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

VEKLURY (remdesivir), indicated for:
- the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for VEKLURY please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html

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Submission Control No: 250729

Date of Initial Authorization:
July 27, 2020

Date of Revision:
August 12, 2021

What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of **promising** evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

RECENT MAJOR LABEL CHANGES

Dosage and Administration, Dosing Considerations (4.1)	08/2021

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

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

VEKLURY (remdesivir) is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen.

1.1 Pediatrics

Pediatrics (<12 years and weighing <40 kg): No data have been submitted to Health Canada for the safety and efficacy of VEKLURY in children under the age of 12 years and weighing <40 kg; therefore, 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

Use of VEKLURY is confined to healthcare facilities in which patients can be monitored closely.

All patients should have estimated glomerular filtration rate (eGFR) determined prior to starting VEKLURY and while receiving it as clinically appropriate. VEKLURY treatment should not be initiated in patients with an eGFR <30 mL/min. VEKLURY should be discontinued immediately in patients with an eGFR <30 mL/min (see **10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency**).

Liver function should be determined in all patients prior to starting VEKLURY and should be monitored while receiving it as clinically appropriate. VEKLURY should not be initiated in patients with alanine aminotransferase (ALT) ≥5 × upper limit of normal (ULN). VEKLURY should be discontinued in patients who develop ALT ≥5 × ULN during treatment (it may be restarted when ALT is <5 × ULN) or if the ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalized ratio (INR). (see **8 ADVERSE REACTIONS, 8.2 Clinical Trial Adverse Reactions** and **10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Hepatic Insufficiency**).

Prothrombin time should be determined in all patients before starting VEKLURY and monitored while receiving VEKLURY as clinically appropriate (see **8 ADVERSE REACTIONS, 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative**

Data).

4.2 Recommended Dose and Dosage Adjustment

Adults and adolescents (≥12 years of age and weighing ≥40 kg)
The recommended dosage of VEKLURY in patients 12 years of age and older and weighing ≥40 kg is:

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

The total duration of treatment should be at least 5 days and not more than 10 days.

Pediatrics (<12 years of age or weighing <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
The pharmacokinetics of VEKLURY have not been evaluated in patients with renal impairment. VEKLURY should not be used in patients with eGFR <30 mL/min (see **7 WARNINGS AND PRECAUTIONS, Renal** and **10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations and Conditions, Renal Insufficiency**).

Hepatic Impairment
The pharmacokinetics of VEKLURY have not been evaluated in patients with hepatic impairment. No dosing recommendation can be made for patients with hepatic impairment. VEKLURY should not be initiated in patients with ALT ≥5 × ULN (see **7 WARNINGS AND PRECAUTIONS, Hepatic/Biliary/Pancreatic** and **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

<u>Reconstitution</u>

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.
    - 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.

- Using Table 1, determine the volume of sodium chloride 9 mg/mL (0.9%) solution for injection to withdraw from the infusion bag.

Table 1 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 1.
- Withdraw the required volume of reconstituted VEKLURY Powder for solution for infusion 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 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).

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 2 Recommended rate of infusion – for reconstituted and diluted VEKLURY Powder for solution for infusion

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

5 OVERDOSAGE

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 management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 3 Dosage Forms, Strengths, Composition and Packaging

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.

Cardiovascular

QT Prolongation

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

Hepatic/Biliary/Pancreatic

Transaminase elevations have been observed in the VEKLURY clinical trials, including in healthy volunteers and patients with COVID-19. Liver function should be determined in all patients prior to starting VEKLURY and should be monitored while receiving it as clinically appropriate. No clinical studies with VEKLURY have been conducted in patients with hepatic impairment. VEKLURY should not be used in patients with hepatic impairment unless the potential benefit outweighs the potential risk.

- VEKLURY should not be initiated in patients with ALT ≥5 × ULN at baseline
- VEKLURY should be discontinued in patients who develop:
    - ALT ≥5 × ULN during treatment with VEKLURY. It may be restarted when ALT is <5 × ULN.
      OR
    - ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR (see **8 ADVERSE REACTIONS, 8.2 Clinical Trial Adverse Reactions** and **10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations, Hepatic Insufficiency**).

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. 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

In animal studies on rats and monkeys, severe renal toxicity was observed (see **16 NON-CLINICAL TOXICOLOGY, General Toxicology**). The mechanism of this renal toxicity is not fully understood. A relevance for humans cannot be excluded.

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

VEKLURY contains betadex sulfobutyl ether sodium, which is renally cleared and accumulates in patients with decreased renal function, which may potentially adversely affect renal function. Therefore VEKLURY should not be used in patients with eGFR <30 mL/min (see **4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment, Renal Impairment** and **10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations, Renal Insufficiency**).

Reproductive Health: Female and Male Potential

- **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 Toxicity**). The relevance for humans is unknown.

7.1 Special Populations

7.1.1 Pregnant Women

There are no or limited amount of data from the use of VEKLURY in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see **16 NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicity**). VEKLURY should not be used during pregnancy unless the benefits outweigh the risks to the mother and fetus.

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

7.1.2 Breast-feeding

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

In animal studies, the nucleoside analog metabolite GS-441524 has been detected in the blood of nursing rat pups of mothers given 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 breast-feeding infants, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from VEKLURY therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

7.1.3 Pediatrics

Pediatrics (<12 years and weighing <40 kg): No data have been submitted to Health Canada for the safety and efficacy of VEKLURY in children under the age of 12 years and weighing <40 kg; therefore, 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.

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 summary 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
Injury, poisoning and procedural complications	
Rare	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, aspartate aminotransferase (AST) or both in subjects who received VEKLURY were grade 1 (10%) or grade 2 (4%). In a randomized, double-blind, placebo-controlled clinical study of patients with COVID-19 (NIAID ACTT-1) the incidence of grade ≥3 non-serious adverse events of increased aminotransferase levels including ALT, AST, or both was 4% in patients receiving VEKLURY compared with 6% in patients receiving placebo. In a randomized, open-label multi-centre clinical trial (Study GS-US-540-5773) in hospitalized patients with severe COVID-19 receiving VEKLURY for 5 (n=200) or 10 days (n=197), any grade (≥1.25 × ULN) laboratory abnormalities of increased AST and increased ALT occurred in 40% and 42% of patients, respectively, receiving VEKLURY. Grade ≥3 (≥5.0 × ULN) laboratory abnormalities of increased AST and increased ALT both occurred in 7% of patients receiving VEKLURY. In a randomized, open-label multi-centre clinical trial (Study GS-US-540-5774) in hospitalized patients with moderate COVID-19 receiving VEKLURY for 5 (n=191) or 10 days (n=193) compared to standard of care (n=200), any grade laboratory abnormalities of increased AST and increased ALT occurred in 32% and 33% of patients, respectively, receiving VEKLURY, and 33% and 39% of patients, respectively, receiving standard of care. Grade ≥3 laboratory abnormalities of increased AST and increased ALT occurred in 2% and 3% of patients, respectively, receiving VEKLURY and 6% and 7%, respectively, receiving standard of care.

Prothrombin Time Increased

In a clinical study (NIAID ACTT-1) of patients with COVID-19, the incidence of increased prothrombin time (Grades 3-4) was observed frequently in both treatment groups and higher in patients who received VEKLURY (9%, N=469) compared to placebo (4%, N=448). An increased INR was also observed (predominantly Grades 1-2). However, there was no difference observed in the incidence of bleeding events between the two groups (2.1% in VEKLURY and 1.9% in placebo). Prothrombin time should be assessed prior to VEKLURY administration and monitored while receiving VEKLURY as clinically appropriate.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No clinical interaction studies have been performed with VEKLURY. The overall potential for interactions is currently unknown; patients should remain under close observation during the days of VEKLURY administration. 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

Co-administration 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 **10 CLINICAL PHARMACOLOGY, Antiviral Activity**).

VEKLURY should not be co-administered with drugs which reduce renal function (see **7 WARNINGS AND PRECAUTIONS, Renal** and **10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Special Populations, Renal Insufficiency**).

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

The potential of interaction of VEKLURY with inhibitors/inducers of the hydrolytic pathway (esterase) or CYP2C8, 2D6 or 3A4 has not been studied. The risk of clinically relevant interaction is unknown. Strong inhibitors may result in increased VEKLURY exposure. The use of strong inducers (e.g. rifampicin) may decrease plasma concentrations of VEKLURY and is not recommended.

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

Effects of VEKLURY on other medicinal products

In vitro, remdesivir is an inhibitor of CYP3A4, OATP1B1 and OATP1B3. The clinical relevance of these *in vitro* drug interactions has not been established. VEKLURY may transiently increase plasma concentrations of medicinal products that are substrates of CYP3A or OATP 1B1/1B3. No data is available; however it can be suggested that medicinal products that are substrates of CYP3A4 or substrates of OATP 1B1/1B3 should be administered at least 2 hours after VEKLURY. Remdesivir induced CYP1A2 and potentially CYP3A *in vitro.* Co-administration of VEKLURY with CYP1A2 or CYP3A4 substrates with narrow therapeutic index may lead to loss of their efficacy.

Dexamethasone is a substrate of CYP3A4 and although remdesivir inhibits CYP3A4, due to VEKLURY's rapid clearance after intravenous administration, VEKLURY is unlikely to have a significant effect on dexamethasone exposure.

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.

10.2 Pharmacodynamics

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. 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 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.

Effects on Electrocardiogram

QT Prolongation

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

Resistance

Cell culture resistance profiling of remdesivir using the rodent CoV murine hepatitis virus identified 2 substitutions (F476L and V553L) in the viral RNA-dependent RNA polymerase at residues conserved across CoVs that conferred 5.6 fold reduced susceptibility to remdesivir. Introduction of the corresponding substitutions (F480L and V557L) into SARS-CoV resulted in 6 fold reduced susceptibility to remdesivir in cell culture and attenuated SARS-CoV pathogenesis in a mouse model.

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

10.3 Pharmacokinetics

The pharmacokinetic properties of remdesivir have been investigated in healthy volunteers. No pharmacokinetic data is available from patients with COVID-19.

Absorption

The pharmacokinetic properties of remdesivir and the predominant circulating metabolite GS-441524 have been evaluated in healthy adult subjects. Following intravenous administration of remdesivir adult dosage regimen, peak plasma concentration was observed at end of infusion, regardless of dose level, and declined rapidly thereafter with a half-life of approximately 1 hour. Peak plasma concentrations of GS-441524 were observed at 1.5 to 2.0 hours post start of a 30-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, which leads to the formation of the intermediate metabolite, GS-704277. Phosphoramidate cleavage followed by phosphorylation forms the active triphosphate, GS-443902. Dephosphorylation of all phosphorylated metabolites can result in the formation of nucleoside metabolite GS-441524 that itself is not efficiently re-phosphorylated.

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

Elimination

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

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 **9 DRUG INTERACTIONS, 9.5 Drug-Drug Interactions**). At physiologically relevant concentrations (steady-state), remdesivir or its metabolites GS-441524 and GS-704277 did not inhibit CYP1A2, 2B6, 2C8, 2C9, 2C19, and 2D6 *in vitro.* Remdesivir may however transiently inhibit CYP2B6, 2C8, 2C9 and 2D6 on the first day of administration. The clinical relevance of this inhibition was not studied. The potential for time-dependent inhibition of CYP450 enzymes by remdesivir was not studied.

Remdesivir induced CYP1A2 and potentially CYP3A4, but not CYP2B6 *in vitro* (see **9 DRUG INTERACTIONS, 9.5 Drug-Drug Interactions**).

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

Remdesivir inhibited OATP1B1 and OATP1B3 *in vitro* (see **9 DRUG INTERACTIONS, 9.5 Drug-Drug Interactions**). No data is available for OAT1, OAT3 or OCT2 inhibition by remdesivir.

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

Special Populations and Conditions

- **Pediatrics**

  The pharmacokinetics in pediatric patients have not been evaluated.

- **Geriatrics**

  Pharmacokinetic differences for age have not been evaluated.

- **Sex**

  Pharmacokinetic differences for gender have not been evaluated.

- **Ethnic Origin**

  Pharmacokinetic differences for ethnic origin have not been evaluated.

- **Hepatic Insufficiency**

  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.

- **Renal Insufficiency**

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

11 STORAGE, STABILITY AND DISPOSAL

Shelf-life for unopened vials

36 months
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 II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

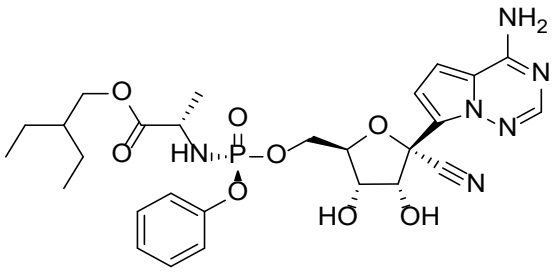
Proper name: remdesivir (USAN)

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

Empirical formula: $C_{27}H_{35}N_6O_8P$

Formula weight: 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 study summarized below.

14.1 Trial Design and Study Demographics

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

	NIAID ACTT-1 Study (CO-US-540-5776)		
Characteristic	**All N = 1063**	**VEKLURY (remdesivir) N = 541**	**Placebo N = 522**
Patients with mild/moderate disease (defined by SpO2 >94% and respiratory rate <24 breaths/min without supplemental oxygen) – no. (%)	120 (11.3)	63 (11.6)	57 (10.9)
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. (%)	943 (88.7)	478 (88.4)	465 (89.1)
Baseline mean age (years)	58.9	58.6	59.2
Patients aged 65 years or older (%)	36.0	34.6	37.98
Sex			
Male sex (%)	64.3	65.1	63.6
Female sex (%)	35.7	34.9	36.4
Race or ethnic group (%)			
White	53.2	51.6	54.8
Black	20.6	20.0	21.3
Asian	12.6	14.2	10.9
Coexisting conditions (%)			
Hypertension	49.6	49.3	49.9
Obesity	37.0	37.7	36.2
Type 2 diabetes mellitus	29.7	30.6	28.7
Coronary artery disease	11.6	13.0	10.0
Patients received a 10-day treatment course with VEKLURY – no. (%)		180 (33.0)	

14.2 Study Results

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

The primary clinical endpoint was time to recovery within 28 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. In an analysis performed after all patients had been followed up for 14 days, the median time to recovery in the overall population was 11 days in the VEKLURY group compared to 15 days in the placebo group (recovery rate ratio 1.32; [95% CI 1.12 to 1.55], p<0.001).

The outcome differed relevantly between the two strata. In the severe disease stratum time to recovery was 12 days in the VEKLURY group and 18 days in the placebo group (recovery rate ratio 1.37 [95% CI: 1.15 to 1.63]; Table 6). The clinical benefit of VEKLURY was most apparent in patients receiving oxygen, however, not on ventilation, at Day 1 (rate recovery ratio 1.47 [95% CI 1.17 to 1.84]). For patients who were receiving mechanical ventilation or ECMO on Day 1 no difference in recovery rate was observed between the treatment groups (0.95 [95% CI 0.64 to 1.42]). For the mild/moderate disease stratum, time to recovery was not different between the two groups (5 days for both, VEKLURY and placebo).

Table 6 Recovery outcomes in the severe disease stratum from NIAID ACTT-1

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

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

There was no difference in efficacy in patients randomized during the first 10 days after onset of symptoms as compared to those with symptoms for more than 10 days.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

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). An unidentified major metabolite (M27) was shown to be present in human plasma (see **10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Metabolism**). The exposure of M27 in rhesus monkeys and rats is unknown. Animal studies may therefore not be informative of potential risks associated with this metabolite.

Carcinogenicity

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

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.

Reproductive and Developmental Toxicity

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

In rats and rabbits, remdesivir demonstrated 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.

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

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Pr VEKLURY®

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

Read this carefully before you start taking **VEKLURY** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **VEKLURY**.

What is VEKLURY 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 adults and adolescents (aged 12 and over who weigh 40 kg or more). It will only be given to patients who have pneumonia, and need extra oxygen to help them breathe.

For the following indication, VEKLURY (remdesivir) has been approved *with conditions* (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

VEKLURY is indicated for:

- the treatment of COVID-19 in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does VEKLURY work?

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.

What are the ingredients in VEKLURY?

Medicinal ingredients: remdesivir. Each vial contains 100 mg.
Non-medicinal ingredients: betadex sulfobutyl ether sodium, hydrochloric acid and sodium hydroxide.

VEKLURY comes in the following dosage forms:

VEKLURY Powder for solution for infusion is a white to off-white to yellow powder, to be reconstituted and then diluted into sodium chloride solution prior to administration by intravenous infusion. It is supplied in a single-use clear glass vial.

Do not use VEKLURY if:

- You are allergic to remdesivir or any of the other ingredients of this medicine (read ***What are the ingredients in VEKLURY?*** above).

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

- Have liver problems. Some people developed increased liver enzymes when given VEKLURY. Your doctor will do blood tests before starting treatment to check whether you can be given it safely.
- Have kidney problems. Some people with severe kidney problems may not be given this medicine. Your doctor will do blood tests to check whether you can be given it safely.
- 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.

Other warnings you should know about:

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

will be stopped if your kidney or liver show signs of damage during treatment. See ***What are the possible side effects from using VEKLURY?*** below.

If you are pregnant or plan to become pregnant:
Tell your doctor or nurse if you are pregnant, or if you might be. There is not enough information to be sure that VEKLURY is safe for use in pregnancy. VEKLURY will only be given if the potential benefits of treatment outweigh the potential risks to the mother and the unborn child. You must use effective contraception while having VEKLURY treatment.

If you are breast-feeding or plan to breast-feed:
Tell your doctor or nurse if you are breast-feeding. It is not yet known whether VEKLURY or the COVID-19 virus pass into human breast milk, or what the effects might be on the baby or milk production. Your doctor will help you decide whether to continue breast-feeding or to start treatment with VEKLURY. You will need to consider the potential benefits of treatment for you, compared with the health benefits and risks of breast-feeding for your baby.

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

Do not take chloroquine or hydroxychloroquine at the same time as VEKLURY.

Certain medicines e.g. midazolam should be taken at least 2 hours after VEKLURY as VEKLURY can affect the way they work.

VEKLURY may affect the way certain medicines (e.g. theophylline or midazolam) work.

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 nurse or doctor, 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 is:
- a single starting dose of 200 mg on day 1
- then daily doses of 100 mg starting on day 2.

You will be given VEKLURY every day for at least 5 days. Your doctor may extend the treatment up to a total of 10 days.

Overdose:

If you think you have received too much VEKLURY, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you have missed a dose, tell your nurse or doctor straight away. If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

What are possible side effects from using VEKLURY?

These are not all the possible side effects you may feel when taking VEKLURY. If you experience any side effects not listed here, contact your healthcare professional.

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Very common side effects
(these may affect more than 1 in 10 patients)

- Blood tests may show an increase in liver enzymes, called *transaminases.*

Common side effects
(these may affect up to 1 in 10 patients)

- Headache
- Feeling sick (nausea)
- Rash

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE *(These may affect up to 1 in 1000 patients)* Allergic reactions or reactions following the infusion. Symptoms:			
• 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		✓	

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 (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

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

Storage:

- **Before use**, store 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. Do not allow more than 24 hours between dilution and administration.

Do not use this medicine if you 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 website; (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.gilead.ca, or by calling 1-866-207-4267.

This leaflet was prepared by Gilead Sciences Canada, Inc.

Date of Preparation: August 12, 2021

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e240551-GS-001