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

The pharmacokinetics of VEKLURY have not been evaluated in patients with renal impairment. Patients with eGFR ≥30 mL/min have received remdesivir for treatment of COVID-19 with no dose adjustment. VEKLURY should not be used in patients with eGFR <30 mL/min (see sections 4.4 and 5.2).

Hepatic impairment

The pharmacokinetics of VEKLURY have not been evaluated in patients with hepatic impairment. It is not known if dosage adjustment is appropriate in patients with hepatic impairment (see sections 4.4 and 5.2).

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.

Transaminase elevations

Transaminase elevations have been observed in the VEKLURY clinical trials, including in healthy volunteers and patients with COVID-19. Liver function should be determined in all patients prior to starting VEKLURY and should be monitored while receiving it as clinically appropriate. No clinical studies with VEKLURY have been conducted in patients with hepatic impairment.

- VEKLURY should not be initiated in patients with alanine aminotransferase (ALT) ≥5 times the upper limit of normal at baseline
- VEKLURY should be discontinued in patients who develop:
    - ALT ≥5 times the upper limit of normal during treatment with VEKLURY. It may be restarted when ALT is <5 times the upper limit of normal.

      OR
    - ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalised ratio (INR) (see sections 4.8 and 5.2).

Renal impairment

In animal studies on rats and monkeys, severe renal toxicity was observed (see section 5.3). The mechanism of this renal toxicity is not fully understood. A relevance for humans cannot be excluded.

All patients should have eGFR determined prior to starting remdesivir and while receiving it as clinically appropriate. VEKLURY should not be used in patients with eGFR <30 mL/min.

Excipients

VEKLURY contains betadex sulfobutyl ether sodium, which is renally cleared and accumulates in patients with decreased renal function, which may potentially adversely affect renal function. Therefore, VEKLURY should not be used in patients with eGFR < 30 mL/min (see sections 4.2 and 5.2).

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

No clinical interaction studies have been performed with remdesivir. The overall potential for interactions is currently unknown; patients should remain under close observation during the days of remdesivir administration. Due to antagonism observed *in vitro*, concomitant use of remdesivir with chloroquine phosphate or hydroxychloroquine sulphate is not recommended.

Effects of other medicinal products on VEKLURY

In vitro, remdesivir is a substrate for esterases in plasma and tissue, drug metabolizing enzymes CYP2C8, CYP2D6, and CYP3A4, and is a substrate for Organic Anion Transporting Polypeptides 1B1 (OATP1B1) and P-glycoprotein (P-gp) transporters.

The potential of interaction of VEKLURY with inhibitors/inducers of the hydrolytic pathway (esterase) or CYP2C8, 2D6 or 3A4 has not been studied. The risk of clinically relevant interaction is unknown. Strong

inhibitors may result in increased VEKLURY exposure. The use of strong inducers (e.g. rifampicin) may decrease plasma concentrations of VEKLURY and is not recommended.

Dexamethasone is reported to be a moderate inducer of CYP3A and P-gp. Induction is dose-dependent and occurs after multiple doses. Dexamethasone is unlikely to have a clinically significant effect on VEKLURY as VEKLURY has a moderate-high hepatic extraction ratio, and is used for a short duration in the treatment of COVID-19.

Effects of VEKLURY on other medicinal products

In vitro, VEKLURY is an inhibitor of CYP3A4, OATP1B1 and OATP1B3. The clinical relevance of these *in vitro* drug interactions has not been established. VEKLURY may transiently increase plasma concentrations of medicinal products that are substrates of CYP3A or OATP 1B1/1B3. No data is available, however it can be suggested that medicinal products that are substrates of CYP3A4 or substrates of OATP 1B1/1B3 should be administered at least 2 hours after VEKLURY. 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 are no or limited amount of data from the use of VEKLURY in pregnant women. VEKLURY should not be used during pregnancy.

Women of child-bearing potential have to use effective contraception during treatment.

Breast-feeding

It is unknown whether VEKLURY is excreted in human milk or the effects on the breast-fed infant, or the effects on milk production.

In animal studies, the nucleoside analog metabolite GS-441524 has been detected in the blood of nursing rat pups of mothers given VEKLURY. Therefore, excretion of VEKLURY and/or metabolites into the milk of lactating animals can be assumed.

Because of the potential for viral transmission to SARS-CoV-2-negative infants and adverse reactions from the drug in breast-feeding infants, 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 2 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 2: Tabulated list of adverse reactions

Frequency	**Adverse reaction**
Immune system disorders	
Rare	hypersensitivity
Not known	Anaphylactic reaction
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 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 grade 1 (10 %) or grade 2 (4 %). In a randomised, double-blind, placebo-controlled clinical study of patients with COVID-19 (NIAID ACTT-1), any grade (≥ 1.25 × upper limit of normal (ULN)) laboratory abnormalities of increased AST and increased ALT occurred in 33 % and 32 % of patients, respectively, receiving remdesivir compared with 44 % and 43 % of patients, respectively, receiving placebo. Grade ≥3 (≥ 5.0 × ULN) laboratory abnormalities of increased AST and increased ALT occurred in 6 % and 3 % of patients, respectively, receiving remdesivir compared with 8 % and 6 % of patients, respectively, receiving placebo. In a randomised, open-label multi-centre clinical trial (Study GS-US-540-5773) in hospitalised patients with severe COVID-19 receiving VEKLURY for 5 (n=200) or 10 days (n=197), any grade laboratory abnormalities of increased AST and increased ALT occurred in 40 % and 42 % of patients, respectively, receiving VEKLURY. Grade ≥3 laboratory abnormalities of increased AST and increased ALT both occurred in 7 % of patients receiving VEKLURY. In a randomised, open-label multi-centre clinical trial (Study GS-US-540-5774) in hospitalised patients with moderate COVID-19 receiving VEKLURY for 5 (n=191) or 10 days (n=193) compared to standard of care (n=200), any grade laboratory abnormalities of increased AST and increased ALT occurred in 32 % and 33 % of patients, respectively, receiving VEKLURY, and 33 % and 39 % of patients, respectively, receiving standard of care. Grade ≥3 laboratory abnormalities of increased AST and increased ALT occurred in 2 % and 3 % of patients, respectively, receiving VEKLURY and 6 % and 7 %, respectively, receiving 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 Grades 1-2) was higher in subjects who received remdesivir compared to placebo, with no difference observed in the incidence of bleeding events between the two groups. Prothrombin time should be monitored while receiving remdesivir as clinically appropriate.

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 asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8

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 with an EC50 value of 280 nM after 72 hours of treatment. 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 3.

Table 3: 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 $\leqslant$ 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.

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. No pharmacokinetic data is available from patients with COVID-19.

Absorption

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

Distribution

Remdesivir is approximately 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. 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. The human mass balance study also indicates presence of a currently unidentified major metabolite (M27) in 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.

Other special populations

Gender, race and age

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

Paediatric patients

The pharmacokinetics in paediatric patients have not been evaluated.

Renal impairment

The pharmacokinetics of remdesivir and GS-441524 in renal impairment have not been evaluated. Remdesivir is not cleared unchanged in urine to any substantial extent, but its main metabolite GS-441524 is renally cleared and the metabolite levels in plasma may increase in patients with impaired

renal function. The excipient betadex sulfobutyl ether sodium is renally cleared and accumulates in patients with decreased renal function. Remdesivir should not be used in patients with eGFR <30 mL/min.

Hepatic impairment

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

Interactions

The potential of interaction of remdesivir as a victim was not studied with regards to the inhibition of the hydrolytic pathway (esterase). The risk of clinically relevant interaction is unknown.

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 may however transiently inhibit CYP2B6, 2C8, 2C9 and 2D6 on the first day of administration. The clinical relevance of this inhibition was not studied. The potential for time-dependent inhibition of CYP450 enzymes by remdesivir was not studied.

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

In vitro data indicates no clinically relevant inhibition of UGT1A1, 1A3, 1A4, 1A6, 1A9 or 2B7 by remdesivir or its metabolites GS-441524 and GS-704277.

Remdesivir inhibited OATP1B1 and OATP1B3 *in vitro* (see section 4.5). No data is available for OAT1, OAT3 or OCT2 inhibition by remdesivir.

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). An unidentified major metabolite (M27) was shown to be present in human plasma (see section 5.2). The exposure of M27 in rhesus monkeys and rats is unknown.

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.

It is unknown if the active nucleoside analog triphosphate GS-443902 and the unidentified major human metabolite M27 are formed in rats and rabbits.

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.

Preparation of VEKLURY solution for infusion

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

Table 4: 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 4.
- Withdraw the required volume of reconstituted remdesivir n using an appropriately sized syringe per Table 4. 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. MARKETING AUTHORISATION HOLDER

Gilead Sciences South Africa (Pty) Ltd,

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8. REGISTRATION NUMBER(S)

55/20.2.1/0458

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 July 2021

10. DATE OF REVISION OF THE TEXT

24 December 2021

RDV-ZA-OCT21-EU-AUG21