▼This medicinal product is subject to additional monitoring in Australia due to provisional approval. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – VEKLURY® (REMDESIVIR) POWDER FOR INJECTION

1 NAME OF THE MEDICINE

Remdesivir.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

VEKLURY (remdesivir) powder for injection, 100 mg, available as a sterile, preservative-free, white to off-white to yellow lyophilized powder that is to be reconstituted with 19 mL of Sterile Water for Injection and further diluted into 0.9% sodium chloride infusion bag prior to administration by intravenous infusion. Following reconstitution, each vial contains 100 mg/20 mL (5 mg/mL) of VEKLURY concentrated solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

VEKLURY has **provisional approval** for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older weighing at least 40 kg) with pneumonia, requiring supplemental oxygen (see section 5.1).

The decision to approve this medicine has been made based on limited data. More comprehensive evidence is required to be submitted.

4.2 DOSE AND METHOD OF ADMINISTRATION

Use of remdesivir is confined to healthcare facilities in which patients can be monitored closely. VEKLURY is for single use in one patient only.

The recommended dosage of VEKLURY in patients 12 years of age and older and weighing at least 40 kg is:

- Day 1 - a single loading dose of VEKLURY 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.

VEKLURY 100 mg powder for injection

Reconstitution Instructions

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

- Aseptically reconstitute VEKLURY lyophilized powder by addition of 19 mL of Sterile Water for Injection using a suitably sized syringe and needle per vial.
- Discard the vial if a vacuum does not pull the Sterile Water for Injection into the vial.
- Immediately shake the vial for 30 seconds.
- Allow the contents of the vial to settle for 2 to 3 minutes. A clear solution should result.
- If the contents of the vial are not completely dissolved, shake the vial again for 30 seconds and allow the contents to settle for 2 to 3 minutes. Repeat this procedure as necessary until the contents of the vial are completely dissolved.
- 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 Instructions

Care should be taken during admixture to prevent inadvertent microbial contamination. As there is no preservative or bacteriostatic agent present in this product, aseptic technique must be used in preparation of the final parenteral solution. It is always recommended to administer IV medication immediately after preparation when possible.

Using Table 1, withdraw and discard the required volume of 0.9% sodium chloride from the infusion bag using an appropriately sized syringe and needle.

Table 1: Recommended Dilution Instructions— Reconstituted VEKLURY Powder for Injection in Adults and Paediatric Patients 12 Years of Age and Older and Weighing at Least 40 kg

VEKLURY Dose	Sodium chloride 9 mg/mL (0.9%) infusion bag volume to be used	Volume to be withdrawn and discarded from 9 mg/mL (0.9%) sodium chloride infusion bag	Required volume of reconstituted VEKLURY
200 mg (2 vials)	250 mL	40 mL	40 mL (2 ´ 20 mL)
	100 mL	40 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 1.
- Withdraw the required volume of reconstituted VEKLURY powder for injection using an appropriately sized syringe per Table 1. Discard any unused portion remaining in the VEKLURY vial.
- Transfer the required volume of reconstituted VEKLURY powder for injection to the selected infusion bag.
- Gently invert the bag 20 times to mix the solution in the bag. Do not shake.
- The prepared infusion solution is stable for 4 hours at room temperature (20 °C to 25 °C) or 24 hours in the refrigerator at 2 °C to 8 °C.

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

Administration Instructions

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.

Administer the diluted solution with the infusion rate described in Table 2.

Table 2: Recommended Rate of Infusion – Diluted VEKLURY Powder for Injection in Adults and Paediatric Patients 12 years of Age and Older 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

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

Special populations

Elderly
No dose adjustment 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 greater than or equal to 30 mL per minute have received VEKLURY for treatment of COVID-19 with no dose adjustment of VEKLURY.

All patients must have an eGFR determined before dosing of VEKLURY and while receiving VEKLURY as clinically appropriate. Because the excipient SBECD is renally cleared accumulates in patients with decreased renal function, administration of drugs formulated with SBECD (such as VEKLURY) is not recommended in patients with eGFR less than 30 mL per minute unless the potential benefit outweighs the potential risk.

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 section 4.4 and 5.2).

Paediatric population
The safety and efficacy of remdesivir in children under the age of 12 years and weighing <40 kg have not yet been established. No data are available.

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, dyspnea, wheezing, angioedema, rash, nausea, vomiting, diaphoresis, and shivering. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration of remdesivir and initiate appropriate treatment.

Transaminase elevations

Transaminase elevations have been observed in VEKLURY clinical development program, including in healthy volunteers and patients with COVID-19. Hepatic laboratory testing should be performed in all patients prior to starting VEKLURY and should be monitored while receiving VEKLURY as clinically appropriate. No clinical studies with remdesivir have been conducted in patients with hepatic impairment VEKLURY should only be used in patients with hepatic impairment if the potential benefit outweighs the potential risk.

- 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. VEKLURY 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 section 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 VEKLURY and while receiving it a clinically appropriate. VEKLURY should not be used in patients with eGFR <30 mL/min.

Excipients

The excipient sulfobutyl betadex sodium 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 section 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 section 4.5, 5.1)

Use in the Elderly

See sections 4.2, 5.1 and 5.2.

Paediatric Use

See section 4.2.

Effects on Laboratory Tests

See section 4.8.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Drug-drug interaction trials of VEKLURY and other concomitant medications have not been conducted. The overall potential for interactions is currently unknown; patients should remain under close observation during the days of VEKLURY administration. Due to antagonism observed in vitro, concomitant use of VEKLURY with chloroquine phosphate or hydroxychloroquine sulphate is not recommended.

Effects of other medicinal products on remdesivir

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 remdesivir 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 remdesivir exposure. The use of strong inducers (e.g. rifampicin) may decrease plasma concentrations of remdesivir 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 significant effect on remdesivir as remdesivir has a moderate-high hepatic extraction ratio, and is used for a short duration in the treatment of COVID-19.

Effects of remdesivir on other medicinal products

In vitro, remdesivir is an inhibitor of CYP3A4, OATP1B1 and OATP1B3. The clinical relevance of these *in vitro* drug interactions has not been established. Remdesivir 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 remdesivir. Remdesivir induced CYP1A2 and potentially CYP3A *in vitro*. Co-administration of remdesivir with CYP1A2 or CYP3A4 substrates with narrow therapeutic index may lead to loss of their efficacy.
Dexamethasone is a substrate of CYP3A4 and although remdesivir inhibits CYP3A4, due to remdesivir's rapid clearance after I.V administration, remdesivir is unlikely to have a significant effect on dexamethasone exposure.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No human data on the effect of VEKLURY 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.

Use in pregnancy – Pregnancy Category B2

No adequate and well-controlled studies of VEKLURY use in pregnant women have been conducted. VEKLURY should be used during pregnancy only if the potential benefit justifies the potential risk for the mother and the foetus.

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

Use in lactation

There is no information regarding the presence of remdesivir in human milk, the effects on the breastfed infant, or the effects on milk production.

In animal studies, the nucleoside analogue metabolite GS 441524 has been detected in the blood of nursing rat pups of mothers given remdesivir, Therefore, excretion of remdesivir 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 breastfeeding infants, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VEKLURY and any potential adverse effects on the breastfed child from VEKLURY or from the underlying maternal condition.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of VEKLURY on the ability to drive and use machines have been performed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Experience from Clinical Studies
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).

Table 3: Tabulated list of adverse reactions

Frequency	Adverse reaction
Immune system disorders	
Rare	hypersensitivity
Nervous system disorders	

Frequency	Adverse reaction
Common	headache
Gastrointestinal disorders	
Common	nausea
Hepatobiliary disorders	
Very Common	transaminases increased
Skin and subcutaneous tissue disorders	
Common	rash
Injury, poisoning and procedural complications	
Rare	infusion-related reaction

Description of selected adverse reactions

Transaminases Increased

In healthy volunteer studies, increases in 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), the incidence of grade ≥3 non-serious adverse events of increased aminotransferase levels including ALT, AST, or both was 4% in patients receiving VEKLURY compared with 6% in 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 (≥ 1.25 × upper limit of normal (ULN)) laboratory abnormalities of increased AST and increased ALT occurred in 40% and 42% of patients, respectively, receiving VEKLURY. Grade ≥ 3 (≥ 5.0 × ULN) 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.

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no human experience of acute overdosage with VEKLURY. 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antivirals for systemic use, direct acting antivirals, other antivirals, ATC code: not yet assigned.

Mechanism of action

Remdesivir is an adenosine nucleotide prodrug that distributes into cells where it is metabolised to form the pharmacologically active nucleoside triphosphate metabolite. Metabolism of remdesivir to remdesivir triphosphate has been demonstrated in multiple cell types. Remdesivir triphosphate acts as an analogue of adenosine triphosphate (ATP) and competes with the natural ATP substrate for incorporation into nascent RNA chains by the SARS-CoV-2 RNA-dependent RNA polymerase, which results in delayed chain termination during replication of the viral RNA. Remdesivir triphosphate is a weak inhibitor of mammalian DNA and RNA polymerases with low potential for mitochondrial toxicity.

Antiviral Activity

Remdesivir exhibited *in vitro* activity against a clinical isolate of SARS-CoV-2 in primary human airway epithelial (HAE) cells with a 50% effective concentration (EC_{50}) of 9.9 nM after 48 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

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

Cell culture resistance profiling of remdesivir using the rodent CoV murine hepatitis virus identified 2 substitutions (F476L and V553L) in the viral RNA-dependant RNA polymerase at residues conserved across CoVs that conferred 5.6-fold reduced susceptibility to remdesivir. The mutant viruses showed reduced viral fitness in vitro, Introduction of the corresponding mutations (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.

Clinical trials

Clinical trials in patients with COVID 19

NIAID ACTT 1 Study (CO-US-540-5776)

A randomised, double-blind, placebo-controlled clinical trial evaluated VEKLURY 200 mg once daily for 1 day followed by VEKLURY 100 mg once daily for 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 1,063 hospitalised patients: 120 (11.3%) patients with mild/moderate disease (defined by SpO2 >94% and respiratory rate <24 breaths/min without supplemental oxygen) and 943 (88.7%) patients with severe disease (defined by SpO2 ≤94% on room air, or respiratory rate ≥ 24 breaths/min and requiring supplemental oxygen or ventilatory support). Patients were randomised 1:1, stratified by disease severity at enrolment, to receive VEKLURY (n=541) or placebo (n=522), 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, 21% were Black, 13% were Asian. The most common comorbidities were hypertension (49.6%), obesity (37.0%), type 2 diabetes mellitus (29.7%), and coronary artery disease (11.6%).

Approximately 33% (180/541) of the patients received a 10 day treatment course with VEKLURY.

The primary clinical endpoint was time to recovery within 28 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. In a preliminary analysis performed after all patients had been followed up for 14 days, the median time to recovery in the overall population was 11 days in the VEKLURY group compared to 15 days in the placebo group (recovery rate ratio 1.32; [95% CI 1.12 to 1.55], p<0.001). The outcome differed relevantly between the two strata. In the severe disease stratum time to recovery was 12 days in the VEKLURY group and 18 days in the placebo group (recovery rate ratio 1.37 [95% CI: 1.15 to 1.63]; Table 4). For the mild/moderate disease stratum, time to recovery was not different between the two groups (5 days for both, VEKLURY and placebo).

Table 4: Recovery outcomes in the severe disease stratum from NIAID ACTT 1

	VEKLURY (N=476)	Placebo (N=464)
	Days to recovery	
Number of recoveries	282	227
Median (95 %CI)	12 (10; 14)	18 (15; 21)
Recovery rate ratio (95% CI)[a]	1.37 (1.15; 1.63)	

a Recovery rate ratio calculated from the stratified Cox model. Recovery rate ratios >1 indicate benefit for remdesivir

There was no difference in efficacy in patients randomised during the first 10 days after onset of symptoms as compared to those with symptoms for more than 10 days.
The clinical benefit of VEKLURY was most apparent in patients receiving oxygen, however, not on ventilation, at Day 1 (rate recovery ratio 1.47 [95% CI 1.17–1.84]).

For patients who were receiving mechanical ventilation or ECMO on Day 1 no difference in recovery rate was observed between the treatment groups (0.95 [95% CI 0.64 to 1.42]).

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.

Study GS-US-540-5773 in patients with severe COVID 19

A randomised, open-label multi-centre clinical trial (Study GS-US-540-5773) of patients at least 12 years of age with confirmed SARS-
air, and radiological evidence of pneumonia compared 197 patients who received VEKLURY for 10 days with 200 patients who received VEKLURY for 5 days. Patients on mechanical ventilation at screening were excluded.

At baseline, the median age of patients was 61 years (range, 20 to 98 years); 64% were male, 75% were White, 12% were Black, and 12% were Asian. More patients in the 10-day group than the 5-day group required invasive mechanical ventilation or ECMO (5% vs 2%), or high-flow oxygen support (30% vs 25%), at baseline. Median duration of symptoms and hospitalization prior to first dose of VEKLURY were similar across treatment groups.

Overall, after adjusting for between-group differences at baseline, patients receiving a 5-day course of VEKLURY had similar clinical status at Day 14 as those receiving a 10-day course (odds ratio for improvement: 0.75; [95% CI 0.51 to 1.12]). In addition, recovery rates were 70% and 58%, and mortality rates were 8% and 11%, in the 5-day and 10-day groups, respectively. There were no significant differences once adjusted for between group differences at baseline.

Study GS-US-540-5774

A randomized, open-label multi-centre clinical trial (Study GS-US-540-5774) of hospitalized patients at least 12 years of age with confirmed SARS-CoV-2 infection and radiological evidence of pneumonia without reduced oxygen levels compared treatment with VEKLURY for 5 days (n=191) and treatment with VEKLURY for 10 days (n=193) with standard of care (n=200). Patients treated with VEKLURY received 200 mg on Day 1 and 100 mg once daily on subsequent days. The primary endpoint was clinical status on Day 11 assessed on a 7-point ordinal scale ranging from hospital discharge to increasing levels of oxygen and ventilatory support to death.

At baseline, the median age of patients was 57 years (range, 12 to 95 years); 61% were male, 61% were White, 19% were Black, and 19% were Asian. Baseline clinical status, oxygen support status, and median duration of symptoms and hospitalization prior to first dose of VEKLURY were similar across treatment groups.

Overall, the odds of improvement in the ordinal scale were higher in the 5-day VEKLURY group at Day 11 when compared to those receiving only standard of care (odds ratio, 1.65; [95% CI, 1.09 to 2.48], p=0.017). The odds of improvement in clinical status with the 10-day treatment group when compared to those receiving only standard of care were not statistically

significant (odds ratio 1.31; [95% CI 0.88 to 1.95]; p=0.18). At Day 11 observed mortality rates for the 5-day, 10-day, and standard of care groups were 0, 1%, and 2%, respectively.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetic properties of VEKLURY has 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 VEKLURY adult dosage regimen, remdesivir was absorbed with a peak plasma concentration observed at end of infusion, regardless of dose level. Peak plasma concentrations of GS-441524 were observed at 1.51 to 2.00 hours post start of a 30 minutes infusion.

Distribution

Remdesivir is approximately 88% bound to human plasma proteins. Protein binding of GS-441524 was low (2% bound) in human plasma. 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.

Metabolism

Remdesivir is extensively metabolized into the pharmacologically active nucleoside analogue triphosphate GS-443902. 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 results in the formation of nucleoside metabolite GS-441524 that is not efficiently re-phosphorylated.

Biotransformation

Remdesivir is extensively metabolized to the pharmacologically active nucleoside analogue 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.

Excretion

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 faeces, 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 age, gender, or race on the exposures of remdesivir 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 has 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 theoretically increase in patients with impaired renal function. The excipient sulfobutyl betadex sodium is renally cleared and accumulates in patients with decreased renal function. VEKLURY should not be used in patients with eGFR <30 mL/min.

Hepatic Impairment
The pharmacokinetics of remdesivir and GS-441524 in hepatic impairment has 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

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

Genotoxicity
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.

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

Impairment of Fertility
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 recommended human dose (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 recommended human dose (RHD).

It is unknown if the active nucleoside analogue triphosphate GS 443902 and the unidentified major human metabolite M27 are formed in rats and rabbits. The reproductive toxicity studies may therefore not be informative of potential risks associated with these metabolites.

Animal Toxicology and/or Pharmacology
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 at the 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. Animal studies may therefore not be informative of potential risks associated with this metabolite.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

VEKLURY 100 mg powder for injection

Sulfobutyl betadex sodium
Hydrochloric acid
Sodium hydroxide

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.1. The compatibility of VEKLURY concentrate for infusion with IV solutions and medications other than saline is not known.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not reuse or save unused VEKLURY for future use. This product contains no preservative; therefore, partially used vials should be discarded.

VEKLURY 100 mg powder for injection

Store below 30 °C.

Reconstituted powder for concentrate for solution for infusion
After reconstitution dilute immediately.

Reconstituted and diluted solution for infusion
Store diluted VEKLURY solution for infusion up to 4 hours at below 25 °C) or 24 hours in refrigerator (2 °C to 8 °C). Dilute within the same day as administration.

6.5 NATURE AND CONTENTS OF CONTAINER

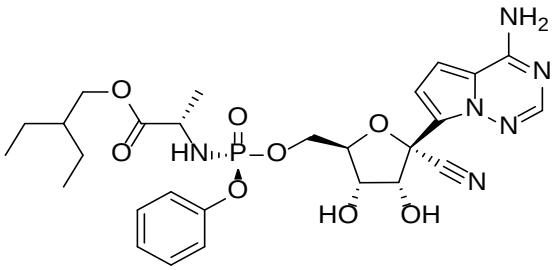
Type I clear glass vial, an elastomeric closure, and an aluminium overseal with a flip-off cap.
Pack size: 1 vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



CAS number

1809249-37-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4

8 SPONSOR

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9 DATE OF FIRST APPROVAL

Not yet available

10 DATE OF REVISION

10 July 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information