Professional Information for Medicines for Human Use

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

VEKLURY Lyophilised Powder for IV Infusion 100 mg

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/ SARS-CoV-2) in adult patients with pneumonia requiring supplemental oxygen (see section 5.1).

4.2 Posology and method of administration

Use of VEKLURY is confined to healthcare facilities in which patients can be monitored closely (see section 4.4).

Posology

The recommended dosage of VEKLURY is:

- Day 1 – single loading dose of remdesivir 200 mg given by intravenous infusion
- Day 2 onwards – 100 mg given once daily by intravenous infusion.

The total duration of treatment should be at least 5 days and not more than 10 days.

Special populations

Elderly

No dose adjustment of VEKLURY 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 VEKLURY 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 VEKLURY in children under the age of 18 years have not yet been established. No data are available.

Method of administration

For intravenous use.

VEKLURY 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 1: Recommended rate of infusion – for reconstituted and diluted remdesivir powder for concentrate for solution for infusion

Infusion Bag Volume	Infusion Time	Rate of Infusion
250 mL	30 min	8.33 mL/min
	60 min	4.17 mL/min
	120 min	2.08 mL/min
100 mL	30 min	3.33 mL/min
	60 min	1.67 mL/min
	120 min	0.83 mL/min

4.3 Contraindications

Hypersensitivity to remdesivir 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 VEKLURY. 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 VEKLURY. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration of VEKLURY 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 VEKLURY. 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 VEKLURY (see section 5.2).

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.

Risk of reduced antiviral activity when coadministered with chloroquine or hydroxychloroquine

Coadministration of VEKLURY 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 VEKLURY (see sections 4.5 and 5.1)

Concomitant use of remdesivir and dexamethasone, interferon and other medicines have not been investigated.

4.5 Interaction with other medicinal products and other forms of interaction

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

Effects of other medicinal products on VEKLURY

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 2 summarises the pharmacokinetic effects of studied drugs on remdesivir and metabolites GS-704277 and GS-441524.

Table 2: 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[29]	remdesivir: C_{max} ↑49% AUC_{inf} ↑89% GS-704277: C_{max} ↑151% AUC_{inf} ↑197% GS-441524: C_{max} ↑17% AUC_{inf} ↔ 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[29]	remdesivir: C_{max} ↓13% AUC_{inf} ↓8% GS-704277: C_{max} ↔ AUC_{inf} ↔ GS-441524: C_{max} ↔ AUC_{inf} ↓17% 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 VEKLURY on other medicinal products

In vitro, VEKLURY is an inhibitor of CYP3A4, UGT1A1, MATE1, OAT3, OCT1, OATP1B1 and OATP1B3. Until respective clinical data become available, the coadministration of sensitive substrates of these enzymes and/or transporters should be considered with caution. VEKLURY induced CYP1A2 and potentially CYP3A *in vitro.* Co-administration of VEKLURY with CYP1A2 or CYP3A4 substrates with narrow therapeutic index may lead to loss of their efficacy.

Dexamethasone is a substrate of CYP3A4 and although VEKLURY inhibits CYP3A4, due to VEKLURY's rapid clearance after IV administration, remdesivir is unlikely to have a significant effect on dexamethasone exposure.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data from the use of VEKLURY 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. 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.

Because of the potential for viral transmission to SARS-CoV-2-negative infants and the limited clinical experience, mothers receiving VEKLURY should not breastfeed their infants.

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 VEKLURY 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

Patients receiving VEKURY must not drive or use machines until all side effects of the medicine and the symptoms of SARS-CoV-2 infection, have resolved.

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 3 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 3: 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*

Frequency	Adverse reaction
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 VEKLURY administration without additional intervention

Description of selected adverse reactions

Transaminases increased

In healthy volunteer studies, increases in alanine transaminase (ALT), aspartate aminotransferase (AST) or both in subjects who received VEKLURY were 1,25 to 2,5 times the upper limit of normal (ULN) (10 %) or 2,5 to 5 times ULN (4 %). In clnical studies of patients with COVID-19, the incidence of increased transaminases was similar in patients treated with VEKLURY 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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-ucm.org) found on SAHPRA website.

4.9 Overdose

Treatment of overdose with VEKLURY 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 VEKLURY.

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[1] with EC50 value 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 normal human bronchial epithelial cells.

Resistance

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 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 cell culture and attenuated SARS-CoV pathogenesis in a mouse model.

The cell culture development of SARS-CoV-2 resistance to remdesivir has not been assessed to date. No clinical data are available on the development of SARS-CoV-2 resistance to remdesivir.

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 %), 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 4.

Table 4: 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)	

ECMO = Extracorporeal membrane oxygenation
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-540-5912 in patients with COVID-19 and renal impairment

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

Current non-clinical and clinical data do not suggest a risk of QT prolongation, but QT prolongation has not been fully evaluated in humans.

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.

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 5.

Table 5: 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)	2700 (2440, 2990)	143 (135, 152)	198 (180, 218)
AUC_{tau} (ng•h/mL)	1710 (1480, 1980)	2410 (2250, 2580)	392 (348, 442)
C_{tan} (ng/mL)	ND	61.5 (56.5, 66.8)	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=147).
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-704277 and GS-441524). 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

The pharmacokinetics in paediatric patients have not been evaluated.

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 26-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 6: 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/1.73m^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 7: 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)	3850 (1530, 8720)	703 (343, 1250)	378 (127, 959)
AUC_{tau} (h•ng/mL)	2950 (1390, 8370)	15400 (7220, 27900)	1540 (767, 3880)

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.

Interactions

Remdesivir inhibited CYP3A4 *in vitro* (see section 4.5). 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 *in vitro.* Remdesivir is not a time-dependent inhibitor of CYP450 enzymes *in vitro*.

Remdesivir induced CYP1A2 and potentially CYP3A4, but not CYP2B6 *in vitro* (see section 4.5).

In vitro data indicates no clinically relevant inhibition of UGT, 1A3, 1A4, 1A6, 1A9 or 2B7 by remdesivir or its metabolites GS-441524 and GS-704277. Remdesivir, but not its metabolites, inhibited UGT1A1 *in vitro.*

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 *in vitro* (see section 4.5).

At physiologically relevant concentrations, remdesivir and its metabolites did not inhibit Pgp and BCRP *in vitro.*

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 (rat 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)

Sodium hydroxide (to adjust pH)

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

3 years

Reconstituted and diluted solution for infusion

Store diluted remdesivir solution for infusion up to 4 hours at below 25 °C or 24 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, a grey elastomeric closure, and an aluminium overseal with a red-coloured polypropylene flip-off cap.

Pack size: 1 vial

6.6 Special precautions for disposal and other handling

Prepare solution for infusion under aseptic conditions and on the same day as administration. VEKLURY should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Should either be observed, the solution should be discarded and fresh solution prepared.

VEKLURY 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.

<u>Preparation of VEKLURY solution for infusion</u>

Reconstitution

Remove the required number of single-use vial(s) from storage. For each vial:

- Aseptically reconstitute VEKLURY 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 always recommended to administer - immediately after preparation when possible.

- Using Table 8, determine the volume of sodium chloride 9 mg/mL (0.9 %) solution for injection to withdraw from the infusion bag.

Table 8: Recommended dilution instructions – Reconstituted VEKLURY 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 8.
- Withdraw the required volume of reconstituted remdesivir n using an appropriately sized syringe per Table 8. Discard any unused portion remaining in the VEKLURY 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 4 hours at room temperature (20 °C to 25 °C) or 24 hours in the refrigerator (2 °C to 8 °C).

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. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER(S)

55/20.2.8/0458

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 July 2021

10. DATE OF REVISION OF THE TEXT

17 September 2025

Mee Towindo Digitally signed by Mee Towindo
Date: 2025.10.07 14:12:16 +02'00'