Table 4 Recommended Rate of Infusion — Diluted VEKLURY for Injection Lyophilized Powder in Pediatric Patients Less Than 12 Years of Age and Weighing 40 kg and Higher

Infusion 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

Administration should be under conditions where management of severe hypersensitivity reactions, such as anaphylaxis, is possible. Monitor patients during infusion and observe patients for at least one hour after infusion is complete for signs and symptoms of hypersensitivity as clinically appropriate.

2.6 Storage of Prepared Dosages

After reconstitution, use vials immediately to prepare diluted solution.

The diluted VEKLURY solution in syringe should be used immediately.

The diluted VEKLURY solution in the infusion bags can be stored up to 24 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) prior to administration.

IMPORTANT:
This product contains no preservative. Any unused portion of a single-dose VEKLURY vial should be discarded after a diluted solution is prepared. Maintain adequate records showing receipt, use, and disposition of VEKLURY. For unused intact vials, maintain adequate records showing disposition of VEKLURY; do not discard unused intact vials.

3. DOSAGE FORMS AND STRENGTHS

VEKLURY for injection,100 mg, available as a sterile, preservative-free white to off-white to yellow lyophilized powder in single-dose vial for reconstitution.

4. CONTRAINDICATIONS

VEKLURY is contraindicated in patients with a history of clinically significant hypersensitivity reactions to VEKLURY or any components of the product *[see Warnings and Precautions (5.1)].*

5. WARNINGS AND PRECAUTIONS

There are limited clinical data available for VEKLURY in pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg. Serious and unexpected adverse events may occur that have not been previously reported with VEKLURY use.

5.1 Hypersensitivity Including Infusion-Related and Anaphylactic Reactions

Hypersensitivity reactions, including infusion-related and anaphylactic reactions, have been observed during and following administration of VEKLURY; most occurred within one hour. Signs and symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, diaphoresis, and shivering. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. Monitor patients during infusion and observe patients for at least one hour after infusion is complete for signs and symptoms of hypersensitivity as clinically appropriate. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration of VEKLURY and initiate appropriate treatment. The use of VEKLURY is contraindicated in patients with known hypersensitivity to VEKLURY or any components of the product *[see Contraindications (4)]*.

5.2 Increased Risk of Transaminase Elevations

Transaminase elevations have been observed in healthy volunteers who received 200 mg of VEKLURY followed by 100 mg doses for up to 10 days; the transaminase elevations were mild (Grade 1) to moderate (Grade 2) in severity and resolved upon discontinuation of VEKLURY. Transaminase elevations have also been reported in patients with COVID-19 who received VEKLURY. Because transaminase elevations have been reported as a clinical feature of COVID-19, including in patients receiving placebo in clinical trials of VEKLURY, and the incidence was similar in patients receiving placebo versus VEKLURY in clinical trials of VEKLURY, discerning the contribution of VEKLURY to transaminase elevations in patients with COVID-19 can be challenging.

Perform hepatic laboratory testing in all patients before starting VEKLURY and while receiving VEKLURY as clinically appropriate.

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

5.3 Risk of Reduced Antiviral Activity When Coadministered with Chloroquine Phosphate or Hydroxychloroquine Sulfate

Coadministration of VEKLURY and chloroquine phosphate or hydroxychloroquine sulfate is not recommended based on data from cell culture experiments demonstrating a potential antagonistic effect of chloroquine

20. No adverse effects on embryo-fetal (rats and rabbits) or pre/postnatal (rats) development were observed in rats and rabbits at nontoxic doses in pregnant animals. During organogenesis, exposures to the predominant circulating metabolite (GS-441524) were 4 times higher (rats and rabbits) than the exposure in humans at the RHD. In a pre/postnatal development study, exposures to the predominant circulating metabolite of remdesivir (GS-441524) were similar to the human exposures at the RHD.

11.2 Lactation

Risk Summary

There are no available data on the presence of remdesivir in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies, remdesivir and metabolites have been detected in the nursing pups of mothers given remdesivir, likely due to the presence of remdesivir in milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VEKLURY and any potential adverse effects on the breastfed child from VEKLURY or from the underlying maternal condition. Breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

Animal Data

Remdesivir and its metabolites were detected in the plasma of nursing rat pups, likely due to the presence of remdesivir and/or its metabolites in milk, following daily intravenous administration of remdesivir to pregnant rats from Gestation Day 6 to Lactation Day 20. Exposures in nursing pups were approximately 1% that of maternal exposure on Lactation Day 10.

11.3 Pediatric Use

The safety and effectiveness of VEKLURY have not been established in pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg, with positive results of direct SARS-CoV-2 viral testing, and who are:

- Hospitalized, or
- Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

VEKLURY for injection (supplied as 100 mg lyophilized powder in vial) *[see Dosage and Administration (2.2, 2.3, 2.4, 2.5)]* is the only authorized dosage form of VEKLURY for pediatric patients in this age group.

Use in this age group is based on extrapolation of pediatric efficacy from adequate and well-controlled studies in adults *[see Overall Safety Summary (6), Clinical Pharmacology (14), Clinical Trial Results and Supporting Data for EUA (18)].*

Pediatric patients (older than 28 days) must have eGFR determined and full-term neonates (at least 7 days to less than or equal to 28 days) must have serum creatinine determined before dosing and daily while receiving VEKLURY. Pediatric patients should be monitored for renal function and consideration given for stopping therapy in the setting of substantial decline *[see Dosage and Administration (2.2, 2.4)].*

11.4 Renal Impairment

The pharmacokinetics of VEKLURY have not been evaluated in patients with renal impairment. Patients with eGFR greater than or equal to 30 mL/min have received VEKLURY for the treatment of COVID-19 with no dose adjustment of VEKLURY.

Pediatric patients (greater than 28 days old) must have eGFR determined and full-term neonates (at least 7 days to less than or equal to 28 days old) must have serum creatinine determined before dosing and while receiving VEKLURY. VEKLURY is not recommended in pediatric patients (at least 28 days old) with eGFR less than 30 mL/min or in full-term neonates (at least 7 days and less than or equal to 28 days old) with serum creatinine greater than or equal to 1 mg/dL *[see Dosage and Administration (2.2, 2.4)].*

11.5 Hepatic Impairment

The pharmacokinetics of VEKLURY have not been evaluated in patients with hepatic impairment *[see Warnings and Precautions (5.2)].*

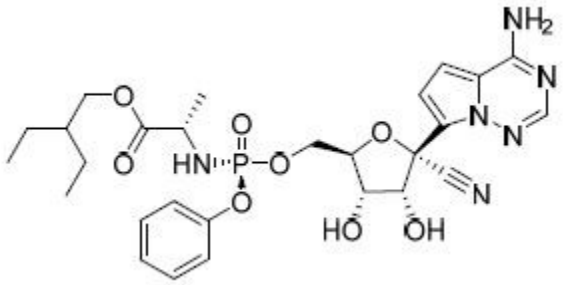
Perform hepatic laboratory testing in all patients before starting VEKLURY and during treatment as clinically appropriate *[see Dosage and Administration (2.2)]*.

12. OVERDOSAGE

There is no human experience of acute overdosage with VEKLURY. Treatment of overdose with VEKLURY should consist of general supportive measures including monitoring of vital signs and observation of the clinical status of the patient. There is no specific antidote for overdose with VEKLURY.

13. PRODUCT DESCRIPTION

VEKLURY contains remdesivir, a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor. The chemical name for remdesivir is 2-ethylbutyl *N*-{(*S*)-[2-*C*-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-2,5-anhydro-d-altrononitril-6-*O*-yl]phenoxyphosphoryl}-L-alaninate. It has a molecular formula of $C_{27}H_{35}N_6O_8P$ and a molecular weight of 602.6 g/mol. Remdesivir has the following structural formula:



13.1 Physical Appearance

VEKLURY for injection contains 100 mg of remdesivir as a sterile, preservative-free lyophilized white to off-white to yellow powder in a single-dose clear glass vial. It requires reconstitution and then further dilution prior to administration by intravenous infusion *[see Dosage and Administration (2.5, 2.6)].*

13.2 Inactive Ingredients

The inactive ingredients are 3 g betadex sulfobutyl ether sodium, and may include hydrochloric acid and/or sodium hydroxide for pH adjustment.

14. CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

Remdesivir is an inhibitor of the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), which is essential for viral replication. Remdesivir is an adenosine nucleotide prodrug that distributes into cells where it is metabolized to a nucleoside monophosphate intermediate by carboxyesterase 1 and/or cathepsin A, depending upon the cell type. The nucleoside monophosphate is subsequently phosphorylated by cellular kinases to form the pharmacologically active nucleoside triphosphate metabolite (GS-443902). Remdesivir triphosphate (RDV TP) acts as an analog of adenosine triphosphate (ATP) and competes with high selectivity (3.65-fold) over 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 (position i+3) during replication of the viral RNA. In a biochemical assay assessing RDV-TP incorporation by the MERS-CoV RdRp complex, RDV-TP inhibited RNA synthesis with an IC_{50} value of 0.032 μM. RDV-TP 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 at higher nucleotide concentrations. When remdesivir

nucleotide is present in the viral RNA template, the efficiency of incorporation of the complementary natural nucleotide is compromised, thereby inhibiting viral RNA synthesis. Remdesivir triphosphate is a weak inhibitor of mammalian DNA and RNA polymerases, including human mitochondrial RNA polymerase.

14.2 Pharmacokinetics

The pharmacokinetic (PK) properties of remdesivir and metabolites have been evaluated in adults in several Phase 1 trials and are provided in Table 12. The multiple dose PK parameters of remdesivir and metabolites in healthy adults are provided in Table 13.

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

	Remdesivir	**GS-441524**	**GS-704277**
Absorption			
T_{max} (h)[a]	0.67-0.68	1.51-2.00	0.75-0.75
Distribution			
% bound to human plasma proteins	88-93.6[b]	2	1
Blood-to-plasma ratio	0.68-1.0	1.19	0.56
Elimination			
$t_{1/2}$ (h)[c]	1	27	1.3
Metabolism			
Metabolic pathway(s)	CES1 (80%) Cathepsin A (10%) CYP3A (10%)	Not significantly metabolized	HINT1
Excretion			
Major route of elimination	Metabolism	Glomerular filtration and active tubular secretion	Metabolism
% of dose excreted in urine[d]	10	49	2.9
% of dose excreted in feces[d]	ND	0.5	ND

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).

20. PATIENT COUNSELING INFORMATION

SEE *Fact Sheet for Parents and Caregivers*

Hypersensitivity Reactions

Inform parents/caregivers that hypersensitivity reactions have been seen in patients receiving VEKLURY during and after infusion. Advise parents/caregivers to inform their healthcare provider if their child experiences any of the following: changes in heart rate; fever; shortness of breath, wheezing; swelling of the lips, face, or throat; rash; nausea; sweating; or shivering *[see Warnings and Precautions (5.1)].*

Increased Risk of Transaminase Elevations

Inform parents/caregivers that VEKLURY may increase the risk of hepatic laboratory abnormalities. Advise parents/caregivers to alert their healthcare provider immediately if their child experiences any symptoms of liver inflammation *[see Warnings and Precaution (5.2)].*

Drug Interactions

Inform parents/caregivers that VEKLURY may interact with other drugs. Advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products, including chloroquine phosphate or hydroxychloroquine sulfate *[see Warnings and Precautions (5.3), Drug Interactions (10), Microbiology/Resistance Information (15)].*

Pregnancy Registry

Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in individuals exposed to VEKLURY during pregnancy *[see Use in Specific Populations (11.1)].*

Pregnancy

Inform patients to notify their healthcare provider immediately in the event of a pregnancy *[see Use in Specific Populations (11.1)].*

Lactation

Inform mothers that it is not known whether VEKLURY can pass into their breast milk *[see Use in Specific Populations (11.2)]*.

21. CONTACT INFORMATION

If you have questions, please contact
www.askgileadmedical.com
1-866-633-4474

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