity of remdesivir was antagonised by chloroquine phosphate in a dose-dependent manner when the two drugs were co-incubated at clinically relevant concentrations in HEp-2 cells infected with respiratory syncytial virus (RSV). Higher remdesivir $EC_{50}$ values were observed with increasing concentrations of chloroquine phosphate. Increasing concentrations of chloroquine phosphate reduced formation of remdesivir triphosphate in A549-hACE2, HEp-2 and normal human bronchial epithelial cells.

Based on in vitro testing, remdesivir retained similar antiviral activity (EC50 fold change values below the in vitro susceptibility change cutoff of 2.8-fold) against clinical isolates of SARS-CoV-2 variants compared to an earlier lineage SARS-CoV-2 (lineage A) isolate, including Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), Epsilon (B.1.429), Zeta (P.2), Iota (B.1.526), Kappa (B.1.617.1), Lambda (C.37) and Omicron variants (including B.1.1.529/BA.1, BA.2, BA.2.12.1, BA.2.75, BA.2.86, BA.4, BA.4.6, BA.5, BF.5, BF.7, BQ.1, BQ.1.1, CH.1.1, EG.1.2, EG.5.1, EG.5.1.4, FL.22, HK.3, HV.1, JN.1, XBB, XBB.1.5, XBB.1.5.72, XBB.1.16, XBB.2.3.2, XBC.1.6, and XBF). For these variants, the EC50 fold change values ranged between 0.2 to 2.3 compared to an earlier lineage SARS-CoV-2 (lineage A) isolate. Using the SARS-CoV-2 replicon system, remdesivir retained similar antiviral activity (EC50 fold change values below the in vitro susceptibility change cutoff of

2.5-fold) against Omicron subvariants JN.1.7, JN.1.18, KP.2, KP.3, LB.1 and XBB.1.9.2 compared to the wildtype reference replicon (lineage B).

Resistance

*In Cell Culture*
SARS-CoV-2 isolates with reduced susceptibility to remdesivir have been selected in cell culture. In one selection with GS-441524, the parent nucleoside of remdesivir, virus pools emerged expressing combinations of amino acid substitutions at V166A, N198S, S759A, V792I, C799F, and C799R in the viral RNA-dependent RNA polymerase, conferring EC50 fold-changes of 2.7 up to 10.4. When individually introduced into a wild-type recombinant virus by site-directed mutagenesis, 1.7- to 3.5-fold reduced susceptibility to remdesivir was observed. In a second selection with remdesivir using a SARS-CoV-2 isolate containing the P323L substitution in the viral polymerase, a single amino acid substitution at V166L emerged. Recombinant viruses with substitutions at P323L alone or P323L+V166L in combination exhibited 1.3- and 1.5-fold changes in remdesivir susceptibility, respectively.

Cell culture resistance profiling of remdesivir using the rodent CoV murine hepatitis virus identified two substitutions (F476L and V553L) in the viral RNA-dependent RNA polymerase at residues conserved across CoVs that conferred 5.6-fold reduced susceptibility to remdesivir. 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. When individually introduced into a SARS-CoV-2 recombinant virus, the corresponding substitutions at F480L and V557L each conferred 2-fold reduced susceptibility to remdesivir.

*In Clinical Trials*
In NIAID ACTT-1 Study (CO-US-540-5776), among 61 patients with baseline and post-baseline sequencing data available, the rate of emerging substitutions in the viral RNA-dependent RNA polymerase was similar in patients treated with remdesivir compared to placebo. In 2 patients treated with remdesivir, substitutions in the RNA-dependent RNA polymerase previously identified in resistance selection experiments (V792I or C799F) and associated with low fold change in remdesivir susceptibility ($\leq$3.4-fold) were observed. No other RNA-dependent RNA polymerase substitutions observed in patients treated with remdesivir were associated with resistance to remdesivir.

In Study GS-US-540-5773, among 19 patients treated with remdesivir who had baseline and post-baseline sequencing data available, substitutions in the viral RNA-dependent RNA polymerase (nsp12) were observed in 4 patients. The substitutions T76I, A526V, A554V and C697F were not associated with resistance to remdesivir ($\leq$ 1.45-fold change in susceptibility). The effect of substitution E665K on susceptibility to remdesivir could not be determined due to lack of replication.

In GS-US-540-9012 Study, among 244 patients with baseline and post-baseline sequencing data available, the rate of emerging substitutions in the viral RNA-dependent RNA polymerase was similar in patients treated with remdesivir compared to placebo. In one patient treated with remdesivir, one substitution in the RNA-dependent RNA polymerase (A376V) emerged and was associated with a decrease in remdesivir susceptibility *in vitro* (12.6-fold). No other substitutions in the RNA-dependent RNA polymerase or other proteins of the replication-transcription complex observed in patients treated with remdesivir were associated with resistance to remdesivir.

In Study GS-US-540-5912, among 60 patients with baseline and post-baseline sequencing data available, substitutions in the viral RNA-dependent RNA polymerase emerged in 8 patients treated with remdesivir. In 4 patients treated with remdesivir, substitutions in the RNA-dependent RNA polymerase (M794I, C799F, or E136V) emerged and were associated with reduced susceptibility to remdesivir *in vitro* (≤3.5-fold). No other substitutions in the RNA-dependent RNA polymerase detected in patients treated with remdesivir were associated with resistance to remdesivir.

In Study GS-US-540-5823, among patients with baseline and post-baseline sequencing data available, substitutions in the viral RNA-dependent RNA polymerase (A656P and G670V) were observed in one of 23 patients treated with remdesivir. The substitutions observed were not associated with resistance to remdesivir.

Clinical efficacy and safety

*Clinical trials in patients with COVID-19*

NIAID ACTT-1 Study (CO-US-540-5776)
A randomised, double-blind, placebo-controlled clinical trial evaluated remdesivir 200 mg once daily for 1 day followed by remdesivir 100 mg once daily for up to 9 days (for a total of up to 10 days of intravenously administered therapy) in hospitalised adult patients with COVID-19 with evidence of lower respiratory tract involvement. The trial enrolled 1,062 hospitalised patients: 159 (15%) patients with mild/moderate disease (15% in both treatment groups) and 903 (85%) patients with severe disease (85% in both treatment groups). Mild/moderate disease was defined as SpO2 > 94% and respiratory rate < 24 breaths/minute without supplemental oxygen; severe disease was defined as SpO2 ≤ 94% on room air, a respiratory rate ≥ 24 breaths/min, and an oxygen requirement, or a requirement for mechanical ventilation. A total of 285 patients (26.8%) (n=131 received remdesivir) were on mechanical ventilation/Extracorporeal Membrane Oxygenation (ECMO). Patients were randomised 1:1, stratified by disease severity at enrolment, to receive remdesivir (n=541) or placebo (n=521), plus standard of care.

The baseline mean age was 59 years and 36% of patients were aged 65 or older. Sixty-four percent were male, 53% were White, 21% were Black, 13% were Asian. The most common comorbidities were hypertension (51%), obesity (45%) and type 2 diabetes mellitus (31%); the distribution of comorbidities was similar between the two treatment groups.

Approximately 38.4% (208/541) of the patients received a 10-day treatment course with remdesivir.

The primary clinical endpoint was time to recovery within 29 days after randomisation, defined as either discharged from hospital (with or without limitations of activity and with or without home oxygen requirements) or hospitalised but not requiring supplemental oxygen and no longer requiring ongoing medical care. The median time to recovery was 10 days in the remdesivir group compared to 15 days in the placebo group (recovery rate ratio 1.29; [95% CI 1.12 to 1.49], p < 0.001).

No difference in time to recovery was seen in the stratum of patients with mild-moderate disease at enrolment (n=159). The median time to recovery was 5 days in the remdesivir and 7 days in the placebo groups (recovery rate ratio 1.10; [95% CI 0.8 to 1.53]); the odds of improvement in the ordinal scale in the remdesivir group at Day

15 when compared to the placebo group were as follows: odds ratio, 1.2; [95% CI 0.7 to 2.2, p = 0.562].

Among patients with severe disease at enrolment (n=903), the median time to recovery was 12 days in the remdesivir group compared to 19 days in the placebo group (recovery rate ratio, 1.34; [95% CI 1.14 to 1.58]; p < 0.001); the odds of improvement in the ordinal scale in the remdesivir group at Day 15 when compared to the placebo group were as follows: odds ratio, 1.6; [95% CI 1.3 to 2.0].

Overall, the odds of improvement in the ordinal scale were higher in the remdesivir group at Day 15 when compared to the placebo group (odds ratio, 1.6; [95% CI 1.3 to 1.9], p < 0.001).

The 29-day mortality in the overall population was 11.6% for the remdesivir group vs 15.4% for the placebo group (hazard ratio, 0.73; [95% CI 0.52 to 1.03]; p=0.07). A post-hoc analysis of 29-day mortality by ordinal scale is reported in Table 8.

**Table 8: 29-Day mortality outcomes by ordinal scale[a] at baseline—NIAID ACTT-1 trial**

| | **Ordinal Score at Baseline** | | | |
|---|---|---|---|---|
| | **5** | | **6** | |
| | **Requiring low-flow oxygen** | | **Requiring high-flow oxygen or non-invasive mechanical ventilation** | |
| | Remdesivir (N=232) | Placebo (N=203) | Remdesivir (N=95) | Placebo (N=98) |
| **29-day mortality** | 4.1 | 12.8 | 21.8 | 20.6 |
| **Hazard ratio[b] (95% CI)** | 0.30 (0.14, 0.64) | | 1.02 (0.54, 1.91) | |

a Not a pre-specified analysis.
b Hazard ratios for baseline ordinal score subgroups are from unstratified Cox proportional hazards models.

Study GS-US-540-5773 in Patients with Severe COVID-19
A randomised, open-label multi-centre clinical trial (Study 5773) of patients at least 12 years of age with confirmed SARS-CoV-2 infection, oxygen saturation of ≤ 94% on room air, and radiological evidence of pneumonia compared 200 patients who received remdesivir for 5 days with 197 patients who received remdesivir for 10 days. All patients received 200 mg of remdesivir on Day 1 and 100 mg once daily on subsequent days, plus standard of care. The primary endpoint was clinical status on Day 14 assessed on a 7-point ordinal scale ranging from hospital discharge to increasing levels of oxygen and ventilatory support to death.

The odds of improvement at Day 14 for patients randomized to a 10-day course of remdesivir compared with those randomized to a 5-day course was 0.67 (odds ratio); [95% CI 0.46 to 0.98]. Statistically significant imbalances in baseline clinical status were observed in this study. After adjusting for between-group differences at baseline, the odds of improvement at Day 14 was 0.75 (odds ratio); [95% CI 0.51 to 1.12]. In addition, there were no statistically significant differences in recovery rates or mortality rates in the 5-day and 10-day groups once adjusted for between group differences at baseline. All-cause 28-day mortality was 12% vs 14% in the 5- and 10-day treatment groups, respectively.
Study GS-US-540-9012 in patients with confirmed COVID-19 at increased risk for disease progression
A randomised, double-blind, placebo-controlled, multi-centre clinical trial to evaluate treatment with remdesivir in an outpatient setting in 562 patients including

8 adolescents (12 years of age and older and weighing at least 40 kg) with confirmed COVID-19 and at least one risk factor for disease progression to hospitalisation. Risk factors for disease progression were: aged ≥ 60 years, chronic lung disease, hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity, immunocompromised state, chronic mild or moderate kidney disease, chronic liver disease, current cancer, or sickle cell disease. Vaccinated patients were excluded from the study.

Patients treated with remdesivir received 200 mg on Day 1 and 100 mg once daily on subsequent days for a total of 3 days of intravenously administered therapy. Patients were randomized in a 1:1 manner, stratified by residence in a skilled nursing facility (yes/no), age (< 60 vs ≥ 60 years), and region (US vs ex-US) to receive remdesivir (n=279) or placebo (n=283), plus standard of care.

At baseline, mean age was 50 years (with 30% of patients aged 60 or older); 52% were male, 80% were White, 8% were Black, 2% were Asian, 44% were Hispanic or Latino; median body mass index was 30.7 $kg/m^2$. The most common comorbidities were diabetes mellitus (62%), obesity (56%), and hypertension (48%). Median (Q1, Q3) duration of symptoms prior to treatment was 5 (3,6) days; median viral load was 6.3 $log_{10}$ copies/mL at baseline. The baseline demographics and disease characteristics were balanced across the remdesivir and placebo treatment groups. Post-hoc exploratory analysis of optional biomarker samples showed 14.8% of patients were serological positive at baseline and 37.7% were serological negative (47.5% did not consent to optional biomarker collection).

The primary endpoint was the proportion of patients with COVID-19 related hospitalisation (defined as at least 24 hours of acute care) or all-cause 28-day mortality. Events (COVID-19-related hospitalisation or all-cause 28-day mortality) occurred in 2 (0.7%) patients treated with remdesivir compared to 15 (5.3%) patients concurrently randomized to placebo, demonstrating an 87% reduction in COVID-19-related hospitalisation or all-cause mortality compared to placebo (hazard ratio, 0.134 [95% CI, 0.031 to 0.586]; p=0.0076). The absolute risk reduction was 4.6% (95% CI, 1.8% to 7.5%). No deaths were observed at Day 28. Six of the 17 hospitalisation events occurred in participants with known baseline serostatus (serological positive: n=0 in remdesivir group and n=2 in placebo group; serological negative: n=2 in remdesivir group and n=2 in placebo group). Eleven of the 17 hospitalisation events occurred in participants with unknown baseline serostatus in placebo group and none in the remdesivir group. No conclusion can be made on efficacy in the subgroups stratified by serostatus due to the small number of patients with known serostatus and overall low event rates.

<u>Study GS-US-540-5912 in patients with COVID-19 and renal impairment</u>
A randomised, double-blind, placebo-controlled clinical study (Study GS-US-540-5912) evaluated remdesivir 200 mg once daily for 1 day followed by remdesivir 100 mg once daily for 4 days (for a total of up to 5 days of intravenously administered therapy) in 243 hospitalised adult patients with confirmed COVID-19 and renal impairment. The trial included 90 patients (37%) with AKI (defined as a 50% increase in serum creatinine within a 48-hour period that was sustained for ≥6 hours despite supportive care), 64 patients (26%) with CKD (eGFR <30 mL/minute), and 89 patients (37%) with ESRD (eGFR <15 mL/minute) requiring haemodialysis. Patients were randomised in a 2:1 manner, stratified by ESRD, high-flow oxygen requirement, and region (US vs ex-US) to receive remdesivir (n=163) or placebo (n=80), plus standard of care.

At baseline, mean age was 69 years (with 62% of patients aged 65 or older); 57% of patients were male, 67% were White, 26% were Black, and 3% were Asian. The most common baseline risk factors were hypertension (89%), diabetes mellitus (79%), and cardiovascular or cerebrovascular disease (51%); the distribution of risk factors was similar between the two treatment groups. A total of 45 patients (19%) were on high-flow oxygen, 144 (59%) were on low-flow oxygen, and 54 (22%) were on room air at baseline; no patients were on invasive mechanical ventilation (IMV). A total of 182 patients (75%) were not on renal replacement therapy, and 31 patients (13%) had received a COVID-19 vaccine. The study closed prematurely due to feasibility issues and was underpowered to assess primary (all-cause death or IMV by Day 29) and secondary efficacy endpoints because of lower than expected enrolment.

QT

In a thorough QT/QTc trial that dosed 60 healthy subjects with 600 mg of remdesivir as a single treatment, no effect was seen on the QTc interval.

Paediatric population

Study GS-US-540-5823 is a single-arm, open-label study that enrolled 58 patients from birth to less than 18 years of age, where the pharmacokinetics and safety of remdesivir in 53 patients at least 28 days of age and weighing at least 3 kg with COVID-19 were assessed. Efficacy endpoints were secondary and descriptively analysed and therefore these should be interpreted with caution.

*Infants, children, and adolescents (Cohorts 1-4 and 8) (n=53):* Patients weighing ≥ 40 kg received 200 mg of remdesivir on Day 1 followed by remdesivir 100 mg once daily on subsequent days (i.e., the adult dose); patients weighing ≥ 3 kg to < 40 kg received remdesivir 5 mg/kg on Day 1 followed by remdesivir 2.5 mg/kg once daily on subsequent days. Median (range) exposure to remdesivir was 5 (1, 10) days.

At baseline, median age was 7 years (range: 0.1 to 17 years); 57% were female; median weight was 24.6 kg (range: 4 kg to 192 kg). A total of 19 patients (37%) were obese (BMI-for-age ≥ 95$^{th}$ percentile); 7 (58%), 2 (17%), 3 (27%), 3 (27%), and 4 (80%) patients in Cohorts 1, 2, 3, 4 and 8 respectively. A total of 12 patients (23%) were on invasive mechanical ventilation (score of 2 in a 7-point ordinal scale), 18 (34%) were on non-invasive ventilation or high-flow oxygen (score of 3); 10 (19%) were on low-flow oxygen (score of 4); and 13 (25%) were on room air (score of 5), at baseline. The overall median (Q1, Q3) duration of symptoms and hospitalisation prior to first dose of remdesivir was 5 (3, 7) days and 1 (1, 3) day, respectively.

In Cohorts 1-4 and 8, the median (Q1, Q3) change from baseline in clinical status (assessed on a 7-point ordinal scale ranging from death [score of 1] to hospital discharge [score of 7]) was +2.0 (1.0, 4.0) points on Day 10. Among those with an ordinal score of ≤ 5 points at baseline, the proportion who had a ≥ 2-point improvement in clinical status on Day 10 was 75.0% (39/52); median (Q1, Q3) time to recovery was 7 (5, 16) days. Overall, 60% of patients were discharged by Day 10. Most patients 92% (49/53) received at least 1 concomitant medication other than remdesivir for the treatment of COVID-19 including immune modulator and anti-inflammatory agents. Three patients died in these cohorts in the study.
*Neonates, and preterm neonates and infants (Cohorts 5-7) (n=5):* Full-term neonates 14 to less than 28 days old and weighing at least 2.5 kg received remdesivir 5 mg/kg on Day 1 followed by remdesivir 2.5 mg/kg once daily on subsequent days; full-term neonates less than 14 days old and weighing at least 2.5 kg at birth and preterm

neonates and infants less than 56 days old and weighing at least 1.5 kg at birth received remdesivir 2.5 mg/kg on Day 1 followed by remdesivir 1.25 mg/kg once daily on subsequent days. Safety and efficacy were not established in these patients. No patients died in these cohorts in the study.

## 5.2 Pharmacokinetic properties

The pharmacokinetic properties of remdesivir have been investigated in healthy volunteers and 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 93% bound to human plasma proteins (ex-vivo data) with free fraction ranging from 6.4% to 7.4%. The binding is independent of drug concentration over the range of 1 to 10 μM, with no evidence for saturation of remdesivir binding. After a single 150 mg dose of [$^{14}$C]-remdesivir in healthy subjects, the blood to plasma ratio of [$^{14}$C]-radioactivity 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. In the liver, carboxylesterase 1 and cathepsin A are the esterases responsible for 80% and 10% of remdesivir metabolism, respectively. Phosphoramidate cleavage followed by phosphorylation forms the active triphosphate, GS-443902. Dephosphorylation of all phosphorylated metabolites can result in the formation of nucleoside metabolite GS-441524 that itself is not efficiently re-phosphorylated. Decyanation of remdesivir and/or its metabolites, followed by subsequent rhodanese mediated conversion generates thiocyanate anion. The levels of thiocyanate detected following administration of 100 mg and 200 mg remdesivir were observed to be significantly below endogenous levels in human plasma.

Elimination

Following a single 150 mg IV dose of [$^{14}$C]-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.

Pharmacokinetics of remdesivir and metabolites in adults with COVID-19

Pharmacokinetic exposures for remdesivir and its metabolites in adults with COVID-19 are provided in Table 9.

**Table 9: Multiple dose PK parameters[a] of remdesivir and metabolites (GS-441524 and GS-704277) following IV administration of remdesivir 100 mg to adults with COVID-19**

| **Parameters Mean[b] (95%CI)** | **Remdesivir** | **GS-441524** | **GS-704277** |
|---|---|---|---|
| $C_{max}$ (ng/mL) | 1650 (1570, 1730) | 85.0 (78.8, 91.7) | 128 (118, 139) |
| $AUC_{tau}$ (ng•h/mL) | 983 (946, 1020) | 1410 (1290, 1530) | 229 (219, 241) |
| $C_{trough}$ (ng/mL) | ND | 38.8 (35.7, 42.2) | ND |

CI=Confidence Interval; ND=Not detectable (at 24 hours post-dose)
a. Population PK estimates for 30-minute IV infusion of remdesivir for 3 days (Study GS-US-540-9012, n=148).
b. Geometric mean estimates

Other special populations

*Gender, race and age*
Based on gender, race and age, pharmacokinetic differences on the exposures of remdesivir were evaluated using population pharmacokinetic analysis. Gender and race did not affect the pharmacokinetics of remdesivir and its metabolites (GS-441524 and GS-704277). Pharmacokinetic exposures of the GS-441524 metabolite were modestly increased in hospitalised COVID-19 patients ≥ 60 years of age, however no dose adjustment is needed in these patients.

*Pregnancy*
In CO-US-540-5961 (IMPAACT 2032) study, mean exposures ($AUC_{tau}$, $C_{max}$, and $C_{tau}$) of remdesivir and its metabolites (GS-441524 and GS-704277) were comparable between pregnant and non-pregnant women of child-bearing potential.

*Paediatric patients*
Population pharmacokinetic models for remdesivir and its circulating metabolites (GS-704277 and GS-441524), developed using pooled data from studies in healthy subjects and in adult and paediatric patients with COVID-19, were used to predict pharmacokinetic exposures in 50 paediatric patients aged ≥ 28 days to < 18 years and weighing ≥ 3 kg (Study GS-US-540-5823) (Table 10). Geometric mean exposures ($AUC_{tau}$, $C_{max}$ and $C_{tau}$) for patients ≥28 days to <18 years old and weighing ≥3 kg (Cohorts 1-4 and 8, n=50) at the doses administered were 1% to 40% higher for remdesivir 26% lower to 4% higher for, GS-441524 , and 13% lower to 95% higher for GS-704277 as compared to those in adult hospitalised patients with COVID-19. The differences were not considered clinically relevant. Plasma exposures of excipient SBECD were generally similar for all paediatric patients at the doses administered in GS-US-540-5823 study and were similar compared to adults with normal renal function, although data are very limited.

**Table 10: Pharmacokinetic parameters[a] estimate of steady-state plasma remdesivir, GS-441524 and GS-704277 in paediatric and adult hospitalised COVID-19 patients**

| Parameters Mean[b] | Paediatric patients | | | | | Adult hospitalised patients (N=289) |
|---|---|---|---|---|---|---|
| | Cohort 1 | Cohort 8 | Cohort 2 | Cohort 3 | Cohort 4 | |
| | 12 to <18 Years and Weighing ≥40 kg (N=12) | <12 Years and Weighing ≥40 kg (N=5) | 28 Days to <18 Years and Weighing 20 to <40 kg (N=12) | 28 Days to <18 Years and Weighing 12 to <20 kg (N=11) | 28 Days to <18 Years and Weighing 3 to <12 kg (N=10) | |
| **Remdesivir** | | | | | | |
| $C_{max}$ (ng/mL) | 2220 | 2440 | 2990 | 2570 | 2460 | 2160 |
| $AUC_{tau}$ (h•ng/mL) | 1450 | 1430 | 1990 | 1940 | 1500 | 1420 |
| **GS-441524** | | | | | | |
| $C_{max}$ (ng/mL) | 85.3 | 96.5 | 106 | 105 | 120 | 116 |
| $AUC_{tau}$ (h•ng/mL) | 1480 | 1460 | 1520 | 1530 | 1660 | 1930 |
| $C_{tau}$ (ng/mL) | 44.1 | 42.3 | 44.5 | 44.3 | 47.8 | 55.3 |
| **GS-704277** | | | | | | |
| $C_{max}$ (ng/mL) | 163 | 219 | 367 | 223 | 267 | 188 |
| $AUC_{tau}$ (h•ng/mL) | 390 | 351 | 574 | 390 | 390 | 400 |

a PK parameters were simulated using PopPK modeling with 0.5 hour of duration for remdesivir infusions.

b Geometric mean estimates.

Paediatric hospitalised patients are from Study GS-US-540-5823; patients received 200 mg on Day 1 followed by remdesivir 100 mg once daily on subsequent days (Cohort 1 and 8), or 5 mg/kg on Day 1 followed by remdesivir 2.5 mg/kg once daily on subsequent days (Cohort 2-4) for a total treatment duration of up to 10 days.

Adult hospitalised patients are from Study CO-US-540-5844 (a phase 3 randomised study to evaluate the safety and antiviral activity of remdesivir in patients with severe COVID-19); patients received 200 mg on Day 1 followed by remdesivir 100 mg once daily on subsequent days (10 days total treatment duration).

*Renal impairment*

The pharmacokinetics of remdesivir and its metabolites GS-441524 and GS-704277) and the excipient SBECD were evaluated in healthy subjects, those with mild (eGFR 60-89 mL/minute), moderate (eGFR 30-59 mL/minute), severe (eGFR 15-29 mL/minute) renal impairment, or with ESRD (eGFR <15 mL/minute) on haemodialysis or not on haemodialysis following a single dose of up to 100 mg of remdesivir (Table 11); and in a Phase 3 study in COVID-19 patients with severely reduced kidney function (eGFR <30 mL/minute) receiving remdesivir 200 mg on Day 1 followed by 100 mg from Day 2 to Day 5 (Table 12).

Pharmacokinetic exposures of remdesivir were not affected by renal function or timing of remdesivir administration around dialysis. Exposures of GS-704277, GS-441524, and SBECD were up to 2.8-fold, 7.9-fold and 20-fold higher, respectively, in those with renal impairment than those with normal renal function which is not considered clinically significant based on limited available safety data. No dose adjustment of remdesivir is required for patients with renal impairment, including those on dialysis.

**Table 11: Statistical comparison of single-dose pharmacokinetic parameters[a] of remdesivir and metabolites (GS-441524 and GS-704277) between adult subjects with decreased renal function[b] (mild, moderate, severe renal impairment and ESRD) and adult subjects[a] with normal renal function**

| GLSM Ratio[c] (90%CI) | 60-89 mL per minute N=10 | 30-59 mL per minute N=10 | 15-29 mL per minute N=10 | <15 mL per minute | | |
|---|---|---|---|---|---|---|
| | | | | Pre-haemodialysis N=6 | Post-haemodialysis N=6 | No dialysis N=3 |
| **Remdesivir** | | | | | | |
| $C_{max}$ (ng/mL) | 96.0 (70.5, 131) | 120 (101, 142) | 97.1 (83.3, 113) | 89.1 (67.1, 118) | 113 (79.4, 160) | 93.9 (65.4, 135) |
| $AUC_{inf}$ (h•ng/mL) | 99.5 (75.3, 132) | 122 (97.5, 152) | 94 (83.0, 107) | 79.6 (59.0, 108) | 108 (71.5, 163) | 88.9 (55.2, 143) |
| **GS-441524** | | | | | | |
| $C_{max}$ (ng/mL) | 107 (90, 126) | 144 (113, 185) | 168 (128, 220) | 227 (172, 299) | 307 (221, 426) | 300 (263, 342) |
| $AUC_{inf}$[d] (h•ng/mL) | 119 (97, 147) | 202 (157, 262) | 326 (239, 446) | 497 (365, 677) | 622 (444, 871) | 787 (649, 953) |
| **GS-704277** | | | | | | |
| $C_{max}$ (ng/mL) | 225 (120, 420) | 183 (134, 249) | 127 (96.1, 168) | 143 (100, 205) | 123 (83.6, 180) | 176 (119, 261) |
| $AUC_{inf}$ (h•ng/mL) | 139 (113, 171) | 201 (148, 273) | 178 (127, 249) | 218 (161, 295) | 206 (142, 297) | 281 (179, 443) |

CI=Confidence Interval; GLSM = geometric least-squares mean

a Exposures were estimated using noncompartmental analysis from a dedicated Phase 1 renal impairment study GS-US-540-9015; single doses up to 100 mg were administered; each subject with renal impairment had a matched adult subject enrolled with normal renal function (eGFR ≥90 mL/min/1.73$m^2$), same sex, and similar body mass index (BMI (± 20%)) and age (± 10 years) Subjects with reduced renal function and matched adult subjects with normal renal function received the same remdesivir dose

b eGFR was calculated using Modification of Diet in Renal Disease equation and reported in mL/min/1.73 m^^2

c Ratio calculated for the comparison of PK parameters of test (subjects with reduced renal function) to reference (subjects with normal renal function)

d $AUC_{0-72h}$ for subjects on haemodialysis

**Table 12: Pharmacokinetic parameters[a] of remdesivir and metabolites (GS-441524 and GS-704277) following IV administration of remdesivir (200 mg on day 1 followed by 100 mg daily on days 2-5) to adults with COVID-19 and severely reduced kidney function (eGFR <30 mL/min /1.73 $m^2$)**

| **Parameter Mean[b] (percentile, 5th, 95th)** | **Remdesivir** | **GS-441524** | **GS-704277** |
|---|---|---|---|
| $C_{max}$ (ng/mL) | 2090 (890, 4360) | 349 (72.4, 818) | 232 (61.9, 613) |
| $AUC_{tau}$ (h•ng/mL) | 1700 (1030, 2970) | 7580 (1630, 18600) | 919 (509, 1620) |

a Population PK estimates for 30-minute IV infusion of remdesivir for 5 days (Study GS-US-540-5912, n=90).
b Geometric mean estimates.

*Hepatic impairment*
The pharmacokinetics of remdesivir and its metabolites (GS-441524 and GS-704277) were evaluated in healthy subjects and those with moderate or severe hepatic impairment (Child-Pugh Class B or C) following a single dose of 100 mg of remdesivir. Relative to subjects with normal hepatic function, mean exposures ($AUC_{inf}$, $C_{max}$) of remdesivir and GS-704277 were comparable in moderate hepatic impairment and up to 2.4 fold higher in severe hepatic impairment; however, the increase was not considered clinically significant.

*Hospitalisation*
Pharmacokinetic exposures for remdesivir in hospitalised patients with severe COVID-19 pneumonia were generally within the range of the exposures in non-hospitalised patients. The GS-704277 and GS-441524 metabolite levels were modestly increased.

*Interactions*
*In vitro:*
Remdesivir inhibited CYP3A4. At physiologically relevant concentrations (steady-state), remdesivir or its metabolites GS-441524 and GS-704277 did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, and 2D6. Remdesivir is not a time-dependent inhibition of CYP450 enzymes.

Remdesivir induced CYP1A2 and potentially CYP3A4, but not CYP2B6.

The data indicate no clinically relevant inhibition of UGT1A3, 1A4, 1A6, 1A9 or 2B7 by remdesivir or its metabolites GS-441524 and GS-704277. Remdesivir, but not its metabolites, inhibited UGT1A1.

For GS-441524 and GS-704277, the only enzyme for which metabolism could be detected was UGT1A3.

Remdesivir inhibited OAT3, MATE1, OCT1, OATP1B1 and OATP1B3. At physiologically relevant concentrations, remdesivir and its metabolites did not inhibit P-gp and BCRP. (see section 4.5)

*In vivo:*
Based on clinical drug interaction studies with remdesivir, no clinically significant drug interactions are expected with substrates of CYP1A2, CYP3A4 (including dexamethasone), UGT1A1, MATE1, OAT3, OCT1, OATP1B1 and OATP1B3.

## 5.3 Preclinical safety data

Toxicology

Following intravenous administration (slow bolus) of remdesivir to rhesus monkeys and rats, severe renal toxicity occurred after short treatment durations. In 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, and an unscheduled death of one animal at the 20 mg/kg/day dose level. In rats, dosage levels of >3 mg/kg/day for up to 4 weeks resulted in findings indicative of kidney injury and/or dysfunction. Systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) were 0.1 times (monkeys at 5 mg/kg/day) and 0.3 times (rats at 3 mg/kg/day) the exposure in humans following intravenous administration at the recommended human dose (RHD).

Carcinogenesis

Long-term animal studies to evaluate the carcinogenic potential of remdesivir have not been performed.

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.

Reproductive toxicity

In female rats, decreases in corpora lutea, numbers of implantation sites, and viable embryos, were seen when remdesivir was administered intravenously daily at a systemically toxic dose (10 mg/kg/day) 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. There were no effects on female reproductive performance (mating, fertility, and conception) at this dose level.

In rats and rabbits, remdesivir demonstrated no adverse effect on embryofoetal development when administered to pregnant animals at systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) that were up to 4 times the exposure in humans at the RHD.

In rats, there were no adverse effects on pre- and post-natal development at systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) that were similar to the exposure in humans at the RHD.

# 6 PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Betadex sulfobutyl ether sodium
Hydrochloric acid (to adjust pH) (E507)
Sodium hydroxide (to adjust pH) (E524)

## 6.2 Incompatibilities

This medicinal product must not be mixed or administered simultaneously with other medicinal products in the same dedicated line except those mentioned in section 6.6.

## 6.3 Shelf life

Unopened vials

4 years

Reconstituted and diluted solution for infusion

Store diluted remdesivir solution for infusion up to 24 hours at below 25°C or 48 hours in a refrigerator (2°C – 8°C).

## 6.4 Special precautions for storage

No special precautions for storage.
For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

## 6.5 Nature and contents of container

Type I clear glass vial, an elastomeric closure, and an aluminium overseal with a flip-off cap.

Pack size: 1 vial

## 6.6 Special precautions for disposal

Prepare solution for infusion under aseptic conditions and on the same day as administration. Remdesivir should be inspected visually for particulate matter and discolouration 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 19 mL sterile water for injections and diluted in sodium chloride 9 mg/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, and insert the needle in the centre of the vial stopper.
  - Discard the vial if a vacuum does not pull the sterile water for injections into the vial.
- Only use **sterile water** for injection to reconstitute remdesivir powder.
- 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 recommended to administer immediately after preparation when possible.

*Adults and paediatric patients (weighing at least 40 kg)*
- Using Table 13, determine the volume of sodium chloride 9 mg/mL (0.9%) solution for injection to withdraw from the infusion bag.

**Table 13: Recommended dilution instructions – Reconstituted remdesivir powder for concentrate for solution for infusion**

| Remdesivir dose | Sodium chloride 9 mg/mL (0.9%) infusion bag volume to be used | Volume to be withdrawn and discarded from sodium chloride 9 mg/mL (0.9%) infusion bag | Required volume of reconstituted remdesivir |
|---|---|---|---|
| 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 |

NOTE: 100 mL 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 9 mg/mL from the bag using an appropriately sized syringe and needle per Table 13.

- Withdraw the required volume of reconstituted remdesivir using an appropriately sized syringe per Table 13. Discard any unused portion remaining in the remdesivir vial.
- Transfer the required volume of reconstituted remdesivir 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 24 hours at room temperature (20°C to 25°C) or 48 hours in the refrigerator (2°C to 8°C).

*Paediatric patients (at least 4 weeks of age and weighing 3 kg to less than 40 kg)*

- Further dilute the 100 mg/20 mL (5 mg/mL) remdesivir concentrate to a fixed concentration of 1.25 mg/mL using 0.9% sodium chloride.
- The total required infusion volume of the 1.25 mg/mL remdesivir solution for infusion is calculated from the paediatric weight-based dosing regimens of 5 mg/kg for the Loading Dose and 2.5 mg/kg for each Maintenance Dose.
- Small 0.9% sodium chloride infusion bags (e.g., 25, 50, or 100 mL) or an appropriately sized syringe should be used for paediatric dosing. The recommended dose is administered via IV infusion in a total volume dependent on the dose to yield the target remdesivir concentration of 1.25 mg/mL.
- A syringe may be used for delivering volumes <50 mL.

After infusion is complete, flush with at least 30 mL of sodium chloride 9 mg/mL.

Disposal

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

## 7 MARKETING AUTHORISATION HOLDER

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## 8 MARKETING AUTHORISATION NUMBER(S)

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