1 VEKLURY® (REMDESIVIR) POWDER FOR INJECTION

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.

Excipients with known effect:
Each vial contains 3 g sulfobutyl betadex sodium.

For the full list of excipients, see Section 6.1, List of excipients.

3 PHARMACEUTICAL FORM

VEKLURY (remdesivir) powder for injection, 100 mg, available as a sterile, preservative-free, white to off-white to yellow lyophilised 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 is indicated for the treatment of coronavirus disease 2019 (COVID-19) in:

- adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg) who have pneumonia due to SARS-CoV-2, and who require supplemental oxygen.
- adults and paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19.

VEKLURY must be used in compliance with official New Zealand COVID-19 treatment guidelines.

4.2 Dose and method of administration

VEKLURY may only be administered in settings in which healthcare providers have immediate access to medications to treat a severe infusion or hypersensitivity reaction, such as anaphylaxis, and access to an emergency medical response.

VEKLURY is for single use in one patient only.

Testing before starting and during treatment with VEKLURY

Perform hepatic laboratory testing in all patients before starting VEKLURY and while receiving VEKLURY as clinically appropriate (see Section 4.4, Special warnings and precautions for use).

Prothrombin time should be determined prior to and monitored while receiving VEKLURY as clinically appropriate (see Section 4.8 Adverse effects (Undesirable effects)).

Dose

Table 1: Recommended dosage of VEKLURY for adults and paediatric patients

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

Treatment duration

Table 2: Treatment duration

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

VEKLURY is to be administered via IV infusion over 30 to 120 minutes.

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 lyophilised powder by addition of 19 mL of Sterile Water for Injection using a suitably sized syringe and needle per vial and insert the needle in the centre of the vial stopper.
- Only use Sterile Water for Injection to reconstitute VEKLURY lyophilised powder.
- 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.
- After reconstitution, vials should be used immediately to prepare diluted solution.

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.

Adults and paediatric patients (weighing at least 40 kg)

Using Table 3, withdraw and discard the required volume of 0.9% sodium chloride from the infusion bag using an appropriately sized syringe and needle.

Table 3: Recommended dilution instructions— Reconstituted VEKLURY powder for injection

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 can be stored for 24 hours at room temperature (20 °C to 25 °C) or 48 hours in the refrigerator at (2 °C to 8 °C) prior to administration.

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

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

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

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 4 and Table 5.

Table 4: Recommended rate of infusion – diluted VEKLURY powder for injection in adults and paediatric patients (weighing at least 40 kg)

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

Table 5: Recommended rate of infusion – diluted VEKLURY powder for injection in paediatric patients at least 4 weeks of age and weighing 3 kg to less than 40 kg

Infusion Bag Volume	Infusion Time	Rate of Infusion[a]
100 mL	30 min	3.33 mL/min
	60 min	1.67 mL/min
	120 min	0.83 mL/min
50 mL	30 min	1.67 mL/min
	60 min	0.83 mL/min
	120 min	0.42 mL/min
25 mL	30 min	0.83 mL/min
	60 min	0.42 mL/min
	120 min	0.21 mL/min

a Rate of infusion may be adjusted based on total volume to be infused.

Special populations

Elderly
No dose adjustment is required in patients over the age of 65 years (see Sections 5.1, Pharmacodynamic properties and 5.2, Pharmacokinetics Properties).

Renal impairment
No dose adjustment of VEKLURY is required for 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 and based on a 5-day treatment duration (see Section 4.8 Adverse Effects (Undesirable Effects), Section 5.1 Pharmacodynamic properties- Clinical Trials, and Section 5.2, Pharmacokinetics Properties).

Hepatic impairment
No dose adjustment of VEKLURY is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C) (see Section 5.2, Pharmacokinetics Properties).

Paediatric population
The safety and efficacy of VEKLURY in children less than 4 weeks of age and weighing less than 3 kg have not yet been established. No data are available.

Immunocompromised population
The safety and efficacy of VEKLURY in immunocompromised patients have not yet been established. Only limited data are available (see Section 4.4, Special warnings and precautions for use).

4.3 Contraindications

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

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, 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. Monitor patients for hypersensitivity reactions during and following administration of VEKLURY as clinically appropriate. Patients receiving VEKLURY in an outpatient setting should be monitored after administration according to local medical practice. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration of VEKLURY and initiate appropriate treatment (see Section 4.8, Adverse effects (Undesirable effects)).

Increased risk of transaminase elevations

Transaminase elevations have been observed in healthy volunteers who received 200 mg of VEKLURY followed by 100 mg doses for up to 100 days; the transaminase elevations were mild (Grade 1) to moderate (Grade 2) in severity and resolved upon discontinuation of VEKLURY. Transaminase elevations have also been reported in patients with COVID-19 who received VEKLURY (see section 4.8 Adverse effects (undesirable effects). Because transaminase elevations have been reported as a clinical feature of COVID-19, and the incidence was similar to patients receiving placebo verses VEKLURY in clinical trials of VEKLURY, discerning the contribution of VEKLURY to transaminase elevations in patients with COVID-19 can be challenging.

Perform hepatic laboratory testing in all patients before starting VEKLURY and while receiving VEKLURY as clinically appropriate (see Sections 4.8, Adverse effects (undesirable effects) and 5.2, Pharmacokinetic properties).

- Consider discontinuing VEKLURY if ALT levels increase to greater than 10 times the upper limit of normal.
- Discontinue VEKLURY if ALT elevation is accompanied by signs or symptoms of liver inflammation.

Renal impairment

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

The use of VEKLURY in paediatric patients with renal impairment is supported by safety data in adults. Limited data are available regarding the safety of VEKLURY in paediatric patients with mild or moderate renal impairment. No data are available regarding the safety of VEKLURY in paediatric patients with severe renal impairment.

Excipients

The excipient sulfobutyl betadex sodium is renally cleared and accumulates in patients with decreased renal function, which may potentially adversely affect renal function.

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* observations demonstrating a potential antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of VEKLURY (see Sections 4.5, Interactions with other medicines and other forms of interactions and 5.1, Pharmacodynamic properties).

Immunocompromised patients

It is unclear if the treatment duration of 3 days is sufficient to clear the virus in immunocompromised patients, in whom prolonged viral shedding occurs. There is a potential risk of resistance development. Only limited data are available.

Use in the elderly

See Sections 4.2, Dose and method of administration, 5.1, Pharmacodynamic properties and 5.2, Pharmacokinetic properties.

Paediatric use

See Section 4.2, Dose and method of administration.

Effects on laboratory tests

See Section 4.8, Adverse effects (Undesirable effects)).

4.5 Interaction with other medicines and other forms of interaction

Chloroquine and hydroxychloroquine reduced the conversion of remdesivir to the active triphosphate form *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 and drug metabolizing enzyme CYP3A4 and is a substrate for Organic Anion Transporting Polypeptides 1B1 (OATP1B1) and P-glycoprotein (P-gp) transporters. GS-704277 is a substrate for OATP1B1 and OATP1B3.

Based on a drug interaction study conducted in healthy subjects with VEKLURY, no clinically significant drug interactions are expected with inducers of CYP3A4 or inhibitors of OATP 1B1/1B3, and P-gp (see section 5.2 Assessment of Drug Interactions, Table 12). 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, Uridine Diphosphate Glucuronosyltransferase1A1 (UGT1A1) , UGT1A3, UGT1A4, OATP1B1, OATP1B3, OAT3, OCT1, MRP4 and MATE1. Based on drug interaction studies with VEKLURY, no clinically significant drug-drug interactions are expected with substrates of CYP3A4, OATP 1B1/1B3 or MATE1. Remdesivir induced CYP1A2 and CYP2B6 and potentially CYP3A *in vitro*. Co-administration of remdesivir with CYP1A2 or CYP2B6 substrates with narrow therapeutic index may lead to loss of their efficacy.

In drug interaction studies conducted in healthy subjects, results suggested that remdesivir was a mild inhibitor of CYP3A. Results did not suggest clinically significant inhibition of OATP1B1/ B3 or induction of CYP3A. See Section 5.2 Assessment of Drug Interactions.

Clinical drug interaction studies of the effects of VEKLURY on probe drugs were conducted in healthy subjects. See Section 5.2 Assessment of Drug Interactions, Table 13.

4.6 Fertility, pregnancy and lactation

Effects on fertility
No human data on the effect of VEKLURY on fertility are available.
In female rats, decreases in corpora lutea, implantation sites, and viable embryos were seen when remdesivir was administered intravenously daily at an intravenous dose of 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 adult human subjects at the recommended clinical dose. There were no effects on male reproductive performance (mating and fertility) at this dose level. Exposures to remdesivir were unquantifiable in rats. Therefore, the animal studies may not be fully informative of potential risks.

Use in pregnancy – Pregnancy Category B2
The safety and pharmacokinetics of VEKLURY were evaluated in a non-randomised, open-label clinical trial (IMPAACT 2032) of hospitalised pregnant (N=25) and non-pregnant women of childbearing potential (N=28) for treatment of COVID-19. Patients received VEKLURY 200 mg once daily for 1 day followed by VEKLURY 100 mg once daily for up to 9 days (for a total of up to 10 days, as appropriate). Patients were enrolled prior to their fourth VEKLURY infusion. Of the 25 pregnant patients, median gestational age was 28 weeks at baseline (range 22 to 33 weeks) and about half of patients were in each of the second or third trimester of pregnancy. Overall, 40 patients (17 pregnant; 23 non-pregnant) completed the study.

There were no new safety findings from infusion to 4 weeks post last infusion when VEKLURY was administered to pregnant and non-pregnant women hospitalised with COVID-19, or 24 hours post-delivery, compared with the known safety profile of VEKLURY in COVID-19 infected adults. There were no adverse reactions on infants born during the study (n=16).

No clinically relevant differences in the pharmacokinetics of remdesivir or its metabolites (GS-704277 and GS-441524) were observed between pregnant (n=21) and non-pregnant (n=22) women.

It is unknown if remdesivir or its metabolites cross the placenta. No adverse effects on embryofetal development were seen in rats and rabbits at ≤ 20 mg/kg/day IV remdesivir. Systemic exposures (AUC) to the predominant circulating metabolite of remdesivir (GS-441524) were up to 4 times the exposure in adult human subjects at the recommended clinical dose, while exposures to remdesivir in rabbits were similar to that expected in adult patients at this dose. Exposures to remdesivir in rats were unquantifiable.

Overall, there are limited data supporting VEKLURY use in pregnant women and there are insufficient pregnancy data available to evaluate the risk of remdesivir exposure during the first trimester and in risk-high or complicated pregnancy. VEKLURY should not be used during the first trimester of pregnancy. Use of VEKLURY in the second or third trimesters of pregnancy may be considered if the potential benefit justifies the potential risk for the mother and the foetus.

Use in lactation
Limited published data reports that, following intravenous administration of VEKLURY, remdesivir and active metabolite GS-441524 are excreted in human milk. There is no information regarding the concentration of remdesivir in human milk, the effects on the breastfed infant, or the effects on milk production.

Available data (n=11) from pharmacovigilance reports do not indicate adverse effects on breastfed infants from exposure to remdesivir and its metabolite through breastmilk. As the

clinical experience is limited, a decision about breastfeeding during VEKLURY treatment should be made after a careful individual benefit-risk assessment.

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 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 6 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).

Table 6: Tabulated list of adverse reactions

Frequency	Adverse reaction
Immune system disorders	
Rare	hypersensitivity
Nervous system disorders	
Common	headache
Gastrointestinal disorders	
Common	nausea
Hepatobiliary disorders	
Very Common	transaminases increased
Skin and subcutaneous tissue disorders	
Common	rash
Investigations	
Very Common	prothrombin time increased
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 participants 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 × ULN) laboratory abnormalities of increased AST and increased ALT occurred in 33% and 32% of patients, respectively, receiving VEKLURY 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 VEKLURY 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 (≥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 8%, respectively, receiving standard of care.

Prothrombin time increased

In a clinical study (NIAID ACTT-1) of patients with COVID-19, the incidence of increased prothrombin time or INR (predominantly Grades 1-2) was higher in patients who received VEKLURY compared to placebo, with no difference observed in the incidence of bleeding events between the two groups. Prothrombin time should be determined prior to and monitored while receiving VEKLURY as clinically appropriate. In Study GS-US-540-9012, the incidence of increased prothrombin time or INR was similar in patients treated with VEKLURY compared to placebo.

Patients with Renal Impairment

No additional adverse reactions to VEKLURY were identified in a double-blind, placebo-controlled clinical study (GS-US-540-5912) in which 163 hospitalised patients with confirmed COVID-19 and acute kidney injury (AKI; N=60), chronic kidney disease (CKD; eGFR <30 mL/minute; N=44), or end-stage kidney disease (ESKD; eGFR <15 mL/minute; N=59) on haemodialysis received VEKLURY for up to 5 days. In Study GS-US-540-5912, the incidence of increased prothrombin time or INR was higher in patients treated with VEKLURY compared to placebo, with no difference observed in the incidence of bleeding events between the two groups (see Section 5.1, Clinical Trials).

Paediatric population

The safety assessment of VEKLURY in children 4 weeks of age and older and weighing at least 3 kg with COVID-19 is based on data from a Phase 2/3, open-label clinical trial (Study GS-US-540-5823) that enrolled 53 patients who were treated with VEKLURY. The adverse reactions observed were consistent with those observed in clinical trials of VEKLURY in adults.

Postmarketing Experience

In addition to adverse reactions from clinical studies, the following adverse reactions were identified during post-approval use of VEKLURY. Because these reactions were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS
Administration site extravasation

IMMUNE SYSTEM DISORDERS
Anaphylactic reaction

CARDIAC DISORDERS
Sinus bradycardia

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. Healthcare professionals are asked to report any suspected adverse reactions at https://pophealth.my.site.com/carmreportnz/s/.

4.9 Overdose

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

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 advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
Remdesivir is an adenosine analogue 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. 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. Remdesivir triphosphate is a weak inhibitor of mammalian DNA and RNA polymerases with low potential for mitochondrial toxicity.

Antiviral Activity

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

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

Based on *in vitro* testing, remdesivir retained similar antiviral activity (EC_{50} -fold change values below the *in vitro* susceptibility change cutoff of 2.8-fold) against clinical isolates of SARS-CoV-2 variants compared to an earlier lineage SARS-CoV-2 (lineage A) isolate, including Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), Epsilon (B.1.429), Zeta (P.2), Iota (B.1.526), Kappa (B.1.617.1), Lambda (C.37), and Omicron variants (B.1.1.529/BA.1, BA.2, BA2.12.1, BA.2.75, BA.4, BA.4.6, BA.5, BF.5, BF.7, BQ.1, BQ.1.1, CH.1.1, EG.1.2, EG.5.1, FL.22 XBB, XBB.1.5, , XBB.1.16, XBB.2.3.2, and XBF)). For these variants, the EC_{50} fold change values ranged between 0.2 to 2.3 compared to an

earlier lineage SARS-CoV-2 (lineage A) isolate. Using the SARS-CoV-2 replicon system, remdesivir retained similar antiviral activity (EC_{50} fold change values below the *in vitro* susceptibility change cutoff of 2.5-fold) against Omicron subvariants BA.2.86 and XBB.1.9.2 compared to the wildtype reference replicon (lineage B). The antiviral activity of remdesivir against SARS-CoV-2 variants is presented in Table 7.

Table 7: Remdesivir Antiviral Activity Against Clinical Isolates of SARS-CoV-2 Variants

SARS-CoV-2 Lineage	WHO Nomenclature	Key nsp12 Substitutions	Fold Change in Susceptibility[a]	Change in Susceptibility
A	-	-	1.0	
B.1.1.7	Alpha	P323L	1.58	No change[b]
B.1.351	Beta	P323L	1.19	No change[b]
P.1	Gamma	P323L	0.82	No change[b]
B.1.617.2	Delta	P323L, G671S	0.59	No change[b]
B.1.429	Epsilon	P323L	1.94	No change[b]
B.1.617.1	Kappa	P323L	0.63	No change[b]
C.37	Lambda	P323L	1.37	No change[b]
B.1.526	Iota	P323L	2.33	No change[b]
P.2	Zeta	P323L	1.17	No change[b]
B.1.1.529/ BA.1	Omicron	P323L	0.45	No change[b]
BA.2	Omicron	P323L	0.23	No change[b]
BA2.12.1	Omicron	P323L	0.20	No change[b]
BA.2.75	Omicron	P323L, G671S	0.30	No change[b]
BA.2.86[c]	Omicron	P323L	1.14	No change[b]
BA.4	Omicron	P323L	0.15	No change[b]
BA.4.6	Omicron	P323L	0.64	No change[b]
BA.5	Omicron	P323L	0.66	No change[b]
BF.5	Omicron	P323L	0.94	No change[b]
BF.7	Omicron	P323L	1.25	No change[b]
BQ.1	Omicron	P323L, Y273H	0.53	No change[b]
BQ.1.1	Omicron	Y273H, P323L	1.12	No change[b]
XBB	Omicron	P323L, G671S	1.07	No change[b]
XBB.1.5	Omicron	P323L, G671S	0.81	No change[b]
XBB.1.9.2[c]	Omicron	P323L, G671S	2.02	No change[b]

SARS-CoV-2 Lineage	WHO Nomenclature	Key nsp12 Substitutions	Fold Change in Susceptibility[a]	Change in Susceptibility
XBB.1.16	Omicron	P323L, G671S	0.73	No change[b]
XBB.2.3.2	Omicron	P323L, G671S	0.29	No change[b]
XBF	Omicron	P323L, G671S	1.22	No change[b]

a. The fold change was calculated by dividing the variant EC_{50} value by the lineage A SARS-CoV-2 WA1 isolate EC_{50} value in each experiment and a mean fold change ± standard deviation was calculated with these values.
b. No change: <2.8-fold (change in in EC_{50} value) reduction in susceptibility using clinical isolates and <2.5-fold reduction in susceptibility using the replicon assay.
c. Variant assessed using replicon assay. The lineage-defining substitutions identified in the replication complex genes were cloned into the replicon. The fold change was calculated by dividing the variant replicon EC_{50} value by the wildtype lineage B replicon reference EC_{50} value in each experiment and a mean fold change ± standard deviation was calculated with these values.

Resistance

In cell culture

SARS-CoV-2 isolates with reduced susceptibility to remdesivir have been selected in cell culture. In one selection with GS-441524, the parent nucleoside of remdesivir, virus pools emerged expressing amino acid substitutions at V166A, N198S, S759A, V792I, C799F, and C799R in the viral RNA-dependent RNA polymerase, which conferred 2.7-10.4 fold reductions in susceptibility to remdesivir. When individually introduced into a wild-type recombinant virus by site-directed mutagenesis, 1.7- to 3.5-fold reduced susceptibility to remdesivir was observed. In a second selection with remdesivir using a SARS-CoV-2 isolate containing the P323L substitution in the viral polymerase, a single amino acid substitution at V166L emerged, which conferred 2.3-3.9 fold reductions in susceptibility to remdesivir. Recombinant viruses with substitutions at P323L alone or P323L+V166L in combination exhibited 1.3- and 1.5-fold changes in remdesivir susceptibility, respectively.

Cell culture resistance profiling of remdesivir using the rodent CoV murine hepatitis virus identified 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 cell culture, and introduction of the corresponding mutations (F480L and V557L) into SARS-CoV resulted in 6-fold reduced susceptibility to remdesivir in cell culture and attenuated SARS-CoV pathogenesis in a mouse model. When individually introduced into a SARS-CoV-2 recombinant virus, the corresponding substitutions at F480L and V557L each conferred 2-fold reduced susceptibility to remdesivir.

In clinical trials
In Adult Patients: In NIAID ACTT-1 Study, among 61 patients with baseline and post-baseline sequencing data available, the rate of emerging substitutions in the viral RNA-dependent RNA polymerase was similar in patients treated with VEKLURY compared to placebo. In 2 patients treated with VEKLURY, substitutions in the RNA-dependent RNA

polymerase previously identified in resistance selection experiments (V792I or C799F) and associated with low fold change in remdesivir susceptibility (≤3.4-fold) were observed. No other RNA-dependent RNA polymerase substitutions observed in patients treated with VEKLURY were associated with resistance to remdesivir.

In Study GS-US-540-9012, among 244 patients with baseline and post-baseline sequencing data available, the rate of emerging substitutions in the viral RNA-dependent RNA polymerase was similar in patients treated with VEKLURY compared to placebo. In one patient treated with VEKLURY, one substitution in the RNA-dependent RNA polymerase (A376V) emerged and was associated with a decrease in remdesivir susceptibility in vitro (12.6-fold). This patient was not hospitalised and showed alleviation of all baseline symptoms, except loss of taste and smell, prior to or on day 14. No other substitutions in the RNA-dependent RNA polymerase or other proteins of the replication-transcription complex observed in patients treated with VEKLURY were associated with resistance to remdesivir.

In Study GS-US-540-5912 (see Clinical Trials), among 60 patients with baseline and post-baseline sequencing data available, substitutions in the viral RNA-dependent RNA polymerase emerged in 8 patients treated with VEKLURY. In 4 patients treated with VEKLURY, substitutions in the RNA-dependent RNA polymerase (M794I, C799F, or E136V) emerged and were associated with reduced susceptibility to remdesivir *in vitro* (≤3.5-fold). No other substitutions in the RNA-dependent RNA polymerase detected in patients treated with VEKLURY were associated with resistance to remdesivir.
In Study GS-US-540-5773 (see Clinical Trials), among 19 patients treated with VEKLURY who had baseline and post-baseline sequencing data available, substitutions in the viral RNA-dependent RNA polymerase (nsp12) were observed in 4 patients. The substitutions observed were not associated with resistance to remdesivir (≤1.45-fold) (T76I, A526V, A554V, C697F) or could not be determined due to lack of replication (E665K).
In Paediatric Patients: In Study GS-US-540-5823, among paediatric patients with baseline and post-baseline sequencing data available, substitutions in the viral RNA-dependent RNA polymerase were observed in 2 of 23 paediatric patients treated with VEKLURY. The substitutions observed were not associated with resistance to remdesivir (0.96-fold) (G670V) or could not be determined due to lack of replication (V495F, A656P, A656P+G670V). No substitutions observed in other proteins of the replication-transcription complex were associated with resistance to remdesivir.

Clinical trials
Clinical trials in patients with COVID-19

Description of Clinical Studies

The efficacy of VEKLURY was evaluated in four Phase 3 studies in hospitalised patients with COVID-19, one Phase 3 study in non-hospitalised patients with COVID-19 and one Phase 3 study in hospitalised paediatric patients with COVID-19 as summarized in Table 8.

Table 8: Studies conducted with VEKLURY in patients with COVID-19

Study	Population	Age Range (Range of ages that met the study inclusion criteria)	Study Arms (Number of Subjects Treated)	Timepoint
NIAID ACTT-1[a]	Hospitalised with mild/moderate and severe COVID-19	21 to 95 years	VEKLURY 10 Days (532) Placebo (516)	29 Days after Randomisation
GS-US-540-5773[b]	Hospitalised with severe COVID-19	20 to 98 years	VEKLURY 5 Days (200) VEKLURY 10 Days (197)	Day 14
GS-US-540-5774[b]	Hospitalised with moderate COVID-19	12 to 95 years	VEKLURY 5 Days (191) VEKLURY 10 Days (193) Standard of care (200)	Day 11
GS-US-540-9012[a]	Non-hospitalised with mild/moderate COVID-19 and at high risk for progression to severe disease	13 to 98 years	VEKLURY 3 Days (279) Placebo (283)	Day 28
GS-US-540-5912[a]	Hospitalised with COVID-19 and renal impairment	≥ 12 years old	VEKLURY 5 Days (163) Placebo (80)	Day 29
GS-US-540-5823 (Cohorts 1-4,8)[c]	Hospitalised paediatric patients 28 days to <18 years of age and weighing at least 3 kg with COVID-19	Cohort 1: 12 to 17 years Cohort 2: 4 to 16 years Cohort 3: 1.9 to 7 years Cohort 4: 1 to 9 months Cohort 8: 8 to 11 years	VEKLURY up to 10 Days (53)	Day 10

COVID-19: coronavirus disease 2019
a. Randomised, double-blind, placebo-controlled trial.
b. Randomised, open-label trial.
c. Open-label trial, descriptive outcome analyses.

These studies were conducted in a population that had not been vaccinated against COVID-19.

Study NIAID ACTT-1 (hospitalised with mild/moderate and severe COVID-19)

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 1,062 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/min 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/Extracorporeal Membrane Oxygenation (ECMO). Patients were randomised 1:1, stratified by disease severity at enrolment, to receive VEKLURY (n=541) or placebo (n=521), plus standard of care.

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

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

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 VEKLURY 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 VEKLURY 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 VEKLURY 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 VEKLURY 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 VEKLURY 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 VEKLURY group at Day 15 when compared to the placebo group (odds ratio, 1.6; [95% CI, 1.3 to 1.9], p < 0.001).

Overall, the 29-day mortality was 11% for the VEKLURY group vs 15% 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 9.

Table 9: 29-Day mortality outcomes by ordinal scale[a] at baseline—NIAID ACTT-1 study

	Ordinal Score at Baseline							
	4		5		6		7	
	Not on oxygen		Requiring low-flow oxygen		Requiring high-flow oxygen or non-invasive mechanical ventilation		Requiring invasive mechanical ventilation or ECMO	
	VEKLURY (N=75)	Placebo (N=63)	VEKLURY (N=232)	Placebo (N=203)	VEKLURY (N=95)	Placebo (N=98)	VEKLURY (N=131)	Placebo (N=154)
29-day mortality	4.1	4.8	4.0	12.7	21.2	20.4	21.9	19.3
Hazard ratio[b] (95% CI)	0.82 (0.17, 4.07)		0.30 (0.14, 0.64)		1.02 (0.54, 1.91)		1.13 (0.67, 1.89)	

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 (hospitalised 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-CoV-2 infection, oxygen saturation ≤ 94% on room 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. All patients received 200 mg of VEKLURY 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.

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 hospitalisation prior to first dose of VEKLURY were similar across treatment groups.

The odds of improvement at Day 14 for patients randomised to a 10-day course of VEKLURY compared with those randomised 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, 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, 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-540-5774 (hospitalised with moderate COVID-19)

A randomised, open-label multi-centre clinical trial (Study GS-US-540-5774) of hospitalised 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 hospitalisation 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.

Study GS-US-540-9012 (non-hospitalised with mild/moderate COVID-19 and at high risk for progression to severe disease)

A randomised, double-blind, placebo-controlled, multi-centre clinical trial evaluated treatment with VEKLURY in an outpatient setting in 562 adult and adolescent (12 years of age and older and weighing at least 40 kg) patients with confirmed COVID-19 and at least one risk factor for disease progression to hospitalisation. Risk factors for disease progression were: aged ≥60 years, chronic lung disease, hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity, immunocompromised state, chronic mild or moderate kidney disease, chronic liver disease, current cancer, or sickle cell disease. Vaccinated patients were excluded from the study.

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

At baseline, mean age was 50 years (with 30% of patients aged 60 or older); 52% were male, 80% were White, 8% were Black, 2% were Asian, 44% were Hispanic or Latino; median body mass index was 30.7 kg/m^2. The most common comorbidities were diabetes mellitus (62%), obesity (56%), and hypertension (48%). Median (Q1, Q3) duration of symptoms prior to treatment was 5 (3,6) days; median viral load was 6.3 log_{10} copies/mL at baseline. The baseline demographics and disease characteristics were balanced across the VEKLURY and placebo treatment groups.

The primary endpoint was the proportion of patients with COVID-19 related hospitalisation (defined as at least 24 hours of acute care) or all-cause 28-day mortality. Events (COVID-19 related hospitalisation or all-cause 28-day mortality) occurred in 2 (0.7%) patients treated with VEKLURY compared to 15 (5.3%) patients concurrently randomised to placebo, demonstrating an 87% reduction in COVID-19-related hospitalisation or all-cause mortality compared to placebo (hazard ratio, 0.134 [95% CI, 0.031 to 0.586]; p=0.0076). The absolute risk reduction was 4.6% (95% CI, 1.8% to 7.5%). No deaths were observed at Day 28.

Study GS-US-540-5912 (hospitalised with COVID-19 and renal impairment)

A randomised, double-blind, placebo-controlled clinical study (Study GS-US-540-5912) evaluated VEKLURY 200 mg once daily for 1 day followed by VEKLURY 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 ESKD (eGFR <15 mL/minute) requiring haemodialysis. Patients were randomised in a 2:1 manner, stratified by ESKD, high-flow oxygen requirement, and region (US vs ex-US) to receive VEKLURY (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.

Study GS-US-540-5912 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.

Study GS-US-540-5823 (hospitalised paediatric patients 28 days to <18 years of age and weighing at least 3 kg with COVID-19)

The primary objectives of this Phase 2/3 single-arm, open-label clinical study (Study GS-US-540-5823) were to evaluate pharmacokinetics and safety of up to 10 days of treatment with VEKLURY in paediatric patients. A total of 53 paediatric patients at least 28 days of age and weighing at least 3 kg with confirmed SARS-CoV-2 infection and mild, moderate, or severe COVID-19 was evaluated in five cohorts: subjects ≥12 years and weighing ≥40 kg (n=12); subjects <12 years and weighing ≥40 kg (n=5); subjects ≥28 days and weighing ≥20 to <40 kg (n=12); subjects ≥28 days and weighing ≥12 to <20 kg (n=12); and subjects ≥28 days and weighing ≥3 to <12 kg (n=12). Subjects weighing ≥40 kg received 200 mg of VEKLURY on Day 1 followed by VEKLURY 100 mg once daily on subsequent days; subjects weighing ≥3 kg to <40 kg received VEKLURY 5 mg/kg on Day 1 followed by VEKLURY 2.5 mg/kg once daily on subsequent days. Assessments occurred at the following intervals: Screening; Day 1 (Baseline); Days 2-10, or until discharge, whichever came earlier; Follow-Up on Day

30 (±5). Treatment with VEKLURY was stopped in patients who were discharged from the hospital prior to the completion of 10 days of treatment.

At baseline, median age was 7 years (Q1, Q3: 2 years, 12 years); 57% were female, 70% were White, 30% were Black, and 44% were Hispanic or Latino; median weight was 25 kg (range: 4 to 192 kg). Patients in this trial were unvaccinated. A total of 12 patients (23%) were on invasive mechanical ventilation, 18 (34%) were on non-invasive ventilation or high-flow oxygen; 10 (19%) were on low-flow oxygen; and 13 (25%) were on room air, at baseline. The overall median (Q1, Q3) duration of symptoms and hospitalisation prior to first dose of VEKLURY was 5 (3, 7) days and 1 (1, 3) day, respectively.

The descriptive outcome analyses showed treatment with VEKLURY for up to 10 days resulted in an overall median (Q1, Q3) change from baseline in clinical status (assessed on a 7-point ordinal scale ranging from death [score of 1] to ventilatory support and decreasing levels of oxygen to hospital discharge [score of 7]) of +2.0 (1.0, 4.0) points on Day 10.

Recovery (defined as an improvement from a baseline clinical status score of 2 through 5 to a score of 6 or 7, or an improvement from a baseline score of 6 to a score of 7) was reported for 62% of subjects on Day 10; median (Q1, Q3) time to recovery was 7 (5, 16) days.

Overall, 60% of patients were discharged by Day 10, and 83% of patients were discharged by Day 30. Three patients (6%) died during the study.

QT

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

5.2 Pharmacokinetic properties

The pharmacokinetic properties of VEKLURY 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 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 minute 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 metabolised into the pharmacologically active nucleoside analogue triphosphate GS-443902. The metabolic activation pathway involves hydrolysis by esterases (80% by carboxylesterase 1 and 10% by cathepsin A), 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 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 VEKLURY were observed to be significantly below endogenous levels in human 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
Population pharmacokinetic models for remdesivir and its circulating metabolites (GS-704277 and GS-441524), developed using pooled data from studies in healthy subjects and in adult and paediatric patients with COVID-19, were used to predict pharmacokinetic exposures in 50 paediatric patients aged ≥28 days to <18 years and weighing ≥3 kg (Study GS-US-540-5823). Mean exposures (AUC_{tau} and C_{max}) of remdesivir, GS-704277, and GS-441524 predicted for these patients at the doses administered were higher as compared to those in adult patients with COVID-19; however, the increases were not considered clinically significant.

Renal impairment
The pharmacokinetics of remdesivir and its metabolites (GS-704277 and GS-441524) and 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 kidney failure (eGFR <15 mL/minute) on dialysis or not on dialysis following a single dose of up to 100 mg of VEKLURY (Table 10); and in a Phase 3 study in COVID-19 patients with severely reduced kidney function (eGFR <30 mL/minute) receiving VEKLURY 200 mg loading dose on Day 1 followed by 100 mg from Day 2 to Day 5 (Table 11).

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

Table 10: 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 11: 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-704277 and GS-441524) 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 VEKLURY. Relative to subjects with normal hepatic function, mean exposures (AUC_{inf}, C_{max}) of remdesivir and GS-704277 were higher in severe hepatic impairment; however, the increase was not considered clinically significant.

No dose adjustment of VEKLURY is required for patients with hepatic impairment.

Interactions

In vitro:

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

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

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

Remdesivir inhibited OCT1, OAT3, MATE1, OATP1B1 and OATP1B3.

At physiologically relevant concentrations, remdesivir and its metabolites did not inhibit P-gp or BCRP (see section 4.*5)*.

Assessment of Drug Interactions

A drug-drug interaction study was conducted with VEKLURY. The effects of coadministered drugs on the pharmacokinetics of remdesivir and metabolites GS-704277 and GS-441524 are shown in Table 12. The effects of remdesivir on the pharmacokinetics of other drugs are shown in Table 13.

Table 12: Drug Interactions: Changes in Pharmacokinetic Parameters for Remdesivir and Metabolites GS-704277 and GS-441524 in the Presence of the Coadministered Drug[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Remdesivir Dose (mg)	N	Mean Ratio (90% CI) of Remdesivir, GS-704277, and GS-441524 PK With/Without Coadministered Drug No Effect = 1.00 (0.70-1.43)		
					C_{max}	AUC_{inf}
Cyclosporin A	400 single dose	100 single dose	9	remdesivir	1.49 (1.38-1.60)	1.89 (1.77-2.02)
				GS-704277	2.51 (2.26-2.78)	2.97 (2.75-3.20)
				GS-441524	1.17 (1.12-1.22)	1.03 (0.99-1.08)
Carbamazepine	300 twice daily	100 single dose	8	remdesivir	0.87 (0.78-0.97)	0.92 (0.83-1.02)
				GS-704277	0.96 (0.84-1.10)	0.98 (0.92-1.05)
				GS-441524	0.97 (0.88-1.07)	0.83 (0.78-0.89)

CI=confidence interval

a. Interaction study conducted in healthy volunteers.

Table 1: Drug Interactions: Changes in Pharmacokinetic Parameters for the Coadministered Drug in the Presence of Remdesivir[a]

Coadministered Drug	Dose of Coadministered Drug (mg)	Remdesivir Dose (mg)	N	Mean Ratio (90% CI) of Coadministered Drug PK With/Without Remdesivir No Effect = 1.00 (0.80-1.25)	
				C_{max}	AUC_{inf}
Midazolam	2.5 single dose	200 single dose	19	1.29 (1.19-1.41)	1.20 (1.14-1.26)
Midazolam	2.5 single dose	200 single dose followed by 100 once daily (10 doses)[b]	14	1.45 (1.23-1.70)	1.30 (1.16-1.45)
Pitavastatin	2 single dose	200 single dose	20	1.05 (0.92-1.20)	1.17 (1.09-1.24)

CI=confidence interval.
Midazolam is a probe substrate for CYP3A; pitavastatin is a probe substrate for OATPI B1/B3.
a. Interaction study conducted in healthy volunteers.
b. Midazolam administered with last dose of remdesivir. Midazolam was also administered alone as a single dose on Day 1 as the reference dose.

5.3 Preclinical safety data

Genotoxicity

Remdesivir was not genotoxic in a bacterial mutagenicity assay and a chromosome aberration assay using human peripheral blood lymphocytes. Negative results were seen in an *in vivo* rat micronucleus assay where exposures to remdesivir were unquantifiable, but exposures to GS-441524 and GS-704277 were significantly above the exposures in adult human subjects at a dose of 200 mg/day.

Carcinogenicity

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

Animal 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 mg/kg/day for 7 days resulted in increased mean urea nitrogen and increased mean creatinine, renal tubular atrophy, and basophilia and casts, and an unscheduled death of one animal at 20 mg/kg/day. A no adverse effect level was not established in this species. 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 metabolites of remdesivir (GS-441524 and GS-704277) were 0.6 and 0.9 times (monkeys at 5 mg/kg/day) and 0.3 and 0.4 times (rats at 3 mg/kg/day), respectively the exposure in adult humans at the 200 mg dose.

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, List of excipients. The compatibility of VEKLURY concentrate for infusion with IV solutions and medications other than saline is not known.

6.3 Shelf life

48 months for VEKLURY 100 mg powder for injection.

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, vials should be used immediately to prepare diluted solution.

Reconstituted and diluted solution for infusion
VEKLURY diluted solution for infusion can be stored up to 24 hours at room temperature (20 °C to 25 °C or 48 hours in refrigerator (2 °C to 8 °C) prior to 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 New Zealand, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

7 MEDICINE SCHEDULE

Prescription medicine

8 SPONSOR

Gilead Sciences (NZ)
c/o Tompkins Wake
Level 17, 88 Shortland Street,
Auckland, 1010
New Zealand

Tel: 0800 443 933

9 DATE OF FIRST APPROVAL

14 September 2023

10 DATE OF REVISION OF THE TEXT

17 March 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Sponsor address update