Product Monograph

Including Patient Medication Information

PrVEKLURY®

Remdesivir for injection,
Powder for solution for infusion, 100 mg/vial (5 mg/mL when reconstituted)

Nucleotide Prodrug

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1 Indications	2023-06
4 Dosage and Administration, Dosing Considerations (4.1)	2023-11
4 Dosage and Administration, Recommended Dose and Dosage Adjustment (4.2)	2023-11
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4 Dosage and Administration, Reconstitution (4.3)	2023-06
4 Dosage and Administration, Administration (4.4)	2023-06
7 Warnings and Precautions, Renal	2023-11

Table of Contents

Sections or subsections that are not applicable at the time of authorization are not listed

Table of Contents **2**

Part 1: Healthcare Professional Information **4**

1 Indications **4**
- 1.1 Pediatrics 4
- 1.2 Geriatrics 4

2 Contraindications **4**

4 Dosage and Administration **4**
- 4.1 Dosing Considerations 4
- 4.2 Recommended Dose and Dosage Adjustment 5
- 4.3 Reconstitution 6
- 4.4 Administration 8

5 Overdose **9**

6 Dosage Forms, Strengths, Composition, and Packaging **10**

7 Warnings and Precautions **10**
- 7.1 Special Populations 11
- 7.1.1 Pregnancy 11
- 7.1.2 Breastfeeding 11
- 7.1.3 Pediatrics 12
- 7.1.4 Geriatrics 12

8 Adverse Reactions **12**
- 8.1 Adverse Reaction Overview 12
- 8.2 Clinical Trial Adverse Reactions 12
- 8.2.1 Clinical Trial Adverse Reactions – Pediatrics 14
- 8.3 Less Common Clinical Trial Adverse Reactions 14
- 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data 14
- 8.5 Post-Market Adverse Reactions 15

9 Drug Interactions **15**

9.2 Drug Interactions Overview 15
9.4 Drug-Drug Interactions 15
9.5 Drug-Food Interactions 17
9.6 Drug-Herb Interactions 17
9.7 Drug-Laboratory Test Interactions 17

10 Clinical Pharmacology 18
10.1 Mechanism of Action 18
10.2 Pharmacodynamics 18
10.3 Pharmacokinetics 18

11 Storage, Stability and Disposal 24

12 Special Handling Instructions 25

Part 2: Scientific Information 26

13 Pharmaceutical Information 26

14 Clinical Trials 26
14.1 Clinical Trials by Indication 26
COVID-19 in Hospitalized Adults and Pediatric Patients 26
COVID-19 in Adults at High Risk of Disease Progression Not Requiring Supplemental Oxygen 29

15 Microbiology 30

16 Non-Clinical Toxicology 33

Patient Medication Information 35

Part 1: Healthcare Professional Information

1 Indications

VEKLURY (remdesivir) is indicated for the treatment of coronavirus disease 2019 (COVID-19) in:

- Hospitalized adults and pediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen.
- Non-hospitalized adults and pediatric patients (weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death (see 14 Clinical Trials).

1.1 Pediatrics

Pediatrics (< 4 weeks of age or weighing < 3 kg): No data have been submitted to Health Canada for the safety and efficacy of VEKLURY in children under the age of 4 weeks or weighing < 3 kg; therefore, Health Canada has not authorized an indication in this population.

Non-hospitalized pediatrics (≥ 4 weeks of age and ≥ 3 kg to < 40 kg): No adequate clinical efficacy and safety data have been available. Health Canada has not authorized an indication in this population.

1.2 Geriatrics

Geriatrics (> 65 years of age): Reported clinical experience has not identified differences in response between the elderly and younger patients.

2 Contraindications

VEKLURY is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition and Packaging.

4 Dosage and Administration

4.1 Dosing Considerations

Patients should be monitored closely when receiving VEKLURY.

Patients receiving VEKLURY in an outpatient setting should be monitored according to local medical practice. Use under conditions where treatment of severe hypersensitivity reactions, including anaphylaxis, is possible.

As clinically appropriate, patients should have estimated glomerular filtration rate (eGFR) determined prior to starting VEKLURY and while receiving it. Adult patients with renal impairment demonstrate elevated exposures of the metabolites GS-704277, GS-441524, and the drug excipient sulfobutylether-β-cyclodextrin (SBECD), which increase as renal function worsens. Moreover, safety data for VEKLURY use in pediatric patients with renal impairment is

limited. Therefore, adult patients with severe renal impairment (eGFR < 30 mL/min) and pediatric patients with any degree of renal impairment should be closely monitored during treatment with VEKLURY (see 7 Warnings and Precautions, Renal and 10 Clinical Pharmacology, 10.3 Pharmacokinetics, Special populations and conditions, Renal Insufficiency).

4.2 Recommended Dose and Dosage Adjustment

Table 1 Recommended Dose in Adults and Pediatric Patients

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

Table 2 Treatment Duration

	Adults and Pediatric patients (weighing at least 40 kg)	**Pediatric patients at least 4 weeks old (weighing at least 3 kg but less than 40 kg)**
Hospitalized patients with **pneumonia and requiring supplemental oxygen**	Daily for **at least 5 days and not more than 10 days.**	Daily for up to a **total of 10 days**.
Non-hospitalized patients who **are at increased risk for progressing to severe COVID-19**	Daily for **3 days**, starting as soon as possible after diagnosis of COVID-19 and within 7 days of the onset of symptoms.	Not applicable.

Pediatrics (< 4 weeks of age or weighing < 3 kg): Health Canada has not authorized an indication in this population.

Non-hospitalized pediatrics (≥ 4 weeks of age and ≥ 3 kg to < 40 kg): Health Canada has not authorized an indication in this population.

Geriatrics (> 65 years of age): No dose adjustment of VEKLURY is required in patients over the age of 65 years (see 1 Indications, 1.2 Geriatrics and 10 Clinical Pharmacology, 10.3 Pharmacokinetics, Special populations and conditions, Geriatrics).

Renal Impairment
No dose adjustment of VEKLURY is required in patients with renal impairment, including those on dialysis. However, safety data in patients with severe renal impairment and end stage renal disease (ESRD) are limited and based on a 5-day treatment duration. The timing of administration of VEKLURY is without regard to dialysis (see 7 Warnings and Precautions, Renal and 10 Clinical Pharmacology, 10.3 Pharmacokinetics, Special populations and conditions, Renal Insufficiency).

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). However, due to limited data in subjects with severe hepatic impairment, monitoring of liver function should be considered. The pharmacokinetics of VEKLURY have not been evaluated in pediatric patients with hepatic impairment. No dosing recommendation can be made for pediatric patients with hepatic impairment (see 10 Clinical Pharmacology, 10.3 Pharmacokinetics, Special populations and conditions, Hepatic Insufficiency).

4.3 Reconstitution

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

VEKLURY must be reconstituted with 19 mL sterile water for injections and diluted in sodium chloride 9 mg/mL (0.9%) solution for injection before being administered via intravenous infusion over 30 to 120 minutes.

Preparation of VEKLURY solution for infusion

Reconstitution

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

- Aseptically reconstitute VEKLURY powder for solution for infusion by addition of 19 mL of sterile water for injections using a suitably sized syringe and needle per vial and insert the needle in the centre of the vial stopper.
    - Discard the vial if a vacuum does not pull the sterile water for injections into the vial.
- Only use sterile water for injections to reconstitute VEKLURY powder for solution for infusion.
- Immediately shake the vial for 30 seconds.
- Allow the contents of the vial to settle for 2 to 3 minutes. A clear solution should result.
- If the contents of the vial are not completely dissolved, shake the vial again for 30 seconds and allow the contents to settle for 2 to 3 minutes. Repeat this procedure as necessary until the contents of the vial are completely dissolved.
- Inspect the vial to ensure the container closure is free from defects and the solution is free of particulate matter.
- Dilute immediately after reconstitution.

Dilution

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

Adults and Pediatric Patients (weighing ≥ 40 kg)

- Using Table 3, determine the volume of sodium chloride 9 mg/mL (0.9%) solution for injection to withdraw from the infusion bag.

Table 3 Recommended Dilution Instructions – Reconstituted VEKLURY Powder For Solution For Infusion

VEKLURY dose	Sodium chloride 9 mg/mL (0.9%) infusion bag volume to be used	Volume to be withdrawn and discarded from sodium chloride 9 mg/mL (0.9%) infusion bag	Required volume of reconstituted VEKLURY
200 mg (2 vials)	250 mL	40 mL	2 × 20 mL
	100 mL	40 mL	2 × 20 mL
100 mg (1 vial)	250 mL	20 mL	20 mL
	100 mL	20 mL	20 mL

NOTE: 100 mL should be reserved for patients with severe fluid restriction, e.g. with acute respiratory distress syndrome 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 3.
- Withdraw the required volume of reconstituted VEKLURY powder for solution for infusion using an appropriately sized syringe per Table 3. Discard any unused portion remaining in the VEKLURY vial.
- Transfer the required volume of reconstituted VEKLURY powder for solution for infusion to the selected infusion bag.
- Gently invert the bag 20 times to mix the solution in the bag. Do not shake.
- The prepared solution is stable for up to 4 hours below 25°C or up to 24 hours in the refrigerator (2°C to 8°C) (including any time before dilution into intravenous infusion fluids).

Hospitalized Pediatric Patients (≥ 4 weeks of age and weighing 3 kg to < 40 kg)

- Further dilute the 100 mg/20 mL (5 mg/mL) VEKLURY concentrate to a fixed concentration of 1.25 mg/mL using 0.9% sodium chloride, per Table 4.
- The total required infusion volume of the 1.25 mg/mL VEKLURY solution for infusion is calculated from the pediatric weight-based dosing regimens of 5 mg/kg for the Loading Dose and 2.5 mg/kg for each subsequent dose.
- Small 0.9% sodium chloride infusion bags (e.g., 25, 50, or 100 mL) or an appropriately sized syringe should be used for pediatric dosing. The recommended dose is administered via IV infusion in a total volume dependent on the dose to yield the target VEKLURY concentration of 1.25 mg/mL.
- A syringe may be used for delivering volumes < 50 mL.

Table 4 Preparation of Diluted VEKLURY Infusion Solution from Reconstituted Solution for Hospitalized Pediatric Patients ≥ 4 Weeks of Age and Weighing 3 kg to < 40 kg

Weight-based VEKLURY pediatric dose	Sodium chloride 9 mg/mL (0.9%) infusion bag volume to be used	Volume to be withdrawn and discarded from sodium chloride 9 mg/mL (0.9%) infusion bag	Required volume of reconstituted VEKLURY (5 mg/mL) to reach final concentration of 1.25 mg/mL	Final volume of the diluted VEKLURY (1.25 mg/mL)
5 mg/kg First day	100 mL	40 mL	20 mL	80 mL
2.5 mg/kg subsequent days	50 mL	20 mL	10 mL	40 mL
	25 mL	10 mL	5 mL	20 mL

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

4.4 Administration

For intravenous infusion use.

It must not be given as an intramuscular (IM) injection.

VEKLURY powder for solution for infusion is for administration by intravenous infusion after reconstitution and further dilution.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 4 Dosage and Administration, 4.3 Reconstitution**.**

Table 5 Recommended Rate of Infusion – For Reconstituted and Diluted VEKLURY Powder For Solution For Infusion in Adults and Pediatric Patients Weighing ≥ 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 6 Recommended Rate of Infusion – For Reconstituted and Diluted VEKLURY Powder For Solution For Infusion in Hospitalized Pediatric Patients at Least 4 Weeks of Age and Weighing 3 kg to < 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.

5 Overdose

Treatment of overdose with VEKLURY should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with VEKLURY. In one clinical pharmacology trial, 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 aminotransferase (AST) and alanine transaminase (ALT) (Grade 4) without elevation of bilirubin.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6 Dosage Forms, Strengths, Composition, and Packaging

Table 7 Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	**Powder for solution for infusion, 100 mg/vial (5 mg/mL when reconstituted)** Each vial of VEKLURY Powder for solution for infusion contains 100 mg of remdesivir. After reconstitution, each vial contains 5 mg/mL of remdesivir solution. The powder is white to off-white to yellow.	Betadex sulfobutyl ether sodium, hydrochloric acid, sodium hydroxide

Packaged in a single Type 1 clear glass vial, an elastomeric closure, and an aluminum overseal with a flip-off cap.

7 Warnings and Precautions

General

Coadministration of VEKLURY and chloroquine phosphate or hydroxychloroquine sulphate is not recommended. This is based on *in vitro* data, which demonstrated an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of VEKLURY.

Immune

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. Monitor patients for hypersensitivity reactions during and following administration of VEKLURY. For infusion-related reactions, slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration of VEKLURY and initiate appropriate treatment.

Renal

Exposures of the metabolites GS-704277 and GS-441524, as well as the excipient SBECD are elevated in patients with renal impairment (see 10 Clinical Pharmacology, 10.3 Pharmacokinetics, Special populations and conditions, Renal Insufficiency). As clinically appropriate, patients should have eGFR determined prior to starting VEKLURY and while

receiving it. Safety data from adult patients with severe renal impairment and ESRD were comparable to the known safety profile of VEKLURY. However, there are limited safety data in this patient population. Therefore, taking the significantly higher exposures of GS-704277, GS-441524, and SBECD into account, adult patients with severe renal impairment and ESRD should be closely monitored for adverse events during treatment with VEKLURY. There are limited data regarding the use of VEKLURY in pediatric patients with mild or moderate renal impairment and no data regarding the use of VEKLURY in pediatric patients with severe renal impairment. Therefore, pediatric patients with renal impairment should be closely monitored during treatment with VEKLURY.

Reproductive Health

Women of child-bearing potential have to use effective contraception during treatment (see 7.1.1 Pregnancy).

- **Fertility**

  No human data on the effect of VEKLURY on fertility are available. In male rats, there was no effect on mating or fertility with remdesivir treatment. In female rats, however, an impairment of fertility was observed (see 16 Non-Clinical Toxicology, Reproductive and developmental toxicology). The relevance for humans is unknown.

7.1 Special Populations

7.1.1 Pregnancy

There is a limited amount of data from the use of VEKLURY in pregnant women. A study evaluating the pharmacokinetics of VEKLURY during pregnancy demonstrated no clinically relevant differences between pregnant and non-pregnant individuals. Most of the study participants were in second or third trimester of pregnancy. There are insufficient data to evaluate VEKLURY exposure during the first trimester. Taken together, the available data did not identify any risk of drug-associated maternal or fetal adverse events.

Animal studies did not indicate any adverse effects with respect to reproductive toxicity at exposures of the major metabolite of VEKLURY that were around human therapeutic exposures (see 16 Non-Clinical Toxicology, Reproductive and developmental toxicology).

Due to very limited experience, VEKLURY should not be used during first trimester in pregnancy unless the clinical condition of the woman requires treatment with it. Use in the second and third trimester of pregnancy may be considered.

Use of effective contraception during treatment should be considered in women of child-bearing potential.

7.1.2 Breastfeeding

VEKLURY and its major metabolite (GS-441524) are excreted in human breast milk after intravenous administration. Pharmacovigilance reports have not revealed adverse effects on breastfed infants from exposure to VEKLURY through breast milk.

As the clinical experience is limited, a decision about breast-feeding during treatment should be made after a careful individual benefit-risk assessment.

7.1.3 Pediatrics

Pediatrics (< 4 weeks of age or weighing < 3 kg): No data have been submitted to Health Canada for the safety and efficacy of VEKLURY in children under the age of 4 weeks or weighing < 3 kg; therefore, Health Canada has not authorized an indication in this population.

Non-hospitalized pediatrics (≥ 4 weeks of age and ≥ 3 kg to < 40 kg): No adequate clinical efficacy and safety data have been available. Health Canada has not authorized an indication in this population.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): Reported clinical experience has not identified differences in response between the elderly and younger patients.

8 Adverse Reactions

8.1 Adverse Reaction Overview

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%).

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates of adverse drug reactions in real-world use.

Clinical Trials Experience in Subjects with COVID-19

The primary safety assessment of VEKLURY was based on Study NIAID ACTT-1, a randomized, double-blind, placebo-controlled clinical trial in hospitalized subjects with mild, moderate, and severe COVID-19 treated with VEKLURY (n=532) or placebo (n=516) for up to 10 days. Subjects treated with VEKLURY received 200 mg on Day 1 and 100 mg once daily on subsequent days (see 14 Clinical Trials). The collection of adverse event data in this trial was limited to severe (Grade 3) or potentially life-threatening (Grade 4) adverse events, serious adverse events, adverse events leading to study drug discontinuation, and moderate (Grade 2) severity or higher drug-related hypersensitivity reactions.

Tabulated summary of adverse reactions

The adverse reactions in Table 8 are listed below by system organ class and frequency. Frequencies are defined as follows: Very common (≥1/10); common (≥1/100 to <1/10).

Table 8 Tabulated Summary of Adverse Reactions

Frequency	Adverse reaction
Nervous system disorders	
Common	headache
Gastrointestinal disorders	
Common	nausea
Hepatobiliary disorders	
Very common	transaminases increased
Skin and subcutaneous tissue disorders	
Common	rash

Rate of adverse reactions (≥ Grade 3), serious adverse reactions, and adverse reactions leading to treatment discontinuation are presented in Table 9.

Table 9 Summary of Adverse Reaction Rates in Subjects with Mild, Moderate, or Severe COVID-19 in NIAID ACTT-1

Types of Adverse Reactions	VEKLURY N=532 n (%)	Placebo N=516 n (%)
Adverse reactions, Grades ≥3	41 (8%)	46 (9%)
Serious adverse reactions	2 (0.4%)[a]	3 (0.6%)
Adverse reactions leading to treatment discontinuation	11 (2%)[b]	15 (3%)

a. Seizure (n=1), infusion-related reaction (n=1).
b. Seizure (n=1), infusion-related reaction (n=1), transaminases increased (n=3), ALT increased, and AST increased (n=1), GFR decreased (n=2), acute kidney injury (n=3).

Study GS-US-540-9012 was a randomized, double-blind, placebo-controlled clinical trial in subjects who were non-hospitalized, were symptomatic for COVID-19 for ≤ 7 days, had confirmed SARS-CoV-2 infection, and had at least one risk factor for progression to hospitalization treated with VEKLURY (n=279) or placebo (n=283) for 3 days. Subjects treated with VEKLURY received 200 mg on Day 1 and 100 mg once daily on subsequent days (see 14 Clinical Trials). Adverse reactions (all grades) were reported in 34 (12%) subjects in the VEKLURY group and 25 (9%) subjects in the placebo group. The most common adverse reaction occurring in at least 5% of subjects in the VEKLURY group was nausea (6%). There were no serious adverse reactions or adverse reactions leading to treatment discontinuation in either treatment group.

Clinical Trials Experience in Subjects with COVID-19 and Renal Impairment

In Study GS-US-540-5912, 163 hospitalized subjects with confirmed COVID-19 and acute kidney injury, chronic kidney disease or ESRD on hemodialysis received VEKLURY for up to 5 days. Safety data from these subjects were comparable to the known safety profile of VEKLURY. The percentage of subjects experiencing any adverse reactions was 8% in those administered VEKLURY and 3.8% in those administered placebo. Adverse reactions experienced by >1 subject were lipase increase (2 subjects administered VEKLURY, 1 subject administered placebo), abdominal pain, ALT increase, AST increase, diarrhea, and nausea (2 subjects administered VEKLURY for each). In this same study, the following Grade 3 or Grade 4 abnormalities were observed that occurred at higher incidence in subjects administered VEKLURY compared to subjects administered placebo: hyperuricemia (10.8% vs 4.3%) and increased prothrombin time (10.7% vs 4.3%). No difference was observed in the incidence of

bleeding events between the two groups.

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

Study GS-US-540-5823 is an on-going Phase 2/3, single-arm, open-label clinical trial in hospitalized subjects from birth to < 18 years of age with COVID-19. The safety of VEKLURY evaluated in the interim report of the trial was in subjects 4 weeks of age and older and weighing at least 3 kg. These subjects were treated with weight-based VEKLURY (n=53) for up to 10 days (see 14 Clinical Trials):

- Subjects ≥ 12 years and weighing ≥ 40 kg (n=12) and subjects < 12 years and weighing ≥ 40 kg (n=5): Received 200 mg on Day 1 and 100 mg once daily on subsequent days.
- 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): Received 5 mg/kg on Day 1 and 2.5 mg/kg once daily on subsequent days.

The adverse reactions observed were consistent with those observed in clinical trials of VEKLURY in adults. Adverse reactions (all grades) were reported in 8 (15%) subjects. The most common adverse reaction occurring in at least 5% of subjects was ALT increased (6%). No subjects experienced serious adverse reactions. Two (4%) subjects permanently discontinued treatment due to adverse reactions (ALT increased [n=1], ALT increased and AST increased and hyperbilirubinemia [n=1]). Laboratory abnormalities (Grades 3-4) occurring in at least 3% of subjects with COVID-19 receiving VEKLURY in Trial 5823 and who had at least one post-baseline value for the specified test were hemoglobin decreased (18%, 9/51), eGFR decreased (18%, 7/40), creatinine increased (10%, 5/52), direct bilirubin increased (9%, 2/23), prothrombin time increased (7%, 3/46), APTT increased (7%, 3/45), lymphocytes decreased (6% 2/33), proteinuria (6%, 2/36), WBC decreased (4%, 2/51), ALT increased (4%, 2/51), glucose increased (4%, 2/52), glycosuria (4%, 2/46), potassium decreased (4%, 2/52).

8.3 Less Common Clinical Trial Adverse Reactions

Clinically significant adverse reactions that were reported in ≥ 1/10,000 to < 1/1,000 of subjects exposed to VEKLURY in clinical trials are listed below:

Immune system disorders:	hypersensitivity
Injury, poisoning and procedural complications:	infusion related reaction

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Clinical Trial Findings

Transaminases Increased

In healthy volunteer studies, increases in ALT, AST or both in participants who received VEKLURY were 1.25 to 2.5 times the upper limit of normal (ULN) (10%) or 2.5 to 5 times ULN (4%). In clinical studies of participants with COVID-19, the incidence of increased transaminases was similar in participants treated with VEKLURY compared to placebo or standard of care.

Prothrombin Time Increased

In a clinical study (NIAID ACTT-1) of participants with COVID-19, the incidence of increased prothrombin time or INR (predominantly less than 2 times ULN) was higher in participants who received VEKLURY compared to placebo, with no difference observed in the incidence of bleeding events between the two groups. In Study GS-US-540-9012, the incidence of increased prothrombin time or INR was similar in participants treated with VEKLURY compared to placebo.

8.5 Post-Market Adverse Reactions

In addition to adverse reactions from clinical studies, the following adverse reactions were identified during post-approval use of VEKLURY. These events have been chosen for inclusion due to either their seriousness, frequency of reporting, potential causal connection VEKLURY, or a combination of these factors. Because these reactions were reported voluntarily from a population of unknown size, estimates of frequency cannot be made.

Cardiovascular:	sinus bradycardia
Immune system disorders:	anaphylactic reaction

9 Drug Interactions

9.2 Drug Interactions Overview

Due to potential antagonism based on *in vitro* observations, concomitant use of VEKLURY with chloroquine phosphate or hydroxychloroquine sulphate is not recommended.

9.4 Drug-Drug Interactions

Effects of other medicinal products on VEKLURY

Coadministration of VEKLURY and chloroquine phosphate or hydroxychloroquine sulphate is not recommended based on *in vitro* data demonstrating an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of remdesivir (see 15 Microbiology, Antiviral Activity).

VEKLURY should not be coadministered with drugs which reduce renal function (see 7 Warnings and Precautions, Renal and 10 Clinical Pharmacology, 10.3 Pharmacokinetics, Special populations and conditions, Renal Insufficiency).

In vitro, remdesivir is a substrate for esterases in plasma and tissue, drug metabolizing enzyme CYP3A4 and is a substrate for Organic Anion Transporting Polypeptide 1B1 (OATP1B1) and P-glycoprotein (P-gp) transporters. GS-704277 is a substrate for OATP1B1 and OATP1B3. Based on a drug interaction study conducted with VEKLURY (Study GS-US-540-9013), coadministration of a single-dose of 400 mg cyclosporin A (a potent OATP1B1 and OATP1B3 inhibitor) caused a moderate 2.51-fold increase in C_{max} and an almost 3-fold increase in AUC_{inf} for GS-704277. However, the increase was not considered clinically significant. Coadministration of a single dose of VEKLURY following multiple doses of carbamazepine (strong inducer of CYP3A4) did not result in clinically significant changes in exposure of remdesivir, GS-704277, or GS-441524.

The effects of coadministered drugs on the pharmacokinetics of remdesivir and metabolites GS-704277 and GS-441524 are shown in Table 10.

The potential of interaction of remdesivir with inhibitors/inducers of the hydrolytic pathway (esterase) or CYP3A4 inhibitors has not been studied; however, the risk of clinically relevant interactions is low. Strong inhibitors may result in increased exposure of remdesivir.

Table 10 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 single dose	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 (GS-US-540-9013).

Effects of VEKLURY on other medicinal products

Remdesivir did not cause significant changes in plasma PK of midazolam (CYP3A4 substrate) or pitavastatin (OATP1B1/B3 substrate) when assessed clinically, with mean increases in AUC_{inf} of 17-30% following single or multiple doses of VEKLURY being within the prespecified no-effect boundary (Table 11). Based on these data, no clinically significant drug interactions are expected with remdesivir and substrates of CYP3A4 (including dexamethasone), OATP1B1 and OATP1B3. Furthermore, *in vitro* data and extrapolation of findings from clinical studies indicate no clinically significant drug interactions are expected with remdesivir and substrates of UGT1A1, MATE1, OAT1, OAT3, OCT1, and OCT2. Although remdesivir showed *in vitro* induction of CYP1A2, the plasma half-life of remdesivir is approximately 1 hour, and thus unlikely to result in sustained plasma concentrations high enough to cause clinically significant induction *in vivo*.

Table 11 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)[c]	14	1.45 (1.23-1.70)[b]	1.30 (1.16-1.45)[b]
Pitavastatin	2 single dose	200 single dose	20	1.05 (0.92-1.20)	1.17 (1.09-1.24)

CI=Confidence Interval
a. Interaction study conducted in healthy volunteers (GS-US-611-6409 and GS-US-540-6587).
b. No effect = 1.00 (0.70-1.43).
c. Midazolam administered with last dose of remdesivir.

In vitro, at physiologically relevant concentrations (steady-state), remdesivir inhibited CYP3A4 but neither remdesivir nor its metabolites GS-704277 and GS-441524 inhibited CYP1A2, 2B6, 2C8, 2C9, 2C19, and 2D6. Remdesivir is not a time-dependent inhibitor of CYP450 enzymes.

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

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

At physiologically relevant concentrations, remdesivir and its metabolites did not inhibit P-gp and BCRP.

9.5 Drug-Food Interactions

Interactions of VEKLURY with food have not been established.

9.6 Drug-Herb Interactions

Interactions of VEKLURY with herbs have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions of VEKLURY with laboratory tests have not been established.

10 Clinical Pharmacology

10.1 Mechanism of Action

Remdesivir is an adenosine nucleotide prodrug that is metabolized within host cells to form the pharmacologically active nucleoside triphosphate metabolite. Remdesivir triphosphate acts as an analog of adenosine triphosphate (ATP) and competes with the natural ATP substrate for incorporation into nascent RNA chains by the SARS-CoV-2 RNA-dependent RNA polymerase, which results in delayed chain termination during replication of the viral RNA. As an additional mechanism, remdesivir triphosphate can also inhibit viral RNA synthesis following its incorporation into the template viral RNA as a result of read-through by the viral polymerase that may occur in the presence of higher nucleotide concentrations. When remdesivir nucleotide is present in the viral RNA template, the efficiency of incorporation of the complementary natural nucleotide is compromised, thereby inhibiting viral RNA synthesis.

10.2 Pharmacodynamics

Effects on Electrocardiogram

QT Prolongation

In a thorough QT/QTc trial, no effect was seen on the QTc interval in 54 healthy subjects administered a single dose of 600 mg VEKLURY.

10.3 Pharmacokinetics

The pharmacokinetic properties of remdesivir have been investigated in healthy volunteers (see Table 12). The multiple dose pharmacokinetic parameters of remdesivir and metabolites in adults with COVID-19 are provided in Table 13.

Table 12 Pharmacokinetic Properties of Remdesivir and Metabolites (GS-704277 and GS-441524)

	Remdesivir	**GS-704277**	**GS-441524**
Absorption			
T_{max} (h)[a]	0.67-0.68	0.75-0.75	1.51-2.00
Distribution			
% bound to human plasma proteins	88-93.6[b]	1	2
Blood-to-plasma ratio	0.68-1.0	0.56	1.19
Elimination			
$t_{1/2}$ (h)[c]	1	1.3	27
Metabolism			
Metabolic pathway(s)	CES1 (80%) Cathepsin A (10%) CYP3A (10%)	HINT1	Not significantly metabolized
Excretion			

	Remdesivir	GS-704277	GS-441524
Major route of elimination	Metabolism	Metabolism	Glomerular filtration and active tubular secretion
% of dose excreted in urine[d]	10	2.9	49
% of dose excreted in feces[d]	ND	ND	0.5

ND=not detected

a. Remdesivir administered as a 30-minute IV infusion (Study GS-US-399-5505); range of median observed on Day 1 and Day 5 or 10.
b. Range of protein binding for remdesivir from 2 independent experiments show no evidence of concentration-dependent protein binding for remdesivir.
c. Median (Study GS-US-399-4231).
d. Mean (Study GS-US-399-4231).

Table 13 Multiple Dose PK Parameters[a] of Remdesivir and Metabolites (GS-704277 and GS-441524) Following IV Administration of VEKLURY 100 mg to Adults with COVID-19

Parameter Mean[b] (95%CI)	Remdesivir	GS-704277	GS-441524
C_{max} (ng/mL)	2700 (2440, 2990)	198 (180, 218)	143 (135, 152)
AUC_{tau} (ng•h/mL)	1710 (1480, 1980)	392 (348, 442)	2410 (2250, 2580)
C_{trough} (ng/mL)	ND	ND	61.5 (56.5, 66.8)

CI=Confidence Interval; ND=Not detectable (at 24 hours post-dose)

a. Population PK estimates for 30-minute IV infusion of remdesivir for 3 days (Study GS-US-540-9012, n=147).
b. Geometric mean estimates.

Absorption

The pharmacokinetic properties of remdesivir and the predominant circulating metabolite GS-441524 have been evaluated in healthy adult subjects. Following intravenous administration of remdesivir adult dosage regimen, peak plasma concentration was observed at end of infusion, regardless of dose level, and declined rapidly thereafter with a half-life of approximately 1 hour. Peak plasma concentrations of GS-441524 were observed at 1.5 to 2.0 hours post start of a 30-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 metabolized to the pharmacologically active nucleoside analog triphosphate GS-443902 (formed intracellularly). 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 of all phosphorylated metabolites can result in the formation of nucleoside metabolite GS-441524 that itself is not efficiently re-phosphorylated. Decyanation of remdesivir and/or its metabolites, followed by subsequent rhodanese mediated conversion generates thiocyanate anion. The levels of thiocyanate detected following administration of 100 mg and 200 mg remdesivir were observed to be significantly below endogenous levels in human plasma.

Elimination

Following a single 150 mg IV dose of [^{14}C]-remdesivir, mean total recovery of the dose was 92%, consisting of approximately 74% and 18% recovered in urine and feces, respectively. The majority of the remdesivir dose recovered in urine was GS-441524 (49%), while 10% was recovered as remdesivir. These data indicate that renal clearance is the major elimination pathway for GS-441524. The median terminal half-lives of remdesivir and GS-441524 were approximately 1 and 27 hours, respectively.

Special populations and conditions

- **Pediatrics**

  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 pediatric patients with COVID-19, were used to predict pharmacokinetic exposures in 50 hospitalized pediatric 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 increase was not considered clinically significant. A summary of pharmacokinetic parameters for remdesivir, GS-704277, and GS-441524 in pediatric and adult COVID-19 patients are presented in Table 14 and Table 15.

Table 14 Pharmacokinetic Parameters Estimate of Steady-State Plasma Remdesivir, GS-704277, and GS-441524 in Pediatric and Adult COVID-19 Patients

Parameter Mean[a] (95%CI)	Pediatric (all cohorts)[b] N=50	Adult (hospitalized)[c] N=277	Adult (non-hospitalized) N=147

Remdesivir			
C_{max} (ng/mL)	4830 (4330, 5380)	2650 (2430, 2900)	2700 (2440, 2990)
AUC_{tau} (ng•h/mL)	3050 (2560, 3630)	1590 (1430, 1770)	1710 (1480, 1980)
GS-704277			
C_{max} (ng/mL)	373 (325, 429)	233 (217, 250)	198 (180, 218)
AUC_{tau} (ng•h/mL)	725 (609, 865)	501 (476, 528)	392 (348, 442)
GS-441524			
C_{max} (ng/mL)	181 (155, 212)	170 (161, 180)	143 (135, 152)
AUC_{tau} (ng•h/mL)	2840 (2380, 3400)	3060 (2870, 3250)	2410 (2250, 2580)
C_{tau} (ng/mL)	79.2 (66.0, 95.0)	78.4 (73.9, 83.1)	61.5 (56.5, 66.8)

CI=Confidence Interval; C_{max}=maximum observed concentration; AUC_{tau}=area under the concentration versus time curve over the dosing interval; C_{tau}=observed drug concentration at the end of the dosing interval

a. Geometric mean estimates.
b. Phase 2/3 hospitalized COVID participants.
c. Phase 3 hospitalized (N=277) and non-hospitalized (N=147) COVID participants.

Table 15 Clearance Rate of Remdesivir, GS-704277, and GS-441524 in Pediatric and Adult COVID-19 Patients

Parameter Mean[a] (95%CI)	**Pediatric[b]**					**Adult[c]**
	3 to < 12 kg (n=10)	12 to < 20 kg (n=11)	20 to < 40 kg (n=12)	≥ 40 kg (n=17)	Overall (n=50)	≥ 40 kg (N=424)
Remdesivir						
CL (L/h)	4.8 (2.9, 7.9)	9.5 (5.3, 17.1)	19.6 (13.8, 27.9)	41.3 (33.5, 50.9)	16.2 (12.1, 21.7)	61.5 (56.5, 67.0)
GS-704277						
CL (L/h)	16.3 (9.9, 26.9)	40.8 (28.5, 58.4)	73.4 (56.9, 94.7)	111.0 (72.4, 170.2)	55.0 (41.9, 72.2)	173.2 (163.7, 183.2)
GS-441524						
CL (L/h)	2.5 (1.8, 3.5)	7.8 (6.0, 10.0)	10.9 (7.8, 15.1)	15.5 (9.8, 24.6)	8.5 (6.6, 11.0)	16.9 (16.0, 17.8)

CI=Confidence Interval; CL=clearance

a. Geometric mean estimates.
b. Phase 2/3 hospitalized COVID participants.
c. Phase 3 hospitalized (N=277) and non-hospitalized (N=147) COVID participants.

- **Geriatrics**

  Pharmacokinetic differences for age have not been evaluated.

- **Sex**

Pharmacokinetic differences were evaluated using population pharmacokinetic analysis. Sex did not affect the pharmacokinetics of remdesivir and its metabolites (GS-704277 and GS-441524).

- **Pregnancy and breastfeeding**

  In the CO-US-540-5961 (IMPAACT 2032) study, mean exposures (AUC_{tau}, C_{max}, and C_{tau}) of remdesivir and its metabolites (GS-704277 and GS-441524) were comparable between pregnant and non-pregnant women of child-bearing potential.

- **Ethnic origin**

  Pharmacokinetic differences for ethnic origin have not been evaluated.

- **Hepatic Insufficiency**

  The pharmacokinetics of remdesivir and its metabolites (GS-441524 and GS-704277) were evaluated in healthy subjects and those with moderate or severe hepatic impairment (Child-Pugh Class B or C) following a single dose of 100 mg of remdesivir (see Table 16). Relative to subjects with normal hepatic function, mean exposures (AUC_{inf}, C_{max}) of remdesivir, GS-704277, and GS-441524 were comparable in moderate hepatic impairment and up to 2.4-fold higher in severe hepatic impairment.

Table 16 Comparison of Pharmacokinetic Parameters of Remdesivir, GS-704277, and GS-441524 Following IV Administration of Single Dose VEKLURY to Adults with Hepatic Impairment as Compared to Adults with Normal Hepatic Function

GLSM Ratio[a] (90% CI)	Moderate Hepatic Impairment N=10	Severe Hepatic Impairment N=6
Remdesivir		
AUC_{inf}	1.21 (0.87, 1.67)	1.56 (1.20, 2.03)
C_{max}	1.10 (0.75, 1.60)	1.03 (0.70, 1.51)
Unbound AUC_{inf}	1.15 (0.86, 1.54)	2.44 (1.93, 3.08)
Unbound C_{max}	1.04 (0.73, 1.48)	1.57 (1.08, 2.29)
GS-704277		
AUC_{inf}	1.38 (0.92, 2.07)	2.41 (1.70, 3.42)
C_{max}	1.29 (0.54, 3.08)	1.07 (0.70, 1.63)
GS-441524		
AUC_{inf}	0.90 (0.69, 1.17)	1.31 (0.93, 1.84)
C_{max}	1.09 (0.86, 1.38)	1.48 (1.17, 1.86)
C_{24}	0.93 (0.69, 1.24)	1.16 (0.76, 1.77)

CI=Confidence Interval; GLSM = geometric least-squares mean
a. No effect=1.0 (0.5-2.0)

- **Renal Insufficiency**

  The pharmacokinetics of remdesivir and its metabolites (GS-441524 and GS-704277) and the excipient SBECD were evaluated in healthy subjects, those with mild (eGFR 60-89

mL/minute), moderate (eGFR 30-59 mL/minute), severe (eGFR 15-29 mL/minute) renal impairment, or with ESRD (eGFR <15 mL/minute) on hemodialysis or not on hemodialysis following a single dose of up to 100 mg of remdesivir (Table 17); and in a Phase 3 study in COVID-19 patients with severely reduced kidney function (eGFR <30 mL/minute) receiving remdesivir 200 mg on Day 1 followed by 100 mg from Day 2 to Day 5 (Table 18). Pharmacokinetic exposures of remdesivir were not affected by renal function or timing of remdesivir administration around dialysis.

Exposures of GS-704277, GS-441524, and SBECD were up to 2.8-fold, 7.9-fold and 21-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 17 Statistical comparison of single-dose pharmacokinetic parameters[a] of remdesivir and metabolites (GS-704277 and GS-441524) 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-hemodialysis N=6	Post-hemodialysis 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-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)
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)

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. $AUC_{0\text{-}72h}$ for subjects on hemodialysis.

Table 18 Pharmacokinetic parameters[a] of remdesivir and metabolites (GS-704277 and GS-441524) 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-704277	GS-441524
C_{max} (ng/mL)	3850 (1530, 8720)	378 (127, 959)	703 (343, 1250)
AUC_{tau} (h•ng/mL)	2950 (1390, 8370)	1540 (767, 3880)	15400 (7220, 27900)

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.

11 Storage, Stability and Disposal

Unopened vials

Store below 30°C

Reconstituted and diluted solution for infusion

Store diluted remdesivir solution for infusion up to 4 hours below 25°C or up to 24 hours in a refrigerator (2°C to 8°C).
Once reconstituted, the drug product should be diluted immediately.

General Instructions

Once diluted, the drug product should be used immediately. If necessary, bags of diluted solution can be stored for up to 4 hours below 25°C, or for up to 24 hours in a refrigerator. Do not allow more than 24 hours between dilution and administration. Do not reuse or save unused remdesivir powder or diluted solution for infusion for future use. This product contains no preservative.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

12 Special Handling Instructions

Prepare solution for infusion under aseptic conditions and on the same day as administration. VEKLURY should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. Should either be observed, the solution should be discarded and fresh solution prepared (see 4 Dosage and Administration, 4.3 Reconstitution).

Part 2: Scientific Information

13 Pharmaceutical Information

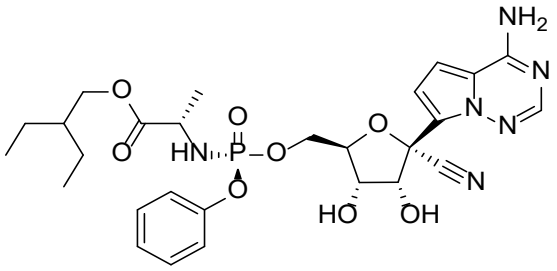
Drug Substance

Non-proprietary name of the drug substance: remdesivir (USAN)

Chemical name: 2-Ethylbutyl (2*S*)-2-{[(*S*)-{[(2*R*,3*S*,4*R*,5*R*)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl]methoxy}(phenoxy)phosphoryl]amino}propanoate

Molecular formula and molecular mass: $C_{27}H_{35}N_6O_8P$
602.6

Structural formula:



Physicochemical properties:

Description: Remdesivir is a white to off-white to yellow solid.

Solubility: Remdesivir is very slightly soluble (0.35 mg/mL) at pH 2, practically insoluble (0.04 mg/mL) at pH 4, and practically insoluble (0.03 mg/mL) at pH 7. The partition coefficient (log P) is 3.2 and the pKa is 3.3.

14 Clinical Trials

The clinical efficacy and safety of VEKLURY were evaluated in the studies summarized below.

14.1 Clinical Trials by Indication

COVID-19 in Hospitalized Adults and Pediatric Patients

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

A randomized, double-blind, placebo-controlled clinical trial evaluated 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 of intravenously administered therapy) in hospitalized adult patients with COVID-19 with evidence of lower respiratory tract involvement.

Table 19 Summary of Patient Demographics for NIAID ACTT-1 Study in Adult Patients with COVID-19

	NIAID ACTT-1 Study (CO-US-540-5776)		
Characteristic	**All N = 1062**	**VEKLURY (remdesivir) N = 541**	**Placebo N = 521**
Patients with mild/moderate disease (defined by SpO2 >94% and respiratory rate <24 breaths/min without supplemental oxygen) – no. (%)	105 (9.9)	55 (10.2)	50 (9.6)
Patients with severe disease (defined by SpO2 ≤94% on room air, or respiratory rate ≥24 breaths/min and requiring supplemental oxygen or ventilatory support) – no. (%)	957 (90.1)	486 (89.8)	471(90.4)
Baseline mean age (years)	58.9	58.6	59.2
Patients aged 65 years or older (%)	36.2	34.6	37.9
Sex			
Male sex (%)	64.4	65.1	63.7
Female sex (%)	35.6	34.9	36.3
Race or ethnic group (%)			
White	53.3	51.6	55.1
Black	21.3	20.1	22.5
Asian	12.7	14.6	10.7
Coexisting conditions (%)			
Hypertension	50.7	50.6	50.9
Obesity	45.4	45.6	45.2
Type 2 diabetes mellitus	30.6	30.8	30.4
Coronary artery disease	11.9	12.8	10.9
Patients received a 10-day treatment course with VEKLURY – no. (%)		208 (38.4)	

Results of NIAID ACTT-1 Study (CO-US-540-5776) in Adult Patients with COVID-19

The primary clinical endpoint was time to recovery within 29 days after randomization, defined as either discharged from hospital (with or without limitations of activity and with or without home oxygen requirements) or hospitalized 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 observed between the treatment groups for patients with mild to moderate disease at enrolment (n=159); the median time to recovery was 5 days in the VEKLURY group and 7 days in the placebo group (recovery rate ratio 1.10; [95% CI 0.8 to 1.53]). Among patients with severe disease at enrolment (n=957), the median time to recovery

was 11 days in the VEKLURY group compared to 18 days in the placebo group (recovery rate ratio, 1.31; [95% CI, 1.12 to 1.52]; p < 0.001). This clinical benefit of VEKLURY was primarily observed in patients receiving supplemental oxygen (baseline clinical status: ordinal score 5). No difference in time to recovery was observed between the treatment groups for patients who were receiving mechanical ventilation or ECMO at enrolment (n=285; baseline clinical status: ordinal score 7); median time to recovery was 29 days in the VEKLURY group and 28 days in the placebo group, (recovery rate ratio 0.98; [95% CI 0.70 to 1.36]).

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, 1.54; [95% CI, 1.25 to 1.91], p < 0.001).

Hospitalized Pediatric Patients (GS-US-540-5823)

The pharmacokinetics and safety of VEKLURY were the primary objectives of this Phase 2/3 single-arm, open-label trial of up to 10 days of VEKLURY dosing in pediatric subjects from birth to less than 18 years of age. The interim report for 53 pediatric patients in 5 cohorts from at least 4 weeks of age and weighing at least 3 kg was evaluated.

Five cohorts were enrolled: patients ≥ 12 years and weighing ≥ 40 kg (n=12); patients < 12 years and weighing ≥ 40 kg (n=5); patients ≥ 28 days and weighing ≥ 20 to < 40 kg (n=12); patients ≥ 28 days and weighing ≥ 12 to < 20 kg (n=12); and patients ≥ 28 days and weighing ≥ 3 to < 12 kg (n=12).

Patients weighing ≥ 40 kg received 200 mg of VEKLURY on Day 1 followed by VEKLURY 100 mg once daily on subsequent days; patients 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.

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; mean weight was 38 kg (range: 4 to 192 kg). 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.

Results of Study GS-US-540-5823

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 patients on Day 10; median (Q1, Q3) time to recovery was 7 (5, 16) days.

Overall, 60% of patients were discharged by Day 10. Three patients died during the study.

COVID-19 in Adults at High Risk of Disease Progression Not Requiring Supplemental Oxygen

Study GS-US-540-9012 in Non-hospitalized Patients with COVID-19 at High Risk for Disease Progression

A randomized, double-blind, placebo-controlled, clinical trial (Study GS-US-540-9012) evaluated VEKLURY 200 mg once daily for 1 day followed by VEKLURY 100 mg once daily for 2 days (for a total of 3 days of intravenously administered therapy) in 562 adult and pediatric patients (12 years of age and older and weighing at least 40 kg) with confirmed SARS-CoV-2 infection and at least one risk factor for progression to hospitalization. Risks for disease progression included chronic lung disease, hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity, immunocompromised state, chronic mild or moderate kidney disease, chronic liver disease, current cancer, sickle cell disease or aged ≥ 60 years. 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, and 2% were Asian; 44% were Hispanic or Latino; median body mass index was 30.7 kg/m^2. Patients in this trial were unvaccinated. 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 well balanced across the VEKLURY and placebo treatment groups.

Results of Study GS-US-540-9012

The primary endpoint was the proportion of patients with COVID-19 related hospitalization (defined as at least 24 hours of acute care) or all-cause mortality through Day 28. Events 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 hospitalization or all-cause mortality through Day 28 compared to placebo (hazard ratio, 0.134; [95% CI 0.031 to 0.586]; p=0.0076). No deaths were observed through Day 28.

Study GS-US-540-5912 in Patients with COVID-19 and Renal Impairment

A randomized, 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 hospitalized adult patients with confirmed COVID-19 and renal impairment. The trial included 90 patients (37%) with AKI (defined as a 50% increase in serum creatinine within a 48-hour period that was sustained for ≥ 6 hours despite supportive care), 64 patients (26%) with CKD (eGFR <30 mL/minute), and 89 patients (37%) with ESRD (eGFR <15 mL/minute) requiring hemodialysis. Patients were randomized in a 2:1 manner, stratified by ESRD, 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.

Results of Study GS-US-540-5912

The study closed prematurely due to feasibility issues and was underpowered to assess primary (all-cause death or IMV by Day 29) and secondary efficacy endpoints because of lower-than-expected enrolment. The safety and pharmacokinetic data from this study support the use of VEKLURY in patients with renal impairment (see 4 Dosage and Administration, 4.1 Dosing Considerations; 7 Warnings and Precautions, Renal; 8 Adverse Reactions, 8.2 Clinical Trial Adverse Reactions, Clinical Trials Experience in Subjects with COVID-19 and Renal Impairment; and 10 Clinical Pharmacology, 10.3 Pharmacokinetics, Special populations and conditions, Renal Insufficiency).

15 Microbiology

Antiviral Activity

Remdesivir exhibited *in vitro* activity against a clinical isolate of SARS-CoV-2 in primary human airway epithelial cells with a 50% effective concentration (EC_{50}) of 9.9 nM after 48 hours of treatment. Remdesivir inhibited the replication of SARS-CoV-2 in the continuous human lung epithelial cell line Calu-3 with an EC_{50} value of 280 nM after 72 hours of treatment. The antiviral activity of remdesivir was antagonized by chloroquine phosphate in a dose-dependent manner when the two drugs were co-incubated at clinically relevant concentrations in HEp-2 cells infected with respiratory syncytial virus (RSV). Higher remdesivir EC_{50} values were observed with increasing concentrations of chloroquine phosphate. Increasing concentrations of chloroquine phosphate reduced formation of remdesivir triphosphate in normal human bronchial epithelial cells.

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, BA.2.12.1, 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 and 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 20.

Table 20 Remdesivir Antiviral Activity Against Clinical Isolates of SARS-CoV-2 Variants

SARS-CoV-2 Lineage	WHO Nomenclature	KEY Substitutions	Fold Change in Susceptibility[a]
B.1.1.7	Alpha	P323L	1.58
B.1.351	Beta	P323L	1.19
P.1	Gamma	P323L	0.82
B.1.617.2	Delta	P323L, G671S	0.59
B.1.429	Epsilon	P323L	1.94
P.2	Zeta	P323L	1.17
B.1.526	Iota	P323L	2.33
B.1.617.1	Kappa	P323L	0.63
C.37	Lambda	P323L	1.37
B.1.1.529/BA.1	Omicron	P323L	0.45
BA.2		P323L	0.23
BA.2.12.1		P323L	0.20
BA.2.75		P323L, G671S	0.30
BA.2.86[b]		P323L	1.14
BA.4		P323L	0.15
BA.4.6		P323L	0.64
BA.5		P323L	0.66
BF.5		P323L	0.94
BF.7		P323L	1.25
BQ.1		P323L, Y273H	0.53
BQ.1.1		P323L, Y273H	1.12
CH.1.1		P323L, G671S	0.95
EG.1.2		P323L, G671S	0.87
EG.5.1		P323L, G671S	0.58
FL.22		P323L, G671S	1.15
XBB		P323L, G671S	1.07
XBB.1.5		P323L, G671S	0.81
XBB.1.9.2[b]		P323L, G671S	2.02
XBB.1.16		P323L, G671S	0.73
XBB.2.3.2		P323L, G671S	0.29
XBF		P323L, G671S	1.22

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. EC_{50} fold change values <2.8-fold using clinical isolates and <2.5-fold using replicon assay represent no change in susceptibility.

b. 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.

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. 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. 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-dependent RNA polymerase at residues conserved across CoVs that conferred 5.6-fold reduced susceptibility to remdesivir. Introduction of the corresponding substitutions (F480L and V557L) into SARS-CoV resulted in 6-fold reduced susceptibility to remdesivir 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 CO-US-540-5776 (ACTT-1), among 61 patients with baseline and post-baseline sequencing data available, the rate of emerging substitutions in the viral RdRp (nsp12) was similar in patients treated with VEKLURY compared to placebo. Two patients treated with VEKLURY had an emergent substitution previously identified in resistance selection experiments (nsp12 V792I in one and C799F in the other). These substitutions are associated with 2.2- and 2.5-fold decreases in remdesivir susceptibility, respectively, based on assessments of clinical isolates. Other treatment emergent substitutions in nsp12 analysed in this study (A16V, K59N, D684N or V764L) either showed little change in remdesivir susceptibility or conferred no replication in an *in vitro* replicon assay.

In Study GS-US-540-5773, among 19 patients treated with VEKLURY who had baseline and postbaseline sequencing data available, substitutions in the viral RNA-dependent RNA polymerase (nsp12) were observed in 4 patients. The substitutions T76I, A526V, A554V and C697F were not associated with resistance to VEKLURY (≤ 1.45-fold change in susceptibility). The effect of substitution E665K on susceptibility to VEKLURY could not be determined due to lack of replication.

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 RdRp (nsp12) was similar in patients treated with VEKLURY compared to placebo. Seven treatment emergent amino acid substitutions in nsp12 were identified; T206I, P232L, T394M, A526S and A634S showed negligible changes in susceptibility to remdesivir (≤1.4-fold) in an *in vitro* subgenomic replicon assay, while S6L conferred no replication. In one patient treated with VEKLURY, an A376V substitution emerged which was associated with a 12.6-fold decrease in remdesivir susceptibility. This patient was not hospitalized and showed alleviation of all baseline symptoms, except loss of taste and smell, prior to or on Day 14.

In Study GS-US-540-5912, 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 remdesivir. In 4 patients treated with remdesivir, 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 remdesivir were associated with resistance to remdesivir.

In Study GS-US-540-5823, among pediatric patients with baseline and post-baseline sequencing data available, substitutions in the viral RNA-dependent RNA polymerase were observed in one of 23 patients treated with remdesivir. The substitutions observed have not previously been associated with resistance to remdesivir.

16 Non-Clinical Toxicology

General toxicology

Due to differences in metabolite profiles, animal studies may not be fully informative of the potential risks associated with VEKLURY administration.

Following intravenous administration (slow bolus) of remdesivir to rhesus monkeys and rats, severe renal toxicity occurred after short treatment durations. In male rhesus monkeys at dosage levels of 5, 10, and 20 mg/kg/day for 7 days resulted, at all dose levels, in increased mean urea nitrogen and increased mean creatinine, renal tubular atrophy, and basophilia and casts, and an unscheduled death of one animal at the 20 mg/kg/day dose level. In rats, dosage levels of >3 mg/kg/day for up to 4 weeks resulted in findings indicative of kidney injury and/or dysfunction. Systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) were 0.1 times (monkeys at 5 mg/kg/day) and 0.3 times (rats at 3 mg/kg/day) the exposure in humans following intravenous administration at the recommended human dose (RHD).

Genotoxicity

Remdesivir was not genotoxic in a battery of assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes, and *in vivo* rat micronucleus assays.

Carcinogenicity

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

Reproductive and developmental toxicology

In female rats, decreases in corpora lutea, numbers of implantation sites, and viable embryos were seen when remdesivir was administered intravenously daily at a systemically toxic dose (10 mg/kg/day) 14 days prior to mating and during conception; exposures of the predominant circulating metabolite (GS-441524) were 1.3 times the exposure in humans at the RHD. There were no effects on female reproductive performance (mating, fertility, and conception) at this dose level.

In rats and rabbits, remdesivir demonstrated few adverse effects on embryo-fetal development when administered to pregnant animals at systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) that were up to 4 times the exposure in humans at the RHD. The rates of vertebral malformations observed in rats and rabbits were higher than historical controls.

In rats, there were no adverse effects on pre- and post-natal development at systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) that were similar to the exposure in humans at the RHD.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr VEKLURY®
remdesivir for injection

This Patient Medication Information is written for the person who will be taking **VEKLURY**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **VEKLURY**, talk to a healthcare professional.

What VEKLURY is used for:

The active substance of VEKLURY is remdesivir. It is an antiviral medicine for treating coronavirus 2019 (COVID-19). VEKLURY will be given to people with COVID-19. It is suitable for:

- hospitalized adults and children (at least 4 weeks of age and weighing at least 3 kg) who have pneumonia, and need extra oxygen to help them breathe;
- non-hospitalized adults and children (weighing at least 40 kg) with positive SARS-CoV-2 test results, and who are at high risk for progression to severe COVID-19, including being hospitalized or dying.

How VEKLURY works:

COVID-19 is caused by a virus called a coronavirus. VEKLURY stops the virus multiplying in cells and this stops the virus multiplying in the body. This can help your body to overcome the virus infection and may help you get better faster.

The ingredients in VEKLURY are:

Medicinal ingredients: remdesivir.
Non-medicinal ingredients: betadex sulfobutyl ether sodium, hydrochloric acid and sodium hydroxide.

VEKLURY comes in the following dosage form:

Powder for solution for infusion; 100 mg/vial (5 mg/mL when reconstituted)

Do not use VEKLURY if:

- You are allergic to remdesivir or any of the other ingredients in VEKLURY.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you receive VEKLURY. Talk about any health conditions or problems you may have, including if you:

- Have severe liver problems. Your healthcare professional may monitor the health of your liver during treatment.
- Have kidney problems. Your healthcare professional may monitor the health of your kidneys during treatment.
- Have any reactions following the infusion. VEKLURY can cause allergic reactions or reactions following the infusion. Symptoms can include:
  - Changes to blood pressure or heart rate
  - Low oxygen level in blood
  - High temperature
  - Shortness of breath, wheezing
  - Swelling of the face, lips, tongue or throat (angioedema)
  - Rash
  - Feeling sick (nausea)
  - Sweating
  - Shivering.

Your healthcare professional will monitor you for allergic reactions or reactions during and after treatment with VEKLURY.

Other warnings you should know about:

- **Blood tests before and during treatment:**
  If you are prescribed VEKLURY, you may be given blood tests before treatment starts. Patients being treated with VEKLURY may have blood tests during their treatment as determined by their healthcare provider. These tests are to check for kidney or liver problems.

- **If you are pregnant or plan to become pregnant:**
  Tell your healthcare professional if you are pregnant, or if you might be. There is not enough information to be sure that VEKLURY is safe for use in the first trimester of pregnancy. VEKLURY should only be given if the potential benefits of treatment outweigh the potential risks to the mother and the unborn child. Talk to your healthcare professional about the need for effective birth control during treatment with VEKLURY.

- **If you are breast-feeding or plan to breast-feed:**
  Tell your healthcare professional if you are breast-feeding or are planning to breast-feed. VEKLURY passes into human breast milk. Talk to your healthcare professional about the best way to feed your baby while you are receiving VEKLURY.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with VEKLURY:
- Chloroquine (used to treat malaria)
- Hydroxychloroquine (used to treat inflammatory autoimmune diseases)
- Medicines that reduce kidney function

It is not yet known if VEKLURY affects other medicines or is affected by them. Your healthcare team will monitor you for signs of medicines affecting each other.

How to take VEKLURY:

VEKLURY will be given to you by a healthcare professional, as a drip into a vein (an intravenous infusion) lasting 30 to 120 minutes, once a day. You will be closely monitored during your treatment.

Usual dose:

The recommended dose for adults and children:

	Adults and Children (weighing at least 40 kg)	**Children at least 4 weeks old (weighing at least 3 kg but less than 40 kg)**
Day 1 (single starting dose)	200 mg	5 mg per kg of body weight
Day 2 and onwards (once daily)	100 mg	2.5 mg per kg of body weight

How long treatment lasts:

	Adults and Children (weighing at least 40 kg)	**Children at least 4 weeks old (weighing at least 3 kg but less than 40 kg)**
Patients admitted to the hospital who have **pneumonia and need extra oxygen**	Daily for **at least 5 days.** May be extended up to a **total of 10 days**.	Daily for up to a **total of 10 days**.
Patients who **are not hospitalized** and are at increased risk for progressing to severe COVID-19	Daily for 3 **days**, starting within 7 days of the onset of COVID-19 symptoms.	Not applicable.

Overdose:

If you think you, or a person you are caring for, have taken too much VEKLURY, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

If you have missed a dose, tell your healthcare professional straight away. If you have any further questions on the use of this medicine, ask your healthcare professional.

Possible side effects from using VEKLURY:

These are not all the possible side effects you may feel during your treatment with VEKLURY. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Headache
- Feeling sick (nausea)
- Rash

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
RARE			
Hypersensitivity (allergic reactions or reactions following the infusion): changes to blood pressure or heart rate, low oxygen level in blood, high temperature, shortness of breath, wheezing, swelling of the face, lips, tongue or throat (angioedema), rash, feeling sick (nausea), sweating, shivering			✓
UNKNOWN FREQUENCY			
Sinus bradycardia (slower than normal heartbeat): fainting or near-fainting, dizziness or lightheadedness, not feeling well, feeling weak or very tired, shortness of breath, chest pains, confusion or memory problems		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

VEKLURY will be stored by your healthcare professional as follows:

- **Before use**, VEKLURY should be stored below 30°C.
- **Once reconstituted**, VEKLURY should be diluted immediately.
- **Once diluted**, VEKLURY should be used immediately. If necessary, bags of diluted solution can be stored for up to 4 hours below 25°C, or for up to 24 hours in a refrigerator. Your healthcare professional should not allow more than 24 hours between dilution and administration.

Your healthcare professional should not use this medicine if they see particles in the vial, or if the solution does not appear colourless to yellow.

Keep out of reach and sight of children.

If you want more information about VEKLURY:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada Drug Product Database website (Drug Product Database: Access the database); the manufacturer's website www.gilead.ca; or by calling 1-866-207-4267.

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