VEKLURY® (remdesivir) for injection, for intravenous use

℞ Only

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

- adults and pediatric patients (28 days of age and older and weighing at least 3 kg) with pneumonia requiring supplemental oxygen. In clinical studies, there were no survival and recovery benefit with VEKLURY in patients under invasive mechanical ventilation (IMV), or under extracorporeal membrane oxygenation (ECMO).
- adults and adolescent patients (aged 12 years and above and weighing at least 40 kg) who do not require supplemental oxygen and who are at high risk of progressing to severe COVID-19.

[see Clinical Studies (13)]

2 DOSAGE AND ADMINISTRATION

2.1 Dosage and Administration Overview

- VEKLURY may only be administered in settings in which healthcare providers have immediate access to medications to treat a severe infusion or hypersensitivity reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary *[see Dosage and Administration (2.6, 2.7), Warnings and Precautions (5.1)]*.
- Administer VEKLURY for the treatment of COVID-19 in adults and pediatric patients (28 days of age and older and weighing at least 3 kg) by intravenous infusion only. Do not administer by any other route.
- VEKLURY for injection (supplied as 100 mg lyophilized powder in vial) must be reconstituted with Sterile Water for Injection prior to diluting with 0.9% sodium chloride injection.
- Carefully follow the product-specific preparation instructions below *[see Dosage and Administration (2.6, 2.7)].*

2.2 Testing Before Starting and During Treatment with VEKLURY

Determine eGFR in all patients before starting VEKLURY and monitor while receiving VEKLURY as clinically appropriate *[see Dosage and Administration (2.4) and Use in Specific Populations (8.3, 8.5)].*

Perform hepatic laboratory testing in all patients before starting VEKLURY and while receiving VEKLURY as clinically appropriate *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.6)].*

Determine prothrombin time in all patients before starting VEKLURY and monitor while receiving VEKLURY as clinically appropriate *[see Adverse Reactions (6.1)].*

2.3 Recommended Dosage in Adults, Adolescent and Pediatric Patients 28 days of Age and Older and Weighing at Least 3 kg

The recommended dosage for adults and adolescent patients weighing at least 40 kg is a single loading dose of VEKLURY 200 mg on Day 1 via intravenous infusion followed by once-daily maintenance doses of VEKLURY 100 mg from Day 2 via intravenous infusion.

The recommended dosage for pediatric patients 28 days of age and older and weighing 3 kg to less than 40 kg is a single loading dose of VEKLURY 5 mg/kg on Day 1 via intravenous infusion followed by once-daily maintenance doses of VEKLURY 2.5 mg/kg from Day 2 via intravenous infusion.

Table 1 Treatment Duration

	Adults	**Adolescent patients aged 12 years and above (weighing at least 40 kg)**	**Pediatric patients at 28 days of age and older (weighing at least 3 kg but less than 40 kg)**
Patients with pneumonia and requiring supplemental oxygen	Daily for at least 5 days and not more than 10 days as soon as possible after diagnosis of COVID-19.	Daily for at least 5 days and not more than 10 days as soon as possible after diagnosis of COVID-19.	Daily for up to a total of 10 days as soon as possible after diagnosis of COVID-19.
Patients who do not require supplemental oxygen and are at increased risk for progression 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.	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.

VEKLURY must be diluted prior to intravenous infusion. Refer to Dosage and Administration (2.6, 2.7) for detailed preparation and administration instructions.

2.4 Renal Impairment

VEKLURY is not recommended in patients with eGFR less than 30 mL per minute *[see Dosage and Administration (2.2) and Use in Specific Populations (8.3, 8.5)].*

2.5 Immunocompromised Population

The safety and efficacy of remdesivir in immunocompromised patients have not yet been established. Only limited data are available (*see section 5.4*).

2.6 Dosage Preparation and Administration in Adults and Adolescent Patients Weighing at Least 40 kg

Carefully follow the product-specific preparation instructions below.

Reconstitution Instructions

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

- Aseptically reconstitute VEKLURY lyophilized powder by adding 19 mL of Sterile Water for Injection using a suitably sized syringe and needle per vial.
- Only use Sterile Water for Injection to reconstitute VEKLURY lyophilized powder.
- Discard the vial if a vacuum does not pull the Sterile Water for Injection into the vial.
- Immediately shake the vial for 30 seconds.
- Allow the contents of the vial to settle for 2 to 3 minutes. A clear, colorless to yellow solution, free of visible particles, 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. Discard the vial if the contents are not completely dissolved.
- Following reconstitution, each vial contains 100 mg/20 mL (5 mg/mL) of remdesivir solution.
- Use reconstituted product immediately to prepare the diluted drug product *[see Dosage and Administration (2.8)].*

Dilution Instructions

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

- Reconstituted VEKLURY for injection, containing 100 mg/20 mL remdesivir solution, must be further diluted in either a 100 mL or 250 mL 0.9% sodium chloride injection infusion bag. Refer to Table 2 for instructions.

Table 2 Recommended Dilution Instructions—Reconstituted VEKLURY for Injection Lyophilized Powder in Adults and Adolescent Patients Weighing at Least 40 kg

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

- Withdraw and discard the required volume of 0.9% sodium chloride injection from the bag following instructions in Table 1, using an appropriately sized syringe and needle.
- Withdraw the required volume of reconstituted VEKLURY for injection from the VEKLURY vial following instructions in Table 1, using an appropriately sized syringe. Discard any unused portion remaining in the reconstituted vial.
- Transfer the required volume of reconstituted VEKLURY for injection to the selected infusion bag.
- Gently invert the bag 20 times to mix the solution in the bag. Do not shake.
- The prepared infusion solution is stable for 24 hours at room temperature (20°C to 25°C) or 48 hours at refrigerated temperature (2°C to 8°C).

Administration Instructions

Do not administer the prepared diluted solution simultaneously with any other medication. The compatibility of VEKLURY injection with intravenous solutions and medications other than 0.9% sodium chloride injection, USP is not known. Administer VEKLURY via intravenous infusion over 30 to 120 minutes.

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 *[see Warnings and Precautions (5.1)]*.

Administer the diluted solution with the infusion rate described in Table 3.

Table 3 Recommended Rate of Infusion—Diluted VEKLURY for Injection Lyophilized Powder in Adults and Adolescent Patients Weighing at Least 40 kg

Infusion bag volume	Infusion time	Rate of infusion
250 mL	30 min	8.33 mL/min
	60 min	4.17 mL/min
	120 min	2.08 mL/min
100 mL	30 min	3.33 mL/min
	60 min	1.67 mL/min
	120 min	0.83 mL/min

2.7 Dosage Preparation and Administration in Pediatric Patients 28 Days of Age and Older and Weighing 3 kg to Less Than 40 kg

Reconstitution Instructions

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

- Aseptically reconstitute VEKLURY lyophilized powder by adding 19 mL of Sterile Water for Injection using a suitably sized syringe and needle per vial.
- Only use Sterile Water for Injection to reconstitute VEKLURY lyophilized powder.
- Discard the vial if a vacuum does not pull the Sterile Water for Injection into the vial.
- Immediately shake the vial for 30 seconds.
- Allow the contents of the vial to settle for 2 to 3 minutes. A clear, colorless to yellow solution, free of visible particles, 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. Discard the vial if the contents are not completely dissolved.
- Following reconstitution, each vial contains 100 mg/20 mL (5 mg/mL) of remdesivir solution.
- Use reconstituted product immediately to prepare the diluted drug product *[see Dosage and Administration (2.7)].*

Dilution Instructions

- For pediatric patients 28 days of age and older and weighing 3 kg to less than 40 kg, the 100 mg/20 mL (5 mg/mL) remdesivir reconstituted solution should be further diluted to a fixed concentration of 1.25 mg/mL using 0.9% sodium chloride injection.
- The final required infusion volume concentration of 1.25 mg/mL remdesivir diluted solution for infusion is based on the pediatric weight-based dosing regimens of 5 mg/kg for the Loading Dose and 2.5 mg/kg for each Maintenance Dose.
- Small 0.9% sodium chloride injection 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 intravenous infusion in a total volume dependent on the dose to yield the target remdesivir concentration of 1.25 mg/mL.
- A syringe and syringe pump may be used for infusion volumes less than 50 mL.

Infusion with IV Bag

- Determine the total infusion volume needed to achieve a final infusion volume concentration of 1.25 mg/mL of remdesivir diluted solution based on the patient's calculated dose.
- Select an appropriately sized infusion bag (either prefilled with 0.9% sodium chloride injection or empty) to prepare VEKLURY diluted solution.
- If using a prefilled 0.9% sodium chloride injection infusion bag, withdraw and discard the amount of diluent equal to the volume of reconstituted VEKLURY solution needed per patient's dose plus a quantity sufficient to achieve a 1.25 mg/mL final volume concentration of remdesivir diluted solution.
- Withdraw the required volume of reconstituted VEKLURY solution into an appropriately sized syringe.
- Transfer the required volume of reconstituted VEKLURY solution to the 0.9% sodium chloride injection infusion bag.
- Gently invert the bag 20 times to mix the solution in the bag. Do not shake.
- If using an empty infusion bag, transfer the required volume of reconstituted VEKLURY solution to the bag, followed by a volume of 0.9% sodium chloride injection sufficient to achieve a 1.25 mg/mL final volume concentration of remdesivir diluted solution.
- The prepared infusion solution is stable for 24 hours at room temperature (20°C to 25°C) or 48 hours at refrigerated temperature (2°C to 8°C).

Infusion with Syringe

- Determine the total infusion volume needed to achieve a final infusion volume concentration of 1.25 mg/mL of remdesivir diluted solution based on patient's calculated dose.
- Select an appropriately sized syringe equal to or larger than the calculated total infusion volume of 1.25 mg/mL remdesivir solution needed.
- Withdraw the required volume of reconstituted VEKLURY solution from the vial into the syringe based on patient's calculated dose, followed by the required volume of 0.9% sodium chloride injection needed to achieve a 1.25 mg/mL final volume concentration of remdesivir diluted solution.

- Gently invert the syringe 20 times to mix the solution in the syringe. Do not shake.
- The prepared diluted solution should be used immediately.

Administration Instructions

The prepared diluted solution should not be administered simultaneously with any other medication. The compatibility of VEKLURY with IV solutions and medications other than 0.9% sodium chloride injection, USP is not known. Administer VEKLURY via intravenous infusion over 30 to 120 minutes. The rate of infusion (mL/min) should be calculated based on the total infusion volume and total infusion time.

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 *[see Warnings and Precautions (5.1)]*.

2.8 Storage of Prepared Dosages

After reconstitution, use vials immediately to prepare diluted solution. The diluted VEKLURY solution in the infusion bags can be stored up to 24 hours at room temperature (20°C to 25°C) prior to administration or 48 hours at refrigerated temperature (2°C to 8°C).

IMPORTANT:

This product contains no preservative. Any unused portion of a single-dose VEKLURY vial should be discarded after a diluted solution is prepared.

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

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 with VEKLURY in the clinical studies, 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 only be used in patients with hepatic impairment if the potential benefit outweighs the potential risk.

- VEKLURY should not be initiated in patients with alanine aminotransferase (ALT) ≥ 5 times the upper limit of normal at baseline.
- VEKLURY should be discontinued in patients who develop:
    - ALT ≥ 5 times the upper limit of normal during treatment with VEKLURY. It may be restarted when ALT is < 5 times the upper limit of normal
      OR
    - ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalized ratio (INR) [*see Dosage and Administration (2.2), Adverse reactions (6.1) and Use in Specific Populations (8.6)*].

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 on the intracellular metabolic activation and antiviral activity of VEKLURY *[see Drug Interactions (7) and Microbiology (11.4)].*

5.4 Renal Impairment

In animal studies on rats and monkeys, severe renal toxicity was observed *[see Nonclinical Toxicology (12.2)]*. The mechanism of this renal toxicity is not fully understood. A relevance for humans cannot be excluded. All patients should have the eGFR determined prior to starting VEKLURY and monitored while receiving VEKLURY as clinically appropriate. VEKLURY should not be used in patients with eGFR < 30 mL/min/1.73 m^2.

5.5 Immunocompromised Patients

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

5.6 Prothrombin Time Increased

In the clinical study (NIAID ACTT-1) of patients with COVID-19, increased prothrombin time (Grades 3-4) was observed at higher incidence in patients who received VEKLURY (9%, N=469) compared to placebo (4%, N=488). An increased INR was also observed (predominantly Grades 1-2) *[see Adverse Reactions (6.1)]*. There was no difference 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. In Study GS-US-540-9012, the incidence of increased prothrombin time or INR was similar in patients treated with VEKLURY compared to placebo.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in other sections of the labeling:

- Hypersensitivity Including Infusion-related and Anaphylactic Reactions *[see Warnings and Precautions (5.1)]*
- Increased Risk of Transaminase Elevations *[see Warnings and Precautions (5.2)]*
- Prothrombin Time Increased *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Clinical Trials in Adult Subjects

Clinical Trials Experience in Adults with COVID-19

NIAID ACTT-1 was 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 Clinical Studies (13.2)]*. 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 hypersensitivity reactions. Rates of adverse reactions (≥ Grade 3), serious adverse reactions, and adverse reactions leading to treatment discontinuation are presented in Table 4.

Table 4 Summary of Adverse Reaction Rates in Hospitalized 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-540-5773 was a randomized, open-label clinical trial in hospitalized subjects with severe COVID-19 treated with VEKLURY 200 mg on Day 1 and 100 mg once daily for 5 (n=200) or 10 days (n=197). Adverse reactions were reported in 33 (17%) subjects in the 5-day group and 40 (20%) subjects in the 10-day group *[see Clinical Studies (13.3)]*. The most common adverse reactions occurring in at least 5% of subjects in either the VEKLURY 5-day or 10-day group, respectively, were nausea (5% vs 3%), AST increased (3% vs 6%), and ALT increased (2% vs 7%). Rates of any adverse reactions, serious adverse reactions, and adverse reactions leading to treatment discontinuation are presented in Table 5.

Table 5 Summary of Adverse Reaction Rates in Hospitalized Subjects with Severe COVID-19 in Study 5773

Types of Adverse Reactions	VEKLURY 5 Days N=200 n (%)	VEKLURY 10 Days N=197 n (%)
Any adverse reaction, all Grades	33 (17%)	40 (20%)
Serious adverse reactions	3 (2%)[a]	4 (2%)[a]
Adverse reactions leading to treatment discontinuation	5 (3%)[b]	9 (5%)[b]

a. Transaminases increased (n=5), hepatic enzyme increased (n=1), hypertransaminasaemia (n=1).
b. Transaminases increased (n=4), hepatic enzyme increased (n=2), LFT increased (n=2), hypertransaminasaemia (n=1), ALT increased (n=1), ALT increased and AST increased (n=2), injection site erythema (n=1), rash (n=1).

Study GS-US-540-5774 was a randomized, open-label clinical trial in hospitalized subjects with moderate COVID-19 treated with VEKLURY 200 mg on Day 1 and 100 mg daily for 5 (n=191) or 10 days (n=193), or standard of care (SOC) only (n=200) *[see Clinical Studies (13.3)]*. Adverse reactions were reported in 36 (19%) subjects in the 5-day group and 25 (13%) subjects in the 10-day group.

The most common adverse reaction occurring in at least 5% of subjects in the VEKLURY groups was nausea (7% in the 5-day group, 4% in the 10-day group). Rates of any adverse reactions, serious adverse reactions, and adverse reactions leading to treatment discontinuation are presented in Table 6.

Table 6 Summary of Adverse Reaction[a] Rates in Hospitalized Subjects with Moderate COVID-19 in Study 5774

Types of Adverse Reactions	VEKLURY 5 Days N=191 n (%)	VEKLURY 10 Days N=193 n (%)
Any adverse reaction, all Grades	36 (19%)	25 (13%)
Serious adverse reactions	1 (<1%)[b]	0
Adverse reactions leading to treatment discontinuation	4 (2%)[c]	4 (2%)[c]

a. Attribution of events to study drug was not performed for the SOC group.
b. Heart rate decreased.
c. ALT increased (n=2), ALT increased and AST increased (n=1), hypertransaminasaemia (n=1), blood alkaline phosphatase increased (n=1), rash (n=2), heart rate decreased (n=1).

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; 276 adults and 3 pediatric subjects 12 years of age and older weighing at least 40 kg) or placebo (n=283; 278 adults and 5 pediatric subjects 12 years of age and older weighing at least 40 kg) for 3 days. Of the 279 subjects treated with VEKLURY, 227 subjects received at least one dose of VEKLURY at an outpatient facility, 44 subjects received at least one dose of VEKLURY in a home healthcare setting, and 8 subjects received at least one dose of VEKLURY at a skilled nursing facility. Subjects treated with VEKLURY received 200 mg on Day 1 and 100 mg once daily on subsequent days *[see Clinical Studies (14.4)]*. 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. Safety in subjects who received VEKLURY in a home healthcare setting was comparable to that observed in the overall GS-US-540-9012 study population, but these findings are based on limited data.

Less Common Adverse Reactions in Adults from Clinical Trials

Clinically significant adverse reactions that were reported in <2% of subjects exposed to VEKLURY in clinical trials are listed below:

- Hypersensitivity reactions *[see Warnings and Precautions (5.1)].*
- Generalized seizure
- Rash

Laboratory Abnormalities

Study GS-US-399-5505 was a Phase 1, randomized, blinded, placebo-controlled clinical trial in healthy volunteers administered VEKLURY 200 mg on Day 1 and 100 mg for either 4 days or 9 days. Mild (Grade 1, n=8) to moderate (Grade 2, n=1) elevations in ALT were observed in 9 of 20 subjects receiving 10 days of VEKLURY; the elevations in ALT resolved upon discontinuation of VEKLURY. No subjects (0 of 9) who received 5 days of VEKLURY had graded increases in ALT.

The frequencies of laboratory abnormalities (Grades 3-4) occurring in at least 3% of subjects with COVID-19 receiving VEKLURY in Trials NIAID ACTT-1, 5773, and 5774 are presented in Table 7, Table 8, and Table 9, respectively.

Table 7 Laboratory Abnormalities (Grades 3-4) Reported in ≥3% of Hospitalized Subjects with Mild, Moderate, or Severe COVID-19 in NIAID ACTT-1

Laboratory Parameter Abnormality[a]	VEKLURY 10 Days N=532	Placebo N=516
ALT increased	3%	6%
AST increased	6%	8%
Bilirubin increased	2%	5%
Creatinine clearance decreased[b]	18%	20%
Creatinine increased	15%	16%
eGFR decreased	18%	24%
Glucose increased	12%	13%
Hemoglobin decreased	15%	22%
Lymphocytes decreased	11%	18%
Prothrombin time increased	9%	4%

a. Frequencies are based on treatment-emergent laboratory abnormalities. Graded per Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017.
b. Based on the Cockcroft-Gault formula.

Table 8 Laboratory Abnormalities (Grades 3-4) Reported in ≥3% of Hospitalized Subjects with Severe COVID-19 in Trial 5773

Laboratory Parameter Abnormality[a]	VEKLURY 5 Days N=200	VEKLURY 10 Days N=197
ALT increased	6%	8%
AST increased	7%	6%
Creatinine clearance decreased[b]	10%	19%
Creatinine increased	5%	15%
Glucose increased	11%	8%
Hemoglobin decreased	6%	8%

a. Frequencies are based on treatment-emergent laboratory abnormalities. Graded per Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017.
b. Based on the Cockcroft-Gault formula.

Table 9 Laboratory Abnormalities (Grades 3-4) Reported in ≥3% of Hospitalized Subjects with Moderate COVID-19 in Trial 5774

Laboratory Parameter Abnormality[a]	VEKLURY 5 Days N=191	VEKLURY 10 Days N=193	SOC N=200
ALT increased	2%	3%	8%
Creatinine clearance decreased[b]	2%	5%	8%
Glucose increased	4%	3%	2%
Hemoglobin decreased	3%	1%	6%

SOC=Standard of care.

a. Frequencies are based on treatment-emergent laboratory abnormalities. Graded per Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017.
b. Based on the Cockcroft-Gault formula.

The frequencies of laboratory abnormalities (Grades 3-4) occurring in at least 2% of subjects with COVID-19 receiving VEKLURY in Trial GS-US-540-9012 are presented in Table 10.

Table 10 Laboratory Abnormalities (Grades 3-4) Reported in ≥2% of Non-Hospitalized Subjects in Trial 9012

Laboratory Parameter Abnormality[a]	VEKLURY 3 Days N=279	Placebo N=283
Creatinine clearance decreased[b]	6%	2%
Creatinine increased	3%	1%
Glucose increased	6%	6%
Lymphocytes decreased	2%	1%
Prothrombin time increased	1%	2%

a. Frequencies are based on treatment-emergent laboratory abnormalities. Graded per Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 2.1 dated July 2017.
b. Based on the Cockcroft-Gault formula.

Clinical Trials in Pediatric Subjects

Study GS-US-540-5823 was a Phase 2/3, single-arm, open-label clinical trial in hospitalized subjects 28 days of age and older and weighing at least 3 kg with mild, moderate, and severe COVID-19 treated with weight-based VEKLURY (n=53) for up to 10 days *[see Clinical Studies (13.6)]*:

- 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).

Post-Marketing Experience

The following adverse reactions have been identified during post-market use of VEKLURY:

- General disorders and administration site conditions: Administration site extravasation
- Skin and subcutaneous tissue disorders: Rash
- Immune system disorders: Anaphylaxis, angioedema, infusion-related reactions, hypersensitivity
- Investigations: Transaminase elevations

7 DRUG INTERACTIONS

Due to potential antagonism based on data from cell culture experiments, concomitant use of VEKLURY with chloroquine phosphate or hydroxychloroquine sulfate is not recommended *[see Warnings and Precautions (5.3) and Microbiology (11.4)].*

Drug-drug interaction trials of VEKLURY and other concomitant medications have not been conducted in humans. Remdesivir and its metabolites are in vitro substrates and/or inhibitors of certain drug metabolizing enzymes and transporters. The clinical relevance of these in vitro assessments has not been established. Based on a drug interaction study conducted with VEKLURY, no clinically significant drug interactions are expected with inducers of cytochrome P450 (CYP) 3A4 or inhibitors of Organic Anion Transporting Polypeptides (OATP) 1B1/1B3, and P-glycoprotein (P-gp) *[see Clinical Pharmacology (11.3)].*

VEKLURY was not administered to subjects who have already received a COVID-19 vaccine.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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 Non-Clinical Toxicology (12)]*. 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.

8.2 Lactation

It is unknown whether VEKLURY is secreted 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.

8.3 Pediatric Use

The safety and effectiveness of VEKLURY for the treatment of COVID-19 in pediatric patients 28 days of age and older and weighing at least 3 kg with pneumonia requiring supplemental oxygen was based on data from a Phase 2/3 open-label, single-arm clinical trial (Study GS-US-540-5823), where 53 hospitalized pediatric subjects were treated with weight-based VEKLURY for up to 10 days in the following cohorts: subjects ≥12 years and weighing ≥40 kg (n=12); subjects <12 years and weighing ≥40 kg (n=5); subjects ≥28 days and weighing ≥20 to <40 kg (n=12); subjects ≥28 days and weighing ≥12 to <20 kg (n=12); and subjects ≥28 days and weighing ≥3 to <12 kg (n=12). The safety and pharmacokinetic results in pediatric subjects in this group were similar to those in adults [see Adverse Reactions (6.1), Clinical Pharmacology (11.3), Clinical Studies (13.5)].

The use of VEKLURY in pediatric patients weighing at least 40 kg is further supported by one clinical study of VEKLURY in non-hospitalized subjects that included 3 pediatric subjects 12 years and older, and clinical studies in hospitalized subjects that included 30 adult subjects weighing 40 to 50 kg. The safety in this weight group was comparable to adult subjects weighing greater than 50 kg. [*see Adverse Reactions (6.1) and Clinical Studies (13*)].

All pediatric patients 28 days of age and older and weighing at least 3 kg must have eGFR determined before starting VEKLURY and while receiving VEKLURY as clinically appropriate [see Dosage and Administration (2.2, 2.4), Adverse Reactions (6.1), Use in Specific Populations (8.5)].

The safety and effectiveness of VEKLURY have not been established in pediatric patients younger than 28 days of age or weighing less than 3 kg.

8.4 Geriatric Use

Of the 1,062 hospitalized subjects with SARS-CoV-2 infection randomized in ACTT-1, 36% were 65 years or older. Of the 397 hospitalized subjects with SARS-CoV-2 infection randomized in Study GS-US-540-5773, 42% were 65 years or older. Of the 584 hospitalized subjects with SARS-CoV-2 infection randomized in Study GS-US-540-5774, 27% were 65 years or older. Of the 562 non-hospitalized subjects with SARS-CoV-2 infection randomized in Study GS-US-540-9012, 17% were 65 years or older. Reported clinical experience has not identified differences in responses between the elderly and younger patients *[see Clinical Studies (13)].* No dosage adjustment is required in patients over the age of 65 years. In general, appropriate caution should be exercised in the administration of VEKLURY and monitoring of elderly patients, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

8.5 Renal Impairment

The pharmacokinetics of VEKLURY have not been evaluated in patients with renal impairment. Patients with eGFR greater than or equal to 30 mL per minute have received VEKLURY for treatment of COVID-19 with no dose adjustment of VEKLURY *[see Clinical Studies (13)].*

All patients must have an eGFR determined before starting VEKLURY and while receiving VEKLURY as clinically appropriate. Because the excipient betadex sulfobutyl ether sodium is renally cleared and accumulates in patients with decreased renal function, administration of drugs formulated with betadex sulfobutyl ether sodium (such as VEKLURY) is not recommended in patients with eGFR less than 30 mL per minute *[see Dosage and Administration (2.2, 2.4)].*

8.6 Hepatic Impairment

The pharmacokinetics of VEKLURY have not been evaluated in patients with hepatic impairment.

Perform hepatic laboratory testing in all patients before starting VEKLURY and while receiving VEKLURY as clinically appropriate *[see Dosage and Administration (2.2) and Warnings and Precautions (5.2)].*

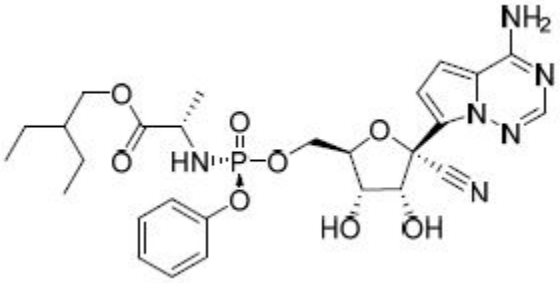
9 OVERDOSAGE

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.

10 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:



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 (2.6, 2.7)]*. The inactive ingredients are 3 g betadex sulfobutyl ether sodium and may include hydrochloric acid and/or sodium hydroxide for pH adjustment.

11 CLINICAL PHARMACOLOGY

11.1 Mechanism of Action

Remdesivir is an antiviral drug with activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) *[see Microbiology (11.4)]*.

11.2 Pharmacodynamics

Remdesivir and metabolites exposure-response relationships and the time course of pharmacodynamics response are unknown.

11.3 Pharmacokinetics

The pharmacokinetic (PK) properties of remdesivir and metabolites are provided in Table 11. The multiple dose PK parameters of remdesivir and metabolites in adults with COVID-19 are provided in Table 12.

Table 11 Pharmacokinetic Properties of Remdesivir and Metabolites (GS-441524 and GS-704277)

	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).

Table 12 Multiple Dose PK Parameters[a] of Remdesivir and Metabolites (GS-441524 and GS-704277) Following IV Administration of VEKLURY 100 mg to Adults with COVID-19

Parameter Mean[b] (95% CI)	Remdesivir	GS-441524	GS-704277
C_{max} (nanogram per mL)	2700 (2440, 2990)	143 (135, 152)	198 (180, 218)

AUC_{tau} (nanogram•h per mL)	1710 (1480, 1980)	2410 (2250, 2580)	392 (348, 442)
C_{trough} (nanogram per mL)	ND	61.5 (56.5, 66.8)	ND

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

Specific Populations

Pharmacokinetic differences based on sex, race, age, renal function, and hepatic function on the exposures of remdesivir were evaluated using population pharmacokinetic analysis. Sex and race did not affect the pharmacokinetics of remdesivir and its metabolites (GS-704277 and GS-441524).

Pediatric Patients

Population pharmacokinetic models for remdesivir and its circulating metabolites (GS-704277 and GS-441524), developed using pooled data from studies in healthy subjects and in adult and pediatric patients with COVID-19, were used to estimate pharmacokinetic exposures in pediatric patients aged ≥28 days to <18 years and weighing ≥3 kg (Study 5823). Geometric mean estimated exposures (AUC_{tau}, C_{max}, and C_{tau}) for these patients at the doses administered were higher for remdesivir (33% to 129%), GS-441524 (0% to 60%), and GS-704277 (37% to 124%) as compared to those in adult patients with COVID-19; however, the increases were not considered clinically significant *[see Use in Specific Populations (8.3)].*

The multiple dose PK parameters of remdesivir and metabolites in pediatric patients with COVID-19 are provided in Table 13.

Table 13 Multiple Dose PK Parameters[a] of Remdesivir and Metabolites (GS-441524 and GS-704277) Following Intravenous Administration of VEKLURY 100 mg (Cohorts 1 and 8) or 2.5 mg/kg (Cohorts 2-4) to Pediatric Patients with COVID-19

	Cohort 1	**Cohort 8**	**Cohort 2**	**Cohort 3**	**Cohort 4**
Parameter Mean[b] (95% CI)	**12 to <18 Years and Weighing ≥40 kg (N=12)**	**<12 Years and Weighing ≥40 kg (N=5)**	**28 Days to <18 Years and Weighing 20 to <40 kg (N=12)**	**28 Days to <18 Years and Weighing 12 to <20 kg (N=11)**	**28 Days to <18 Years and Weighing 3 to <12 kg (N=10)**
Remdesivir					
C_{max} (nanogram per mL)	3910 (3140, 4870)	3920 (2270, 6790)	5680 (4660, 6930)	5530 (4240, 7210)	4900 (3790, 6340)

AUC_{tau} (nanogram•h per mL)	2470 (1940, 3150)	2280 (1200, 4300)	3500 (2570, 4780)	3910 (2140, 7160)	2930 (1900, 4520)
GS-441524					
C_{max} (nanogram per mL)	197 (123, 316)	162 (57.4, 458)	181 (132, 248)	158 (116, 215)	202 (171, 238)
AUC_{tau} (nanogram•h per mL)	3460 (2010, 5960)	2640 (772, 9030)	2870 (2020, 4080)	2400 (1740, 3320)	2770 (2230, 3450)
C_{tau} (nanogram per mL	98.3 (59.0, 164)	76.2 (24.0, 242)	73.8 (49.9, 109)	69.4 (48.1, 100)	78.4 (58.5, 105)
GS-704277					
C_{max} (nanogram per mL)	307 (212, 443)	278 (145, 532)	423 (309, 578)	444 (336, 585)	390 (305, 500)
AUC_{tau} (nanogram•h per mL)	815 (474, 1400)	537 (203, 1420)	754 (547, 1040)	734 (513, 1050)	691 (494, 966)

CI=Confidence Interval

a. Population PK estimates for 30-minutes IV infusion of remdesivir for up to 10 days (Study GS-US-540-5823).

b. Geometric mean estimates.

Drug Interaction Studies

Clinical drug-drug interaction studies have not been performed with VEKLURY.

Effects of other medicinal products on VEKLURY

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 Pglycoprotein (P-gp) transporters. GS-704277 is a substrate for OATP1B1 and OATP1B3. The clinical relevance of these in vitro assessments has not been established.

The potential of interaction of VEKLURY with inhibitors/inducers of the hydrolytic pathway (esterase) or CYP3A4 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. Based on modelling and simulation, no clinically significant drug-drug interactions are expected with substrates of CYP3A4,

OATP 1B1/1B3 or MATE1. 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.

Assessment of Drug Interactions

A drug-drug interaction study was conducted with VEKLURY. Table 14 summarizes the pharmacokinetic effects of other drugs on remdesivir and metabolites GS-704277 and GS-441524.

Table 14 Effect of Other Drugs on Remdesivir and Metabolites GS-704277 and GS-441524 [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)		
					Cmax	AUCinf
Cyclosporin A[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[a]	300 twice daily	100 single dose	8	remdesivir	0.87 (0.78-0.97)	0.92 (0.83-1.02)
				GS-704277	0.96 (0.84-1.10)	0.98 (0.92-1.05)
				GS-441524	0.97 (0.88-1.07)	0.83 (0.78-0.89)

a. Interaction study conducted in healthy volunteers.

11.4 Microbiology

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.

Antiviral Activity

Cell Culture Antiviral Activity

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

Remdesivir EC_{50} values for SARS-CoV-2 in A549-hACE2 cells were not different when combined with chloroquine phosphate or hydroxychloroquine sulfate at concentrations up to 2.5 μM. In a separate study, 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 or hydroxychloroquine sulfate reduced formation of remdesivir triphosphate in A549-hACE2, HEp-2, and normal human bronchial epithelial cells.

Based on cell culture susceptibility testing by virus yield reduction assay and/or N protein ELISA assay, remdesivir retained similar antiviral activity (<2.5-fold change) against clinical isolates of SARS-CoV-2 variants containing the P323L substitution in the viral polymerase including the Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Epsilon (B.1.429), Kappa (B.1.617.1), Lambda (C.37), Iota (B.1.526), and Zeta (P.2) variants compared to earlier lineage SARS-CoV-2 (lineage A) isolates. For

the clinical isolates of the Delta (B.1.627.2) and Omicron (B.1.1.529, BA.1, BA.2, BA.2.12.1, BA.4 and BA.5) variants, remdesivir maintained antiviral activity (<0.7-fold change). The antiviral activity of remdesivir against SARS-CoV-2 variants is presented in Table 15.

Table 15: Remdesivir antiviral activity against clinical isolates of SARS-CoV-2 variants

SARS-CoV-2 Lineage	Country First Identified	WHO Nomenclature	Key Substitutions	Remdesivir EC_{50} (nM)	Fold Change in Susceptibility	Change in Susceptibility
A	USA	-	-	110	1.0	
B.1.1.7	UK	Alpha	P323L	192	1.58	No change[a]
B.1.351	South Africa	Beta	P323L	141	1.19	No change[a]
P.1	Brazil	Gamma	P323L	97	0.82	No change[a]
B.1.617.2	India	Delta	P323L, G671S	70	0.59	No change[a]
B.1.429	USA	Epsilon	P323L	210	1.94	No change[a]
P.2	Brazil	Zeta	P323L	151	1.17	No change[a]
B.1.526	USA	Iota	P323L	258	2.33	No change[a]
B.1.617.1	India	Kappa	P323L	77	0.63	No change[a]
C.37	Peru	Lambda	P323L	175	1.37	No change[a]
B.1.1.529	South Africa	Omicron				
BA.1			P323L	44	0.45	No change[a]
BA.2			P323L	25	0.23	No change[a]
BA.2.12.1			P323L	33	0.20	No change[a]
BA.4			P323L	25	0.15	No change[a]
BA.5			P323L	106	0.66	No change[a]

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

Clinical Antiviral Activity

SARS-CoV-2 RNA shedding results from GS-US-540-5776 (ACTT-1) indicate that remdesivir does not significantly reduce the amount of detectable SARS-CoV-2 RNA in oropharyngeal or nasopharyngeal swabs or plasma samples in hospitalized patients compared to placebo, and SARS-CoV-2 RNA shedding results from GS-US-540-9012 indicate that remdesivir does not significantly reduce the amount of detectable SARS-CoV-2 RNA in nasopharyngeal swabs in non-hospitalized patients compared to placebo.

Resistance

Cell Culture Resistance

SARS-CoV-2 isolates with reduced susceptibility to remdesivir have been selected in cell culture. In a selection with GS-441524, the parent nucleoside of remdesivir, virus pools emerged expressing amino acid substitutions at V166A, N198S, S769, V792I, C799F, and C799R in the viral RNA-dependent RNA polymerase (nsp12). When these substitutions were individually introduced into a

wild-type recombinant virus by site-directed mutagenesis, 1.7- to 3.5-fold reductions in susceptibility to remdesivir were observed. In a cell culture resistance selection experiment with remdesivir, nsp12 amino acid substitution E802D emerged, resulting in a 2.5-fold reduction in susceptibility to remdesivir. In another 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 SARS-CoV-2 with substitutions at P323L alone or P323L+V166L in a combination exhibited 1.3- and 1.5-fold reductions in remdesivir susceptibility, respectively.

Cell culture resistance profiling of remdesivir using the rodent CoV murine hepatitis virus identified two substitutions (F476L and V553L) in the viral RNA-dependent RNA polymerase at residues conserved across CoVs. Introduction of the corresponding substitutions (F480L and V557L) into SARS-CoV resulted in 6-fold reduction in 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.

Treatment-Emergent Resistance

SARS-CoV-2 nsp12 E802D substitution has emerged in one individual treated with remdesivir. The E802D substitution resulted in a 2.5-fold increase in the remdesivir EC_{50} value.

12 NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Given the short-term administration of VEKLURY for the treatment of COVID-19, long-term animal studies to evaluate the carcinogenic potential of remdesivir were not conducted.

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.

Impairment of Fertility

Nonclinical toxicity studies in rats demonstrated no adverse effect on male fertility at exposures of the predominant circulating metabolite (GS-441524) approximately 2 times the exposure in humans at the RHD.

Reproductive toxicity, including decreases in corpora lutea, numbers of implantation sites, and viable embryos, was seen when remdesivir was administered by daily intravenous administration at a systemically toxic dose (10 mg/kg) in female rats 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.

12.2 Animal Toxicology and/or Pharmacology

Intravenous administration (slow bolus) of remdesivir to 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.

Intravenous administration (slow bolus) of remdesivir to rats at dosage levels of ≥3 mg/kg/day for up to 4 weeks resulted in findings indicative of kidney injury and/or dysfunction.

Kidney-related effects in rats and monkeys were observed at exposures of the predominant circulating metabolite (GS-441524) that are lower than the exposure in humans at the RHD.

13 CLINICAL STUDIES

13.1 Description of Clinical Trials

The efficacy and safety of VEKLURY were evaluated in the trials summarized in Table 16.

Table 16 Trials Conducted with VEKLURY in Subjects with COVID-19

Trial	Population	Trial Arms (N)	Timepoint
NIAID ACTT-1[a] (NCT04280705)	Hospitalized with mild/moderate and severe COVID-19	VEKLURY 10 Days (532) Placebo (516)	29 Days after Randomization
GS-US-540-5773[b] (NCT04292899)	Hospitalized with severe COVID-19	VEKLURY 5 Days (200) VEKLURY 10 Days (197)	Day 14
GS-US-540-5774[b] (NCT04292730)	Hospitalized with moderate COVID-19	VEKLURY 5 Days (191) VEKLURY 10 Days (193) Standard of care (200)	Day 11
GS-US-540-9012[a] (NCT04501952)	Non-hospitalized with mild-to-moderate COVID-19 and at high risk for progression to severe disease	VEKLURY 3 Days (279) Placebo (283)	Day 28
GS-US-540-5823 (Cohorts 1-4, 8)[c] (NCT04431453)	Hospitalized pediatric subjects 28 days to <18 years of age and weighing at least 3 kg with COVID-19	VEKLURY up to 10 Days (53)	Day 10

COVID-19: coronavirus disease 2019

a. Randomized, double-blind, placebo-controlled trial.
b. Randomized, open-label trial.
c. Open-label trial, descriptive outcome analyses.

13.2 NIAID ACTT-1 Study in Hospitalized Subjects with Mild/Moderate and Severe COVID-19

This was a randomized, double-blind, placebo-controlled clinical trial of hospitalized adult subjects with confirmed SARS-CoV-2 infection and mild, moderate, or severe COVID-19 compared treatment with VEKLURY for 10 days (n=541) with placebo (n=521). Mild/moderate disease was defined as SpO_2 >94% and respiratory rate <24 breaths/minute without supplemental oxygen; severe disease was defined as an SpO_2 ≤94% on room air, a respiratory rate ≥24 breaths/minute, an oxygen requirement, or a requirement for mechanical ventilation. Subjects had to have at least one of the following to be enrolled in the trial: radiographic infiltrates by imaging, SpO_2 ≤94% on room air, a requirement for supplemental oxygen, or a requirement for mechanical ventilation. Subjects treated with VEKLURY received 200 mg on Day 1 and 100 mg once daily on subsequent days, for 10 days of treatment via intravenous infusion. Treatment with VEKLURY was stopped in subjects who were discharged from the hospital prior to the completion of 10 days of treatment.

At baseline, mean age was 59 years (with 36% of subjects aged 65 or older); 64% of subjects were male, 53% were White, 21% were Black, and 13% were Asian; 24% were Hispanic or Latino; 105 subjects had mild/moderate disease (10% in both treatment groups); 957 subjects had severe disease (90% in both treatment groups). Subject in this trial were not vaccinated with COVID-19 vaccine. A total of 285 subjects (27%) (n=131 received VEKLURY) were on invasive mechanical ventilation or ECMO. The most common comorbidities were hypertension (51%), obesity (45%), and type 2 diabetes mellitus (31%); the distribution of comorbidities was similar between the two treatment groups.

The primary clinical endpoint was time to recovery within 29 days after randomization. Recovery was defined as discharged from the hospital without limitations on activities, discharged from the hospital with limitations on activities and/or requiring home oxygen, 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). Among subjects with mild/moderate disease at enrollment (n=105), the median time to recovery was 5 days in both the VEKLURY and placebo groups (recovery rate ratio 1.22 [95% CI 0.82 to 1.81]). Among subjects with severe disease at enrollment (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]).

A key secondary endpoint was clinical status on Day 15 assessed on an 8-point ordinal scale consisting of the following categories:

1. not hospitalized, no limitations on activities;
2. not hospitalized, limitation on activities and/or requiring home oxygen;
3. hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;
4. hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);

5. hospitalized, requiring supplemental oxygen;
6. hospitalized, on noninvasive ventilation or high-flow oxygen devices;
7. hospitalized, on invasive mechanical ventilation or ECMO; and
8. death.

The clinical benefit of VEKLURY was most apparent in patients receiving supplemental oxygen and not on ventilation (ordinal score 5 at baseline) (recovery rate ratio 1.45 [95% CI: 1.18-1.79]). For patients who were receiving non-invasive ventilation or high-flow oxygen device on Day 1 (ordinal score 6 at baseline), no difference in recovery rate was observed between VEKLURY group and placebo group (recovery rate ratio 1.09 [95% CI: 0.76 – 1.57]. For patients who were receiving mechanical ventilation or ECMO at Day 1 (baseline ordinal score 7), no difference in recovery rate was observed between the Veklury group and the placebo group (recovery rate ratio 0.98 [95% CI: 0.70 to 1.36]).

There was also no difference in the mortality rate at 29-day in patients who were receiving invasive mechanical ventilation or ECMO on Day 1 (baseline ordinal score 7) (22.0% and 19.6%; hazard ratio 1.13 [95% CI: 0.67 to 1.89]).

In clinical studies, there was no survival and recovery benefit with VEKLURY in patients under invasive mechanical ventilation (IMV), or under extracorporeal membrane oxygenation (ECMO).

The 29-day mortality in the overall population was 11.6% for the VEKLURY group vs 15.4% for the placebo group (hazard ratio, 0.73; [95% CI 0.52 to 1.03]; p=0.07). A post-hoc analysis of the 29-day mortality outcomes by ordinal scale is presented in Table 17.

Table 17: 29-Day Mortality Outcomes by Ordinal Scale[a] at Baseline—NIAID ACTT-1 Trial

	Ordinal Score at Baseline			
	5		**6**	
	Requiring low-flow oxygen		**Requiring high-flow oxygen or non-invasive mechanical ventilation**	
	VEKLURY (N=232)	Placebo (N=203)	VEKLURY (N=95)	Placebo (N=98)
29-day mortality	4.1	12.8	21.8	20.6
Hazard ratio[b] (95% CI)	0.30 (0.14, 0.64)		1.02 (0.54, 1.91)	

a Not a pre-specified analysis.
b Hazard ratios for baseline ordinal score subgroups are from unstratified Cox proportional hazards models.
29-day mortality is based of participants with known mortality status at Day 29

13.3 Study GS-US-540-5773 in Hospitalized Subjects with Severe COVID-19

A randomized, open-label multi-center clinical trial (Study 5773) in adult subjects with confirmed SARS-CoV-2 infection, an SpO_2 of ≤94% on room air, and radiological evidence of pneumonia compared 200 subjects who received VEKLURY for 5 days with 197 subjects who received VEKLURY for 10 days. Treatment with VEKLURY was stopped in subjects who were discharged from the hospital prior to completion of their protocol-defined duration of treatment. Subjects on

mechanical ventilation at screening were excluded. All subjects received 200 mg of VEKLURY on Day 1 and 100 mg once daily on subsequent days via intravenous infusion, plus standard of care.

At baseline, the median age of subjects was 61 years (range, 20 to 98 years); 64% were male, 75% were White, 12% were Black, and 12% were Asian; 22% were Hispanic or Latino. More subjects in the 10-day group than the 5-day group required invasive mechanical ventilation or ECMO (5% vs 2%), or high-flow oxygen support (30% vs 25%), at baseline. Subjects in this trial were unvaccinated.

Median duration of symptoms and hospitalization prior to first dose of VEKLURY were similar across treatment groups.

The primary endpoint was clinical status on Day 14 assessed on a 7-point ordinal scale consisting of the following categories:

1. death;
2. hospitalized, receiving invasive mechanical ventilation or ECMO;
3. hospitalized, receiving noninvasive ventilation or high-flow oxygen devices;
4. hospitalized, requiring low-flow supplemental oxygen;
5. hospitalized, not requiring supplemental oxygen but receiving ongoing medical care (related or not related to COVID-19);
6. hospitalized, requiring neither supplemental oxygen nor ongoing medical care (other than that specified in the protocol for remdesivir administration); and
7. not hospitalized.

Overall, after adjusting for between-group differences at baseline, subjects receiving a 5-day course of VEKLURY had similar clinical status at Day 14 as those receiving a 10-day course (odds ratio for improvement 0.75 [95% CI 0.51 to 1.12]). There were no statistically significant differences in recovery rates or mortality rates in the 5-day and 10-day groups once adjusted for between-group differences at baseline. All-cause mortality at Day 28 was 12% vs 14% in the 5- and 10-day treatment groups, respectively.

13.4 Study GS-US-540-9012 in Patients with Confirmed COVID-19 at Increased Risk for Disease Progression

A randomised, double-blind, placebo-controlled, multi-center clinical trial to evaluate treatment with remdesivir in an outpatient setting in 562 patients including 8 adolescents (12 years of age and older and weighing at least 40 kg) with confirmed COVID-19 and at least one risk factor for disease progression to hospitalisation. Risk factors for disease progression were: aged ≥ 60 years, chronic lung disease, hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, obesity, immunocompromised state, chronic mild or moderate kidney disease, chronic liver disease, current cancer, or sickle cell disease. Vaccinated patients were excluded from the study.

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

At baseline, mean age was 50 years (with 30% of subjects 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. 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. Post-hoc exploratory analysis of optional biomarker samples showed 14.8% of patients were serological positive at baseline and 37.7% were serological negative (47.5% did not consent to optional biomarker collection).

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 (COVID-19-related hospitalisation or all-cause 28-day mortality) occurred in 2 (0.7%) patients treated with VEKLURY compared to 15 (5.3%) patients concurrently randomized to placebo , demonstrating an 87% reduction in COVID-19-related hospitalisation or all-cause mortality compared to placebo (hazard ratio 0.134 [95% CI 0.031 to 0.586]; p=0.0076). The absolute risk reduction was 4.6% (95% CI, 1.8% to 7.5%). No deaths were observed at Day 28. Six of the 17 hospitalization events occurred in participants with known baseline serostatus (serological positive: n=0 in remdesivir group and n=2 in placebo group; serological negative: n=2 in remdesivir group and n=2 in placebo group). Eleven of the 17 hospitalization events occurred in participants with unknown baseline serostatus in placebo group and none in the remdesivir group. No conclusion can be made on efficacy in the subgroups stratified by serostatus due to the small number of patients with known serostatus and overall low event rates.

13.5 Pediatric Population

Study GS-US-540-5823 is a single-arm, open-label study where the pharmacokinetics and safety of remdesivir in paediatric patients at least 28 days of age and weighing at least 3 kg with COVID-19 (n=53) was assessed. Efficacy endpoints were secondary and descriptively analysed and therefore these should be interpreted with caution. The study is ongoing.

Patients weighing ≥ 40 kg received 200 mg of remdesivir on Day 1 followed by remdesivir 100 mg once daily on subsequent days (i.e., the adult dose); patients weighing ≥ 3 kg to < 40 kg received remdesivir 5 mg/kg on Day 1 followed by remdesivir 2.5 mg/kg once daily on subsequent days. Median (range) exposure to remdesivir was 5 (1, 10) days.

At baseline, median age was 7 years (range: 0.1 to 17 years); 57% were female; median weight was 24.6 kg (range: 4 kg to 192 kg). A total of 19 patients (37%) were obese (BMI-for-age ≥ 95th percentile); 7 (58%), 2 (17%), 3 (27%), 3 (27%), and 4 (80%) patients in Cohorts 1, 2, 3, 4 and 8 respectively. A total of 12 patients (23%) were on invasive mechanical ventilation (score of 2 in a 7-point ordinal scale), 18 (34%) were on non-invasive ventilation or high-flow oxygen (score of 3); 10 (19%) were on low flow oxygen (score of 4); and 13 (25%) were on room air (score of 5), at baseline. The overall median (Q1, Q3) duration of symptoms and hospitalisation prior to first dose of remdesivir was 5 (3, 7) days and 1 (1, 3) day, respectively.

In the overall population of the study, the median (Q1, Q3) change from baseline in clinical status (assessed on a 7-point ordinal scale ranging from death [score of 1] to hospital discharge [score of 7]) was +2.0 (1.0, 4.0) points on Day 10. Among those with an ordinal score of ≤ 5 points at baseline, the proportion who had a ≥ 2-point improvement in clinical status on Day 10 was 75.0% (39/52); median (Q1, Q3) time to recovery was 7 (5, 16) days. Overall, 60% of patients were discharged by Day 10. Most patients 92% (49/53) received at least 1 concomitant medication other than remdesivir for the treatment of COVID-19 including immune modulator and anti-inflammatory agents. Three patients died during the study.

14 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

VEKLURY for injection: 100 mg, is supplied as a single-dose vial containing a sterile, preservative-free white to off-white to yellow lyophilized powder. It requires reconstitution and further dilution prior to administration by intravenous infusion *[see Dosage and Administration (2.5 2.6)]*. Discard unused portion. The container closure is not made with natural rubber latex.

Storage and Handling

Do not reuse or save reconstituted or diluted VEKLURY for future use. The product contains no preservative; therefore, partially used vials should be discarded *[see Dosage and Administration (2.7)]*.

Store VEKLURY for injection, 100 mg vials below 30°C until required for use.

After reconstitution, use vials immediately to prepare diluted solution. Dilute the reconstituted solution in 0.9% sodium chloride injection, USP within the same day as administration. The diluted VEKLURY solution in the infusion bags can be stored up to 24 hours at room temperature (20°C to 25°C) prior to administration or 48 hours at refrigerated temperature (2°C to 8°C).

15 PATIENT COUNSELING INFORMATION

Hypersensitivity Reactions

Inform patients that hypersensitivity reactions have been seen in patients receiving VEKLURY during and after infusion. Advise patients to inform their healthcare provider if they experience 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 patients that VEKLURY may increase the risk of hepatic laboratory abnormalities. Advise patients to alert their healthcare provider immediately if they experience any symptoms of liver inflammation *[see Warnings and Precaution (5.2)].*

Drug Interactions

Inform patients 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 (7), and Microbiology (11.4)].*

Pregnancy

Inform patients to notify their healthcare provider immediately in the event of a pregnancy *[see Use in Specific Populations (8.1)].*

Lactation

Inform mothers that it is not known whether VEKLURY can pass into their breast milk *[see Use in Specific Populations (8.2)]*.

16 PRODUCT OWNER

Gilead Sciences, Inc

333 Lakeside Drive

Foster City, CA 94404

USA

17 DATE OF REVISION OF THE TEXT

March 2023

SG-MAR23