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 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.

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

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 prior to and during use of VEKLURY**

All patients must have an estimated glomerular filtration rate (eGFR) determined prior to or when initiating VEKLURY and while receiving VEKLURY as clinically appropriate. VEKLURY is not recommended in patients with eGFR less than 30 mL per minute unless the potential benefit outweighs the potential risk (see section 4.2 Renal impairment and section 4.4).

Hepatic laboratory testing should be performed in all patients prior to or when initiating VEKLURY and while receiving VEKLURY as clinically appropriate (see section 4.4).

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

Dose

The recommended dosage of VEKLURY for adults and paediatric patients (weighing at least 40 kg) is:

- Day 1 - a single loading dose of VEKLURY 200 mg given by intravenous (IV) infusion
- Day 2 onwards - 100 mg given once daily by intravenous infusion.

The recommended dosage of VEKLURY in paediatric patients at least 4 weeks of age and weighing 3 kg to less than 40 kg is:

- Day 1 – a single loading dose of VEKLURY 5 mg/kg given by intravenous infusion
- Day 2 onwards – 2.5 mg/kg given once daily by intravenous infusion.

Treatment duration

*Patients with pneumonia requiring supplemental oxygen:*

- *Adults:* The total duration of treatment should be at least 5 days and not more than 10 days.
- *Paediatric patients at least 4 weeks of age and weighing at least 3 kg*: The total duration of treatment should not be more than 10 days.

*Patients who do not require supplemental oxygen and are at high risk of progressing to severe COVID-19:*

- *Adults and paediatric patients (weighing at least 40 kg):* Treatment should be initiated as soon as possible after diagnosis of COVID-19 and within 7 days after symptom onset. The total duration of treatment should be 3 days.

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 lyophilized powder by addition of 19 mL of Sterile Water for Injection using a suitably sized syringe and needle per vial.
- Only use Sterile Water for Injection to reconstitute VEKLURY lyophilized 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.
- 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.

*Adults and paediatric patients (weighing at least 40 kg)*

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**

| 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 up to 24 hours at room temperature (20 °C to 25 °C) or 48 hours in the refrigerator at (2 °C to 8 °C).

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

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

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

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 and Table 3.

**Table 2: 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 3: Recommended rate of infusion – diluted VEKLURY powder for infusion 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 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. The safety and efficacy of VEKLURY have not been studied in patients with eGFR less than 30 mL per minute, and the excipient accumulates in patients with severe renal impairment.

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 has 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 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 remdesivir in immunocompromised patients have not yet been established. Only limited data are available (see section 4.4).

### 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 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).

Transaminase elevations

Transaminase elevations have been observed in the VEKLURY clinical development program, including in healthy volunteers and patients with COVID-19. Hepatic laboratory testing should be performed in all patients prior to or when initiating VEKLURY and liver function should be monitored while administering VEKLURY as clinically appropriate. No clinical studies with VEKLURY 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 (ULN) at baseline
- VEKLURY should be discontinued in patients who develop:
    - ALT ≥5 times the ULN during treatment with VEKLURY. VEKLURY may be restarted when ALT is <5 times the ULN.
      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 or when initiating VEKLURY and while receiving it as 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* observations demonstrating a potential antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of VEKLURY (see section 4.5, 5.1).

Immunocompromised patients

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

*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. 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. The clinical relevance of these *in vitro* assessments has not been established.

The potential of interaction of remdesivir with inhibitors/inducers of the hydrolytic pathway (esterase) or 3A4 has not been studied. 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, UGT1A1, UGT1A3, UGT1A4, OATP1B1, OATP1B3, OAT3, OCT1, MRP4 and MATE1. Based on modelling and simulation, no clinically significant drug-drug interactions are expected with substrates of CYP3A4, OATP 1B1/1B3 or MATE1. VEKLURY 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.

### 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**

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 fetus.

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

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.

**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 4 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 4: 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 |

| Frequency | Adverse reaction |
|---|---|
| *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 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.
*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.

IMMUNE SYSTEM DISORDERS
Anaphylactic reaction

CARDIAC DISORDERS
Sinus bradycardia

**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: 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 (<2.5-fold change) against clinical isolates of SARS-CoV-2 variants containing the P323L substitution in the viral polymerase including Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Epsilon (B.1.429), Kappa (B.1.617.1), Lambda (C.37), Iota (B.1.526) and Zeta (P.2) variants compared to earlier lineage SARS-CoV-2 (lineage A) isolates. For the clinical isolates of the Delta (B.1.617.2) and Omicron (B.1.1.529) variants, remdesivir maintained antiviral activity (<0.6-fold change). The antiviral activity of remdesivir against SARS-CoV-2 variants is presented in Table 5.

**Table 5: Remdesivir Antiviral Activity Against Clinical Isolates of SARS-CoV-2 Variants**

| SARS-CoV-2 Lineage | Country First Identified | WHO Nomenclature | Key Substitutions | Remdesivir $EC_{50}$ (nM) Replicates (n) | Fold Change in Susceptibility[a] | Change in Susceptibility |
|---|---|---|---|---|---|---|
| A | USA | - | - | 110 (17) | 1.0 | |
| B.1.1.7 | UK | Alpha | P323L | 192 (6) | 1.58±0.48 | No change[b] |
| B.1.351 | South Africa | Beta | P323L | 141 (6) | 1.19±0.47 | No change[b] |
| P.1 | Brazil | Gamma | P323L | 97 (6) | 0.82±0.42 | No change[b] |
| B.1.617.2 | India | Delta | P323L, G671S | 70 (13) | 0.59±0.20 | No change[b] |
| B.1.429 | USA | Epsilon | P323L | 210 (8) | 1.94±1.18 | No change[b] |
| B.1.617.1 | India | Kappa | P323L | 77 (6) | 0.63±0.19 | No change[b] |
| C.37 | Peru | Lambda | P323L | 175 (6) | 1.37±0.48 | No change[b] |

| SARS-CoV-2 Lineage | Country First Identified | WHO Nomenclature | Key Substitutions | Remdesivir $EC_{50}$ (nM) Replicates (n) | Fold Change in Susceptibility[a] | Change in Susceptibility |
|---|---|---|---|---|---|---|
| B.1.526 | USA | Iota | P323L | 258 (8) | 2.33±0.74 | No change[b] |
| P.2 | Brazil | Zeta | P323L | 151 (5) | 1.17±0.40 | No change[b] |
| B.1.1.529 | South Africa | Omicron | P323L | 44 (6) | 0.45±0.13 | No change[b] |

a Values from the N protein ELISA assay. $EC_{50}$ for WA1 = 110 ± 42 nM for assays harvested at 48 hours and 97 ± 15 nM for assays harvested at 72 hrs (Omicron variant). A fold change was calculated for each experiment using the lineage A WA1 isolate and a mean fold change ± SD was calculated with these values.

b Fold-change: <2.5- is not significant. All variants show no reduction in susceptibility.

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 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 one of 23 paediatric patients treated with VEKLURY. The substitutions observed have not previously been associated with resistance to VEKLURY.

## Clinical trials

*Clinical trials in patients with COVID-19*

### *Description of Clinical Studies*

The efficacy of VEKLURY was evaluated in three 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 6.

**Table 6: 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)<br>Placebo (516) | 29 Days after Randomization |
| GS-US-540-5773[b] | Hospitalised with severe COVID-19 | 20 to 98 years | VEKLURY 5 Days (200)<br>VEKLURY 10 Days (197) | Day 14 |
| GS-US-540-5774[b] | Hospitalised with moderate COVID-19 | 12 to 95 years | VEKLURY 5 Days (191)<br>VEKLURY 10 Days (193)<br>Standard of care (200) | Day 11 |

| Study | Population | Age Range (Range of ages that met the study inclusion criteria) | Study Arms (Number of Subjects Treated) | Timepoint |
|---|---|---|---|---|
| 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)<br>Placebo (283) | Day 28 |
| 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:<br>12 to 17 years<br>Cohort 2:<br>4 to 16 years<br>Cohort 3:<br>1.9 to 7 years<br>Cohort 4:<br>1 to 9 months<br>Cohort 8:<br>8 to 11 years | VEKLURY up to 10 Days (53) | Day 10 |

COVID-19: coronavirus disease 2019
a. Randomized, double-blind, placebo-controlled trial.
b. Randomized, 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 7.

**Table 7: 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 randomized to a 10-day course of VEKLURY compared with those randomized to a 5-day course was 0.67 (odds ratio); [95% CI, 0.46 to 0.98]. Statistically significant imbalances in baseline clinical status were observed in this study., After adjusting for between-group differences at baseline, 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 randomized, 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 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.

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 randomized in a 1:1 manner, stratified by residence in a skilled nursing facility (yes/no), age (<60 vs ≥60 years), and region (US vs ex-US) to receive 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 randomized to placebo, demonstrating an 87% reduction in COVID-19-related hospitalisation or all-cause mortality compared to placebo (hazard ratio, 0.134 [95% CI, 0.031 to 0.586]; p=0.0076). The absolute risk reduction was 4.6% (95% CI, 1.8% to 7.5%). No deaths were observed at Day 28.

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

## 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 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 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 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, 2C19 and 2D6 on the first day of administration. The clinical relevance of this inhibition was not studied. The lack of clinical relevance of this inhibition was confirmed using modelling and simulation. Remdesivir is not a time-dependent inhibitor of CYP450 enzymes *in vitro*.

Remdesivir induced CYP1A2, CYP2B6 and potentially CYP3A4 *in vitro* (see section 4.5).

Remdesivir inhibited OCT1, OAT3, MATE1, OATP1B1 and OATP1B3 *in vitro* (see section 4.5).The lack of clinical relevance of this inhibition was confirmed using modelling and simulation.

At physiologically relevant concentrations, remdesivir, and its metabolites did not inhibit P-gp nor BCRP *in vitro.*

**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 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. 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 24 hours at below 25 °C or 48 hours in refrigerator (2 °C to 8 °C). Dilute within the same day as administration.

### 6.5 NATURE AND CONTENTS OF CONTAINER

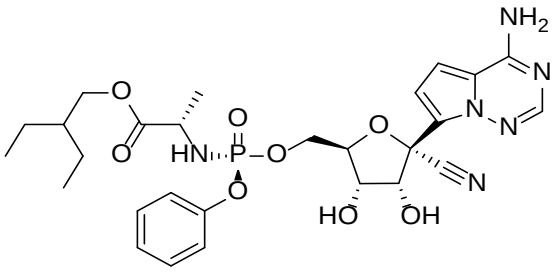
Type I clear glass vial, an elastomeric closure, and an aluminium overseal with a flip-off cap.
Pack size: 1 vial.

### 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

Gilead Sciences Pty Ltd
Level 6, 417 St Kilda Road
Melbourne, Victoria 3004

Telephone: 1800 806 112
Email: au.nz.medinfo@gilead.com

## 9 DATE OF FIRST APPROVAL

Not yet available

## 10 DATE OF REVISION

6 May 2022

**SUMMARY TABLE OF CHANGES**

| Section Changed | Summary of new information |
|---|---|
| **4.1** | Indication for paediatric patients – based on Study GS-US-540-5823; non-hospitalised patients – based on Study GS-US-540-9012 |
| **4.2** | Dosing and Method of Administration (revised to align with indications), Testing Prior to and During Use of VEKLURY; updated renal impairment section; Updated storage conditions for reconstituted and diluted solution for infusion |
| **4.5** | Interactions updated: Effects of other medicinal products on remdesivir, Effects of remdesivir on other medicinal products |
| **4.6** | Updated text: Effects on fertility and Use in Pregnancy |

| | |
|---|---|
| **4.8** | Undesirable Effects, Experience from Clinical Studies |
| **5.1** | Clinical Experience - Addition of final safety and efficacy data from the three Phase 3 Studies - CO-US-540-5776 (NIAID ACTT-1), GS-US-540-5773, and GS-US-540-5774 in patients with COVID-19; Paediatric patients on Study GS-US-540-5823; Non-hospitalised patients Study GS-US-540-9012; updated text for Antiviral activity |
| **5.2** | Updated text: Metabolism, Interactions |
| **5.3** | Updated text: Genotoxicity, Animal Toxicology and/or Pharmacology |
| **6.4** | Updated storage conditions for reconstituted and diluted solution for infusion |