

Carta Trámite

14 de febrero de 2022

A: Todos los Proveedores Contratados por First Medical Health Plan, Inc., para el Plan Vital, Región Única y Población Vital-X (Virtual).

Re: *Carta Normativa 22-0127 de la Administración de Seguros de Salud de Puerto Rico (ASES) relacionada a la Actualización en Indicación para Veklury (remdesivir)*

Estimado(a) Proveedor(a):

Reciba un cordial saludo de parte de First Medical Health Plan, Inc., (FMHP).

Adjunto a este comunicado encontrará la Carta Normativa 22-0127 y la Fe de Errata Carta Normativa 22-0127 de la Administración de Seguros de Salud (ASES).

A través de estas, la ASES informa que, desde el 21 de enero del 2022, la Administración de Alimentos y Medicamentos (FDA, por sus siglas en inglés) expandió la indicación para el medicamento Veklury (remdesivir), en pacientes no hospitalizados que tengan COVID-19 de leve a moderado con un alto riesgo de progresar a severo, que incluye la hospitalización o la muerte. Además, la FDA actualizó la Autorización del Uso de Emergencia (EUA, por sus siglas en inglés) para incluir a pacientes pediátricos, con resultados positivos de la prueba viral directa de SARS-CoV-2 que estén o no hospitalizados por COVID-19 de leve a moderado con un alto riesgo de progresar a severo, que incluye la hospitalización o la muerte. Favor de referirse a la siguiente tabla con las indicaciones aprobadas:

Medicamento	Veklury (remdesivir)	
Edad de la población	Indicaciones aprobadas por la FDA: adultos y pediátricos (12 años o más que pesen 40 kg)	Indicaciones bajo EUA: pacientes pediátricos que pesan de 3.5 kg a menos de 40 kg ó pacientes pediátricos menores de 12 años que pesan al menos 3.5 kg
Dosificación	Día 1: dosis de carga de 200mg Día: 2 en adelante: 100mg diarios	Día 1: dosis de carga de 5mg/kg Día 2 en adelante: 2.5mg/kg
Frecuencia de administración	Diario	
Forma de dosificación	Para uso intravenoso: 100mg de polvo liofilizado en un vial de uso sencillo. 100mg/20ml (5mg/ml) de un vial de uso sencillo	
Duración del tratamiento	1-Pacientes hospitalizados en ventilación mecánica: 10 días totales	

	2-Pacientes hospitalizados sin ventilación mecánica: 5 días (se puede extender el tratamiento hasta 10 días totales) 3-Pacientes no hospitalizados: 3 días totales
Casa manufacturera	Gilead

En adición, la ASES incluye los siguientes puntos importantes:

- Este medicamento debe ser administrado en un hospital o Institución de salud capacitado para proveer cuidado agudo comparable al de un hospital.
- Una aprobación para una indicación otorgada por la FDA no es igual a una autorización de uso de emergencia.
- El código establecido por los Centros de Servicio Medicare y Medicaid (CMS, por sus siglas en inglés) para los pacientes no hospitalizados es J0248.

Para detalles específicos sobre la información provista por la ASES, le exhortamos a que lea detenidamente la Fe de Errata de la Carta Normativa 22-0127 y la Carta Normativa 22-0127.

Si usted tiene alguna pregunta o necesita información adicional relacionada a este comunicado, siéntase en la libertad de comunicarse con nuestro Centro de Servicio al Proveedor al número libre de cargos 1-844-347-7802 de lunes a viernes de 7:00 a.m. a 7:00 p.m.

Cordialmente,

Departamento de Cumplimiento
First Medical Health Plan, Inc.



27 de enero de 2022

Carta Normativa 22-0127

A: Organizaciones de Cuidado Coordinado de Salud (MCOs, con sus siglas en inglés) contratadas bajo el Plan de Salud del Gobierno (Plan Vital), Administrador del Beneficio de Farmacia, Farmacias, Grupos Médicos Primarios (GMP) y Proveedores Participantes

Re: Actualización en Indicación para Veklury (remdesivir)

El 21 de enero de 2021 la Administración de Alimentos y Medicamentos (FDA por sus siglas en inglés) expandió las indicaciones del medicamento Veklury (remdesivir). Previamente su uso era en pacientes que requirieran hospitalización, ahora se aprueba la indicación de pacientes no hospitalizados que tengan COVID-19 leve a moderado con un alto riesgo de progresar a severo, que incluye la hospitalización o la muerte. Adicional a la aprobación de las indicaciones oficiales, la FDA actualizó la autorización de uso de emergencia (EUA por sus siglas en inglés) para incluir a pacientes pediátricos que pesan de 3.5 kilogramos a menos de 40 kilogramos o pacientes pediátricos menores de 12 años que pesan al menos 3.5 kilogramos, con resultados positivos de la prueba viral directa de SARS-CoV-2 que estén hospitalizados o *no-hospitalizados* que tengan COVID-19 leve a moderado con un alto riesgo de progresar a severo, que incluye la hospitalización o la muerte.

Medicamento	Veklury	
Edad de la Población	Indicaciones aprobadas por la FDA: Adultos y pediátricos (12 años o más que pesen por lo menos 40kg)	Indicaciones bajo EUA: Pacientes pediátricos que pesan de 3.5 kilogramos a menos de 40 kilogramos o, pacientes pediátricos menores de 12 años que pesan al menos 3.5 kilogramos
Dosificación	Día 1: Dosis de carga de 200mg Día 2 en adelante: 100mg diarios	Día 1: Dosis de carga de 5mg/kg Día 2 en adelante: 2.5mg/kg
Frecuencia de administración	Diario	
Forma de dosificación	Para uso intravenoso: 100mg de polvo liofilizado en un vial de uso sencillo	

	100mg/20mL (5mg/mL) de un vial de uso sencillo
Duración de tratamiento	<ul style="list-style-type: none"> • Pacientes hospitalizados en ventilación mecánica: 10 días totales • Pacientes hospitalizados sin ventilación mecánica: 5 días (se pudiera extender tratamiento hasta 10 días totales) • Pacientes no hospitalizados: 3 días totales
Casa Manufacturera	<i>Gilead</i>

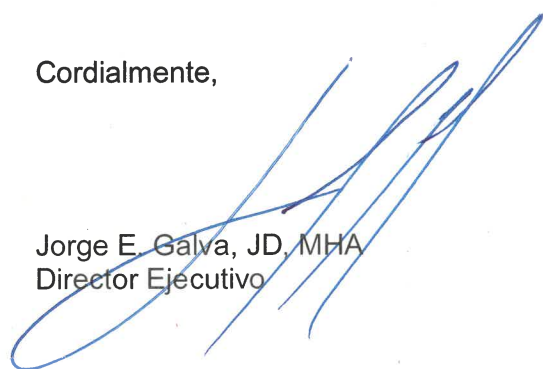
Puntos importantes:

- Este medicamento debe ser administrado en un hospital o Institución de salud capacitado para proveer cuidado agudo comparable al de un hospital.
- Una aprobación para una indicación otorgada por la FDA no es igual a una autorización de uso de emergencia.
- El código establecido por los Centros de Servicio de Medicare y Medicaid (CMS por sus siglas en inglés) para los pacientes no hospitalizados es J0248.

Agradecemos su colaboración y la de sus proveedores en identificar la mejor terapia para nuestros beneficiarios del Plan Vital y para garantizarles el acceso y la continuidad de sus tratamientos.

Todos los MCOs, contratados bajo el Plan de Salud del Gobierno (Plan Vital), Administrador del Beneficio de Farmacia, y Farmacias, serán responsables en cuanto a lo expresado en esta Carta Normativa.

Cordialmente,



Jorge E. Galva, JD, MHA
Director Ejecutivo



9 de febrero de 2022

FE DE ERRATA

A: ORGANIZACIONES DE CUIDADO DIRIGIDO (MCOS) CONTRATADAS POR EL PLAN DE SALUD DEL GOBIERNO DE PR (PSG) VITAL, MÉDICOS PRIMARIOS (PCP), GRUPOS MÉDICOS PRIMARIOS (GMP) Y PROVEEDORES PARTICIPANTES

Re: CORRECCIÓN A CARTA NORMATIVA 22-0127

En la Carta Normativa 22-0127, se menciona el 21 de enero de 2021 como la fecha en la cual la Administración de Alimentos y Medicamentos (FDA por sus siglas en inglés) expandió las indicaciones del medicamento Veklury.

Clarificamos que la fecha correcta de esta expansión de indicaciones es el 21 de enero de **2022**.

Lamentamos cualquier confusión causada por este error y solicitamos que tomen esta Fe de Errata como corrección a la normativa anteriormente mencionada.

Cordialmente,

Jorge E. Galva, JD, MHA
Directora Ejecutiva

**FACT SHEET FOR HEALTHCARE PROVIDERS
EMERGENCY USE AUTHORIZATION (EUA) OF VEKLURY® (remdesivir) FOR
THE TREATMENT OF CORONAVIRUS DISEASE 2019 (COVID-19) 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 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**

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of VEKLURY for the treatment of coronavirus disease 2019 (COVID-19) 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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, 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. Refer to CDC website¹ for additional details.

VEKLURY has been authorized by FDA for the emergency uses described above. VEKLURY is not FDA-approved for these uses.

VEKLURY is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of VEKLURY under section 564(b)(1) of the Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

**This EUA is for the use of VEKLURY to treat COVID-19 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 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.**

¹ <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>. Healthcare providers should consider the benefit-risk for an individual patient.

VEKLURY must be administered by intravenous (IV) infusion.

Healthcare providers must submit a report on all medication errors and **ALL SERIOUS ADVERSE EVENTS** related to VEKLURY. See Sections 8 and 9 of the Full EUA Prescribing Information for reporting requirements.

- See the Full EUA Prescribing Information for complete dosage, preparation, and administration instructions.
- **The only authorized dosage form of VEKLURY for 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 is VEKLURY for injection (supplied as 100 mg lyophilized powder in vial).**
 - The recommended dosage for pediatric patients weighing 3.5 kg to less than 40 kg is a single loading dose of VEKLURY 5 mg/kg on Day 1 followed by VEKLURY 2.5 mg/kg once daily from Day 2 [*see Full EUA Prescribing Information, Recommended Dosage in Pediatric Patients (2.3)*].
 - The recommended dosage for pediatric patients less than 12 years of age and weighing 40 kg and higher is a single loading dose of 200 mg on Day 1 followed by once-daily maintenance doses of 100 mg from Day 2.

Hospitalized patients:

The treatment course of VEKLURY should be initiated as soon as possible after diagnosis of symptomatic COVID-19 has been made.

- The recommended total treatment duration for hospitalized patients requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO) is 10 days.
- The recommended treatment duration for hospitalized patients not requiring invasive mechanical ventilation and/or ECMO is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days for a total treatment duration of up to 10 days.

Non-hospitalized patients:

The treatment course of VEKLURY should be initiated as soon as possible after diagnosis of symptomatic COVID-19 has been made and within 7 days of symptom onset.

- The recommended total treatment duration for non-hospitalized patients diagnosed with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, is 3 days.

Administer VEKLURY via intravenous infusion over 30 to 120 minutes.

For information on clinical trials that are testing the use of VEKLURY in COVID-19, please see www.clinicaltrials.gov.

AUTHORIZED USE

VEKLURY is a drug approved for the treatment of coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, 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 is not approved to treat 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.

VEKLURY is authorized for use under an EUA for the treatment of COVID-19 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, 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. Refer to CDC website² for additional details.

For more information, see the long version of the “Fact Sheet for Healthcare Providers,” available at <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization>.

Contraindications

VEKLURY is contraindicated in patients with a history of clinically significant hypersensitivity reactions to VEKLURY or any components of the product.

Dosing

Patient Selection and Treatment Initiation

- Patients with positive results of direct SARS-CoV-2 viral testing.
- The treatment course of VEKLURY should be initiated as soon as possible after diagnosis of symptomatic COVID-19 has been made and for non-hospitalized patients, within 7 days of symptom onset.
- Pediatric patients (greater than 28 days old) must have an estimated glomerular filtration rate (eGFR) determined and full-term neonates (at

² <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>. Healthcare providers should consider the benefit-risk for an individual patient.

least 7 days to less than or equal to 28 days old) must have serum creatinine determined before starting VEKLURY and be monitored during treatment as clinically appropriate.

- Perform hepatic laboratory testing in all patients before starting VEKLURY and during treatment as clinically appropriate.
- Determine prothrombin time in all patients before starting VEKLURY and monitor during treatment as clinically appropriate.
- **The only authorized dosage form of VEKLURY for 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 is VEKLURY for injection (supplied as 100 mg lyophilized powder in vial).**
- For pediatric patients weighing 3.5 kg to less than 40 kg, administer a body weight-based dosing regimen of VEKLURY.
- For pediatric patients less than 12 years of age and weighing 40 kg and higher, administer a single loading dose of VEKLURY 200 mg on Day 1 followed by once-daily maintenance doses of VEKLURY 100 mg from Day 2.
- Table 1 below provides the recommended dosage and dosage form in pediatric patients under this EUA [see Full EUA Prescribing Information, Recommended Dosage in Pediatric Patients (2.3)].

Table 1 Recommended Dosage Form and Dosage in Pediatric Patients

Body weight	Recommended dosage form	Loading dose (on Day 1)	Maintenance dose (from Day 2)
3.5 kg to less than 40 kg	VEKLURY for injection, lyophilized powder <u>Only</u>	5 mg/kg	2.5 mg/kg
40 kg and higher		200 mg	100 mg

Hospitalized patients:

The treatment course of VEKLURY should be initiated as soon as possible after diagnosis of symptomatic COVID-19 has been made.

- The recommended total treatment duration for hospitalized patients requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO) is 10 days.
- The recommended treatment duration for hospitalized patients not requiring invasive mechanical ventilation and/or ECMO is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days for a total treatment duration of up to 10 days.

Non-hospitalized patients:

The treatment course of VEKLURY should be initiated as soon as possible after diagnosis of symptomatic COVID-19 has been made and within 7 days of symptom onset.

- The recommended total treatment duration for non-hospitalized patients diagnosed with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, is 3 days.

VEKLURY for injection must be reconstituted and further diluted prior to intravenous infusion.

Renal Impairment

VEKLURY is not recommended in pediatric patients (greater than 28 days old) with eGFR less than 30 mL/min or in full-term neonates (at least 7 days to less than or equal to 28 days old) with serum creatinine greater than or equal to 1 mg/dL.

Dose Preparation

See the Full EUA Prescribing Information for complete dosage, preparation, and administration 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.

VEKLURY must be prepared and administered under the supervision of a healthcare provider. VEKLURY must be administered via intravenous infusion only. Do not administer by any other route.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Prior to dilution in a 0.9% sodium chloride infusion bag, reconstituted VEKLURY for injection should be a clear, colorless to yellow solution, free of visible particles. Discard the vial if the lyophilized powder or reconstituted solution is discolored or contains particulate matter.

Important Preparation and Administration Instructions

- **See the full EUA Prescribing Information for complete preparation and administration instructions.**
- **VEKLURY for Injection, 100 mg:** Reconstitute VEKLURY for injection lyophilized powder with 19 mL of Sterile Water for Injection and further dilute in 0.9% sodium chloride prior to administration.

- Only use Sterile Water for Injection to reconstitute VEKLURY lyophilized powder.
- After reconstitution, use vials immediately to prepare diluted solution. Administer diluted VEKLURY as an intravenous infusion over 30 to 120 minutes.
- Discard any remaining reconstituted VEKLURY lyophilized powder and diluted solution.

Storage and Handling of Reconstituted Vial and Diluted Solution

After reconstitution, use VEKLURY for injection vial immediately to prepare diluted solution.

Store diluted VEKLURY solution for infusion for no more than 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.

Warnings

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.

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 Full EUA Prescribing Information, Contraindications (4), Warnings and Precautions (5.1)*].

Increased Risk of Transaminase Elevations

Transaminase elevations have been observed in healthy volunteers who received 200 mg of VEKLURY followed by 100 mg doses 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, 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 [see *Full EUA Prescribing Information, Warnings and Precautions (5.2)*].

Perform hepatic laboratory testing in all patients before starting VEKLURY and during treatment 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.

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 *Full EUA Prescribing Information, Warnings and Precautions (5.3), Drug Interactions (10), Microbiology/Resistance Information (15)*].

Serious Side Effects

Serious adverse reactions have been associated with VEKLURY [see *Full EUA Prescribing Information, Overall Safety Summary (6.1)*].

Additional serious adverse reactions associated with the drug may become apparent with more widespread use.

INSTRUCTIONS FOR HEALTHCARE PROVIDERS

As the healthcare provider, you must communicate to the parent/caregiver and to your patient, as age appropriate, information consistent with the “Fact Sheet for Parents and Caregivers” (and provide a copy of the Fact Sheet) prior to the pediatric patient receiving VEKLURY, including:

- That FDA has authorized the emergency use of VEKLURY for the treatment of coronavirus disease 2019 (COVID-19) 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, 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.

- The parent/caregiver has the option to accept or refuse VEKLURY.
- The significant known and potential risks and benefits of VEKLURY, and the extent to which such risks and benefits are unknown.
- Information on available alternative treatments and the risks and benefits of those alternatives.

If providing this information will delay the administration of VEKLURY to a degree that would endanger the lives of patients, the information must be provided to the parent/caregiver as soon as feasible after VEKLURY is administered.

For information on clinical trials that are testing the use of VEKLURY for COVID-19, please see www.clinicaltrials.gov.

MANDATORY REQUIREMENTS FOR VEKLURY ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION:

In order to mitigate the risks of using this product under EUA and to optimize the potential benefit of VEKLURY for this use, the following items are required. Use of VEKLURY under this EUA is limited to the following (all requirements **must** be met):

1. VEKLURY is authorized for the treatment of COVID-19 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, 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. Please refer to CDC website³ for additional details.
2. As the healthcare provider, communicate to the parent/caregiver and your patient, as age appropriate, information consistent with the “Fact Sheet for Parents and Caregivers” prior to the patient receiving VEKLURY. Healthcare providers (to the extent practicable given the circumstances of the emergency) must document in the patient’s medical record that the parent/caregiver has been:
 - Given the “Fact Sheet for Parents and Caregivers,”
 - Informed of alternatives to receiving VEKLURY, and
 - Informed that VEKLURY is an approved drug that is authorized for this unapproved use under EUA.
3. Pediatric patients (greater than 28 days old) must have an 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 starting VEKLURY and monitored during treatment as clinically appropriate.

³ <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>. Healthcare providers should consider the benefit-risk for an individual patient.

4. Perform hepatic laboratory testing in all patients before starting VEKLURY and during treatment as clinically appropriate.
5. Determine prothrombin time in all patients before starting VEKLURY and monitor during treatment as clinically appropriate.
6. Patients with known hypersensitivity to any ingredient of VEKLURY must not receive VEKLURY.
7. The prescribing healthcare provider and/or the provider's designee are/is responsible for mandatory reporting of all serious adverse events* and medication errors potentially related to VEKLURY within 7 calendar days from the healthcare provider's awareness of the event, using FDA Form 3500 (for information on how to access this form, see below). The FDA requires that such reports, using FDA Form 3500, include the following:
 - Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race)
 - A statement "Veklury (remdesivir) use for COVID-19 under Emergency Use Authorization (EUA)" under the **"Describe Event, Problem, or Product Use/Medication Error"** heading
 - Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes).
 - Patient's preexisting medical conditions and use of concomitant products
 - Information about the product (e.g., dosage, route of administration, NDC #).

Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:

- Complete and submit the report online:
www.fda.gov/medwatch/report.htm
- Complete and submit a postage-paid FDA Form 3500 (<https://www.fda.gov/media/76299/download>) and return by:
 - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
 - Fax to 1-800-FDA-0178, or
- Call 1-800-FDA-1088 to request a reporting form

In addition, please provide a copy of all FDA MedWatch forms to:

Gilead Global Patient Safety

Fax: 1-650-522-5477

E-mail: Safety_fc@gilead.com

Or call Gilead at 1-800-GILEAD-5 to report adverse events

8. The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of VEKLURY.

*Serious Adverse Events are defined as:

- death;
- a life-threatening adverse event;
- inpatient hospitalization or prolongation of existing hospitalization;
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- a congenital anomaly/birth defect;
- a medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly.

APPROVED AVAILABLE ALTERNATIVES

There is no approved available alternative product for the treatment of COVID-19 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.

There are EUAs for other COVID-19 treatments. Additional information on COVID-19 treatments can be found at <https://www.covid19treatmentguidelines.nih.gov/>. The healthcare provider should visit <https://clinicaltrials.gov/> to determine whether the patient may be eligible for enrollment in a clinical trial.

AUTHORITY FOR ISSUANCE OF THE EUA

The Secretary of HHS has declared that circumstances exist that justify the emergency use of drugs and biological products during the COVID-19 pandemic. In response, the FDA has issued an EUA for the approved product, VEKLURY, for the unapproved use to treat COVID-19 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 are⁴:

- Hospitalized, or

⁴ The healthcare provider should visit clinicaltrials.gov to determine whether there is an active clinical trial for the product in this disease/condition and whether enrollment of the patient(s) in a clinical trial is more appropriate than product use under this EUA.

- Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death. Please refer to CDC website⁵ for additional details.

FDA has issued this EUA, requested by Gilead Sciences, Inc. and based on their submitted data. As a healthcare provider, you must comply with the mandatory requirements of the EUA (see above).

Although limited scientific information is available in the pediatric population, based on the totality of the scientific evidence available to date, it is reasonable to believe that VEKLURY may be effective for the treatment of COVID-19 in pediatric patients as specified in this Fact Sheet. You may be contacted and asked to provide information to help with the assessment of the use of the product during this emergency.

This EUA for VEKLURY will end when the Secretary determines that the circumstances justifying the EUA no longer exist or when there is a change in the approval status of the product such that an EUA is no longer needed.

⁵ <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>. Healthcare providers should consider the benefit-risk for an individual patient.

FULL EUA PRESCRIBING INFORMATION

FULL EUA PRESCRIBING INFORMATION: CONTENTS*

1 AUTHORIZED USE

2 DOSAGE AND ADMINISTRATION

- 2.1 Dosage and Administration Overview
- 2.2 Important Testing Before and During Treatment
- 2.3 Recommended Dosage in Pediatric Patients
- 2.4 Renal Impairment
- 2.5 Dose Preparation and Administration, VEKLURY for Injection
- 2.6 Storage of Prepared Dosages

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Hypersensitivity Including Infusion-Related and Anaphylactic Reactions
- 5.2 Increased Risk of Transaminase Elevations
- 5.3 Risk of Reduced Antiviral Activity When Coadministered with Chloroquine Phosphate or Hydroxychloroquine Sulfate

6 OVERALL SAFETY SUMMARY

- 6.1 Clinical Trials Experience

7 PATIENT MONITORING RECOMMENDATIONS

8 ADVERSE REACTIONS AND MEDICATION

ERRORS REPORTING REQUIREMENTS AND INSTRUCTIONS

9 OTHER REPORTING REQUIREMENTS

10 DRUG INTERACTIONS

11 USE IN SPECIFIC POPULATIONS

- 11.1 Pregnancy
- 11.2 Lactation
- 11.3 Pediatric Use
- 11.4 Renal Impairment
- 11.5 Hepatic Impairment

12 OVERDOSAGE

13 PRODUCT DESCRIPTION

- 13.1 Physical Appearance
- 13.2 Inactive Ingredients

14 CLINICAL PHARMACOLOGY

- 14.1 Mechanism of Action
- 14.2 Pharmacokinetics

15 MICROBIOLOGY/RESISTANCE INFORMATION

16 NONCLINICAL TOXICOLOGY

17 ANIMAL PHARMACOLOGIC AND EFFICACY DATA

18 CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

19 HOW SUPPLIED/STORAGE AND HANDLING

20 PATIENT COUNSELING INFORMATION

21 CONTACT INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

1. AUTHORIZED USE

VEKLURY is authorized for use under an EUA for the treatment of coronavirus disease 2019 (COVID-19) 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 severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, 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. Refer to CDC website⁶ for additional details.

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 *Warnings and Precautions* (5.1)].

⁶ <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html>. Healthcare providers should consider the benefit-risk for an individual patient.

- Administer VEKLURY by intravenous infusion only. Do not administer by any other route.

2.2 Important Testing Before and During Treatment

- Pediatric patients (greater than 28 days old) must have an 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 starting VEKLURY and during treatment as clinically appropriate [see *Dosage and Administration (2.4)*, *Use in Specific Populations (11.4)*].
- Perform hepatic laboratory testing in all patients before starting VEKLURY and during treatment as clinically appropriate [see *Warnings and Precautions (5.2)*, *Use in Specific Populations (11.5)*].
- Determine prothrombin time in all patients before starting VEKLURY and monitor during treatment as clinically appropriate [see *Overall Safety Summary (6.1)*].

2.3 Recommended Dosage in Pediatric Patients

The only authorized dosage form of VEKLURY for 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 is VEKLURY for injection (supplied as 100 mg lyophilized powder in vial).

For pediatric patients weighing 3.5 kg to less than 40 kg, administer a body weight-based dosing regimen of VEKLURY via intravenous (IV) infusion. The dosage should be calculated using the mg/kg dose according to the patient's weight.

For pediatric patients less than 12 years of age and weighing 40 kg and higher, administer a single loading dose of VEKLURY 200 mg on Day 1 followed by once-daily maintenance doses of VEKLURY 100 mg from Day 2.

Refer to Table 1 below for recommended dosage form and dosage in pediatric patients according to weight [see *Dosage and Administration (2.5)*, *Use in Specific Populations (11.3)*].

Table 1 Recommended Dosage Form and Dosage in Pediatric Patients

Body weight	Recommended dosage form	Loading dose (on Day 1)	Maintenance dose (from Day 2)
3.5 kg to less than 40 kg	VEKLURY Lyophilized Powder for Injection <u>Only</u>	5 mg/kg	2.5 mg/kg
40 kg and higher		200 mg	100 mg

Hospitalized patients:

The treatment course of VEKLURY should be initiated as soon as possible after diagnosis of symptomatic COVID-19 has been made.

- The recommended total treatment duration for hospitalized patients requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO) is 10 days.
- The recommended treatment duration for hospitalized patients not requiring invasive mechanical ventilation and/or ECMO is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days for a total treatment duration of up to 10 days.

Non-hospitalized patients:

The treatment course of VEKLURY should be initiated as soon as possible after diagnosis of symptomatic COVID-19 has been made and within 7 days of symptom onset.

- The recommended total treatment duration for non-hospitalized patients diagnosed with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, is 3 days.

VEKLURY for injection must be reconstituted and further diluted prior to administration via intravenous infusion.

2.4 Renal Impairment

VEKLURY is not recommended in pediatric patients (greater than 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.

2.5 Dose Preparation and Administration, VEKLURY for Injection

The authorized dosage form of VEKLURY for 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 is VEKLURY for injection (supplied as 100 mg lyophilized powder) only.

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard the vial if the lyophilized powder is discolored or contains particulate matter. Prior to dilution in 0.9% sodium chloride, reconstituted VEKLURY for injection should be a clear, colorless to yellow solution, free of visible particles.
- **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.

Reconstitution Instructions

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

- Aseptically reconstitute VEKLURY lyophilized powder by addition of 19 mL of Sterile Water for Injection using a suitably sized syringe and needle per vial.
- Only use Sterile Water for Injection to reconstitute VEKLURY lyophilized powder.
- Discard the vial if a vacuum does not pull the Sterile Water for Injection into the vial.
- Immediately shake the vial for 30 seconds.
- Allow the contents of the vial to settle for 2 to 3 minutes. A clear, 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 VEKLURY for injection immediately to prepare the diluted solution.

Dilution and Administration Instructions, Pediatric Patients Weighing 3.5 kg to Less Than 40 kg

Dilution Instructions

- For pediatric patients weighing 3.5 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.
- 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 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.
- Refer to Table 2 for recommended rate of infusion.

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 or empty) to prepare VEKLURY diluted solution.
- If using a prefilled 0.9% sodium chloride 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 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 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 [68°F to 77°F]) or 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

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 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 the diluted solution with the infusion rate described in Table 2.

Table 2 Recommended Rate of Infusion—Diluted VEKLURY for Injection Lyophilized Powder for Pediatric Patients Weighing 3.5 kg to Less Than 40 kg

Infusion volume	Infusion time	Rate of infusion^a
100 mL	30 min	3.33 mL/min
	60 min	1.67 mL/min
	120 min	0.83 mL/min
50 mL	30 min	1.67 mL/min
	60 min	0.83 mL/min
	120 min	0.42 mL/min
25 mL	30 min	0.83 mL/min
	60 min	0.42 mL/min
	120 min	0.21 mL/min
7 mL	30 min	0.23 mL/min
	60 min	0.12 mL/min
	120 min	0.06 mL/min

a. Note: Rate of infusion may be adjusted based on total volume to be infused.

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.

Dilution and Administration Instructions, Pediatric Patients Less Than 12 Years of Age and Weighing 40 kg and Higher

Dilution Instructions

For pediatric patients less than 12 years of age and weighing 40 kg and higher, refer to the dilution instructions in Table 3.

Table 3 Recommended Dilution Instructions Using Reconstituted VEKLURY for Injection Lyophilized Powder in Pediatric Patients Less Than 12 Years of Age and Weighing 40 kg and Higher

VEKLURY dose	0.9% sodium chloride infusion bag volume to be used	Volume to be withdrawn and discarded from 0.9% sodium chloride 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 from the infusion bag following instructions in Table 3, using an appropriately sized syringe and needle.
- Withdraw the required volume of reconstituted VEKLURY for injection from the VEKLURY vial following instructions in Table 3. 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 diluted solution is stable for 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]).

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 the diluted solution with the infusion rate described in Table 4.

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

on the intracellular metabolic activation and antiviral activity of VEKLURY [see *Drug Interactions (10), Microbiology/Resistance Information (15)*].

6. OVERALL SAFETY SUMMARY

Completion of FDA MedWatch Form to report all medication errors and adverse events occurring during VEKLURY treatment is mandatory. Please see the ADVERSE REACTIONS AND MEDICATION ERRORS REPORTING REQUIREMENTS AND INSTRUCTIONS section below for details on FDA MedWatch reporting.

6.1 Clinical Trials Experience

The safety of VEKLURY is based on data from three Phase 3 studies in 1,313 hospitalized adult subjects with COVID-19, one Phase 3 study in 279 non-hospitalized adult and pediatric subjects (12 years of age and older weighing at least 40 kg) with mild-to-moderate COVID-19, from four Phase 1 studies in 131 healthy adults, and from adult patients with COVID-19 who received VEKLURY under the Emergency Use Authorization or in a compassionate use program.

NIAID ACTT-1 was a randomized, double-blind, placebo-controlled clinical trial in hospitalized adult 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. 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 (\geq Grade 3), serious adverse reactions, and adverse reactions leading to treatment discontinuation are presented in Table 5.

Table 5 Summary of Adverse Reaction Rates in Hospitalized Adult 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 \geq 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 adult 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. 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 reaction, serious adverse reactions, and adverse reactions leading to treatment discontinuation are presented in Table 6.

Table 6 Summary of Adverse Reaction Rates in Hospitalized Adult 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 adult 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). 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 reaction, serious adverse reactions, and adverse reactions leading to treatment discontinuation are presented in Table 7.

Table 7 Summary of Adverse Reaction^a Rates in Hospitalized Adult 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 Trial Results and Supporting Data for EUA (18)*]. 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

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

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

Emergency Use Authorization Experience in Subjects with COVID-19

The following adverse reactions have been identified during use of VEKLURY primarily in adult subjects under Emergency Use Authorization:

- 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

Laboratory Abnormalities

Study GS-US-399-5505 was a Phase 1, randomized, blinded, placebo-controlled clinical trial in healthy adult 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 adult subjects with COVID-19 receiving VEKLURY in Trials NIAID ACTT-1, 5773, and 5774 are presented in Table 8, Table 9, and Table 10, respectively.

Table 8 Laboratory Abnormalities (Grades 3-4) Reported in $\geq 3\%$ of Hospitalized Adult 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 9 Laboratory Abnormalities (Grades 3-4) Reported in ≥3% of Hospitalized Adult 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 10 Laboratory Abnormalities (Grades 3-4) Reported in ≥3% of Hospitalized Adult 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 11.

Table 11 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.

7. PATIENT MONITORING RECOMMENDATIONS

Patients should have appropriate clinical and laboratory monitoring to aid in early detection of any potential adverse events while receiving VEKLURY [see *Dosage and Administration* (2.2, 2.4)].

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.

Additionally, completion of FDA MedWatch Form to report all medication errors and serious adverse events is mandatory.

For mandatory reporting requirements, please see “**MANDATORY REQUIREMENTS FOR VEKLURY ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION**” above.

8. ADVERSE REACTIONS AND MEDICATION ERRORS REPORTING REQUIREMENTS AND INSTRUCTIONS

See Overall Safety Summary (Section 6) for additional information.

The prescribing healthcare provider and/or the provider’s designee are/is responsible for the mandatory reporting of all serious adverse events* and medication errors potentially related to VEKLURY within 7 calendar days from the healthcare provider’s awareness of the event, using FDA Form 3500 (for information on how to access this form, see below). The FDA requires that such reports, using FDA Form 3500, include the following:

- Patient demographics and baseline characteristics (e.g., patient identifier, age or date of birth, gender, weight, ethnicity, and race)

- A statement "Veklury (remdesivir) use for COVID-19 under Emergency Use Authorization (EUA)" under the "**Describe Event, Problem, or Product Use/Medication Error**" heading
- Information about the serious adverse event or medication error (e.g., signs and symptoms, test/laboratory data, complications, timing of drug initiation in relation to the occurrence of the event, duration of the event, treatments required to mitigate the event, evidence of event improvement/disappearance after stopping or reducing the dosage, evidence of event reappearance after reintroduction, clinical outcomes)
- Patient's preexisting medical conditions and use of concomitant products
- Information about the product (e.g., dosage, route of administration, NDC #).

Submit adverse event and medication error reports, using Form 3500, to FDA MedWatch using one of the following methods:

- Complete and submit the report online:
www.fda.gov/medwatch/report.htm
- Complete and submit a postage-paid FDA Form 3500 (<https://www.fda.gov/media/76299/download>) and return by:
 - Mail to MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787, or
 - Fax to 1-800-FDA-0178, or
- Call 1-800-FDA-1088 to request a reporting form

The prescribing healthcare provider and/or the provider's designee is/are responsible for mandatory responses to requests from FDA for information about adverse events and medication errors following receipt of VEKLURY.

*Serious adverse events are defined as:

- Death or a life-threatening adverse event;
- A medical or surgical intervention to prevent death, a life-threatening event, hospitalization, disability, or congenital anomaly;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
- A congenital anomaly/birth defect.

IMPORTANT: When reporting adverse events or medication errors to MedWatch, please complete the entire form with detailed information. It is important that the information reported to FDA be as detailed and complete as possible. Information to include:

- Patient demographics (e.g., patient initials, date of birth)
- Pertinent medical history
- Pertinent details regarding admission and course of illness
- Concomitant medications

- Timing of adverse event(s) in relationship to administration of VEKLURY
- Pertinent laboratory and virology information
- Outcome of the event and any additional follow-up information if it is available at the time of the MedWatch report. Subsequent reporting of follow-up information should be completed if additional details become available.

The following steps are highlighted to provide the necessary information for safety tracking:

- In section A, box 1, provide the patient's initials in the Patient Identifier
- In section A, box 2, provide the patient's date of birth
- In section B, box 5, description of the event:
 - Write "Veklury (remdesivir) use for COVID-19 under Emergency Use Authorization (EUA)" as the first line
 - Provide a detailed report of medication error and/or adverse event. It is important to provide detailed information regarding the patient and adverse event/medication error for ongoing safety evaluation of this unapproved drug. Please see information to include listed above.
- In section G, box 1, name and address:
 - Provide the name and contact information of the prescribing healthcare provider or institutional designee who is responsible for the report.
 - Provide the address of the treating institution (NOT the healthcare provider's office address).

9. OTHER REPORTING REQUIREMENTS

In addition, please provide a copy of all FDA MedWatch forms to:

Gilead Global Patient Safety

Fax: 1-650-522-5477

E-mail: Safety_fc@gilead.com

Or call Gilead at 1-800-GILEAD-5 to report adverse events

10. 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), Microbiology/Resistance Information (15)*].

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

In vitro, remdesivir is a substrate for drug metabolizing enzyme CYP3A4, and is a substrate for Organic Anion Transporting Polypeptides 1B1 (OATP1B1) and P-glycoprotein (P-gp) transporters. In vitro, remdesivir is an inhibitor of CYP3A4, OATP1B1, OATP1B3, and MATE1. GS-704277 is a substrate for OATP1B1 and OATP1B3. The clinical relevance of these in vitro assessments has not been established.

Remdesivir is not a substrate for CYP1A1, 1A2, 2B6, 2C9, 2C19, or OATP1B3. GS-704277 and GS-441524 are not substrates for CYP1A1, 1A2, 2B6, 2C8, 2C9, 2D6, or 3A5. GS-441524 is also not a substrate for CYP2C19 or 3A4. GS-704277 and GS 441524 are not substrates for OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2K. GS 441524 is also not a substrate for OATP1B1 or OATP1B3.

11. USE IN SPECIFIC POPULATIONS

11.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to VEKLURY during pregnancy. Pregnant and recently pregnant individuals can go to <https://covid-pr.pregistry.com> to enroll or call 1-800-616-3791 to obtain information about the registry.

Risk Summary

Available data from published case reports and compassionate use of remdesivir in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In nonclinical reproductive toxicity studies, remdesivir demonstrated no adverse effect on embryo-fetal development when administered to pregnant animals at systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) that were 4 times (rats and rabbits) the exposure in humans at the recommended human dose (RHD) (see *Data*). There are maternal and fetal risks associated with untreated COVID-19 in pregnancy (see *Clinical Considerations*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo-fetal risk

COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

Animal Data

Remdesivir was administered via intravenous injection to pregnant rats and rabbits (up to 20 mg/kg/day) on Gestation Days 6 through 17, and 7 through 20, respectively, and also to rats from Gestation Day 6 to Lactation/Post-partum Day

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)].

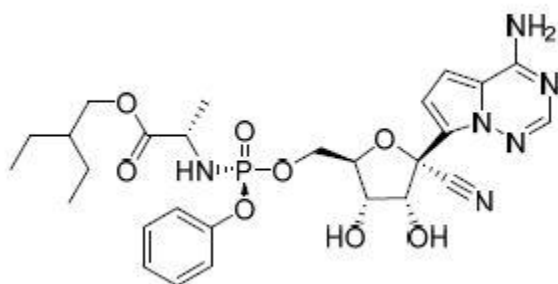
Perform hepatic laboratory testing in all patients before starting VEKLURY and during treatment as clinically appropriate [see *Dosage and Administration* (2.2)].

12. OVERDOSAGE

There is no human experience of acute overdose 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-altronitril-6-O-yl]phenoxyphosphoryl}-L-alaninate. It has a molecular formula of C₂₇H₃₅N₆O₈P 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 carboxylesterase 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 IC₅₀ 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

- 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.
- Range of protein binding for remdesivir from 2 independent experiments show no evidence of concentration-dependent protein binding for remdesivir.
- Median (Study GS-US-399-4231).
- Mean (Study GS-US-399-4231).

Table 13 Multiple Dose PK Parameters^a of Remdesivir and Metabolites (GS-441524 and GS-704277) Following IV Administration of VEKLURY 100 mg to Healthy Adults

Parameter Mean (CV%)	Remdesivir	GS-441524	GS-704277
C_{max} (nanogram per mL)	2229 (19.2)	145 (19.3)	246 (33.9)
AUC_{tau} (nanogram•h per mL)	1585 (16.6)	2229 (18.4)	462 (31.4)
C_{trough} (nanogram per mL)	ND	69.2 (18.2)	ND

CV=Coefficient of Variation; ND=Not detectable (at 24 hours post-dose)

a. Remdesivir administered as a 30-minute IV infusion (Study GS-US-399-5505).

Specific Populations

Pharmacokinetic differences based on sex, race, and age have not been evaluated.

The pharmacokinetics of VEKLURY in pediatric patients have not been evaluated.

Using modeling and simulation, the recommended dosing regimen is expected to result in comparable steady-state plasma exposures of remdesivir and metabolites 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 as observed in healthy adults.

15. MICROBIOLOGY/RESISTANCE INFORMATION

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 (EC₅₀) 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 EC₅₀ values of 280 nM after 72 hours of treatment and 115 nM after 48 hours of treatment, respectively.

Remdesivir EC₅₀ 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 EC₅₀ 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 plaque assay and/or N protein ELISA assay, remdesivir retained similar antiviral activity (≤ 1.5 -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), Delta (B.1.617.2), Gamma (P.1), and Epsilon (B.1.429) variants compared to earlier lineage SARS-CoV-2 (lineage A) isolates.

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

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, S759A, 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 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. 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.

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 EC₅₀ value.

16. NONCLINICAL TOXICOLOGY

Carcinogenesis

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.

Mutagenesis

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 intravenous daily 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.

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.

17. ANIMAL PHARMACOLOGIC AND EFFICACY DATA

- Remdesivir exhibited cell culture antiviral activity against a clinical isolate of SARS-CoV-2 in primary HAE cells (EC₅₀ value= 9.9 nM) after 48 hours of treatment. Remdesivir inhibited the replication of SARS-CoV-2 in the continuous human lung epithelial cell line Calu-3 with an EC₅₀ value of 280 nM after 72 hours of treatment.
- Remdesivir showed antiviral activity in SARS-CoV-2-infected rhesus monkeys. Administration of remdesivir at 10/5 mg/kg (10 mg/kg first dose, followed by 5 mg/kg once daily thereafter) using IV bolus injection initiated 12 hours post-inoculation with SARS-CoV-2 resulted in a reduction in clinical signs of respiratory disease, lung pathology and gross lung lesions, and lung viral RNA levels compared with vehicle-treated animals.

18. CLINICAL TRIAL RESULTS AND SUPPORTING DATA FOR EUA

VEKLURY is an antiviral drug with available data from four randomized clinical trials in adult patients with COVID-19. VEKLURY is approved for use to treat COVID-19 in adults and pediatric patients 12 years of age and older and weighing at least 40 kg. VEKLURY is not approved for use 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.

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

A randomized, double-blind, placebo-controlled clinical trial (ACTT-1, NCT04280705) 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 SpO₂ >94% and respiratory rate <24 breaths/minute without supplemental oxygen; severe disease was defined as an SpO₂ ≤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, SpO₂ ≤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). Subjects in this trial were unvaccinated. 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.

Overall, the odds of improvement in the ordinal scale were higher in the VEKLURY group at Day 15 when compared to the placebo group (odds ratio 1.54 [95% CI 1.25 to 1.91]).

Overall, 29-day mortality was 11% for the VEKLURY group vs 15% for the placebo group (hazard ratio 0.73 [95% CI 0.52 to 1.03]).

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

A randomized, open-label multi-center clinical trial (Study 5773, NCT04292899) in adult subjects with confirmed SARS-CoV-2 infection, an SpO₂ of $\leq 94\%$ 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.

Study GS-US-540-5774 in Hospitalized Subjects with Moderate COVID-19

A randomized, open-label multi-center clinical trial (Study 5774, NCT04292730) of hospitalized adult subjects with confirmed SARS-CoV-2 infection, SpO₂ >94% and radiological evidence of pneumonia compared treatment with VEKLURY for 5 days (n=191) and treatment with VEKLURY for 10 days (n=193) with standard of care (n=200). Treatment with VEKLURY was stopped in subjects who were discharged from the hospital prior to completion of their protocol-defined duration of treatment. Subjects treated with VEKLURY received 200 mg on Day 1 and 100 mg once daily on subsequent days via intravenous infusion.

At baseline, the median age of subjects was 57 years (range, 12 to 95 years); 61% were male, 61% were White, 19% were Black, and 19% were Asian; 18% were Hispanic or Latino. Subjects in this trial were unvaccinated. Baseline clinical status, oxygen support status, and 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 11 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, the odds of improvement in the ordinal scale were higher in the 5-day VEKLURY group at Day 11 when compared to those receiving only standard of care (odds ratio 1.65 [95% CI 1.09 to 2.48], $p=0.017$). The odds of improvement in clinical status with the 10-day treatment group when compared to those receiving only standard of care were not statistically significant (odds ratio 1.31 [95% CI 0.88 to 1.95]). All-cause mortality at Day 28 was $\leq 2\%$ in all treatment groups.

Study GS-US-540-9012 in Non-Hospitalized Subjects with Mild-to-Moderate COVID-19 and at High Risk for Progression to Severe Disease

A randomized, double-blind, placebo-controlled, clinical trial (Study 9012, NCT04501952) evaluated VEKLURY 200 mg once daily for 1 day followed by VEKLURY 100 mg once daily for 2 days (for a total of 3 days of intravenously administered therapy) in 554 adult and 8 pediatric subjects (12 years of age and older and weighing at least 40 kg) who were non-hospitalized, had mild-to-moderate COVID-19, 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. Risk factors for progression to hospitalization included age ≥ 60 years, obesity (BMI ≥ 30), chronic lung disease, hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, immunocompromised state, chronic mild or moderate kidney disease, chronic liver disease, current cancer, and sickle cell disease. Subjects who received, required, or were expected to require supplemental oxygen were excluded from the trial. Subjects were randomized in a 1:1 manner, stratified by residence in a skilled nursing facility (yes/no), age (<60 vs ≥ 60 years), and region (US vs ex-US) to receive VEKLURY ($n=279$) or placebo ($n=283$), plus standard of care.

At baseline, mean age was 50 years (with 30% of 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/m². Subjects in this trial were unvaccinated. VEKLURY or placebo was first administered to subjects in outpatient facilities (84%), home healthcare settings (13%), or skilled nursing facilities (3%). 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 log₁₀

copies/mL at baseline. The baseline demographics and disease characteristics were well balanced across the VEKLURY and placebo treatment groups.

The primary endpoint was the proportion of subjects with COVID-19 related hospitalization (defined as at least 24 hours of acute care) or all-cause mortality through Day 28. Events occurred in 2 (0.7%) subjects treated with VEKLURY compared to 15 (5.3%) subjects concurrently randomized to placebo (hazard ratio 0.134 [95% CI 0.031 to 0.586]; p=0.0076). No deaths were observed through Day 28.

19. 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)*].

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. This product contains no preservative; therefore, partially used vials should be discarded [see *Dosage and Administration (2.6)*].

Store VEKLURY for injection, 100 mg, vials below 30°C (below 86°F) 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 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.

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

© 2022 Gilead Sciences, Inc. All rights reserved.

Revised: 01/2022

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VEKLURY safely and effectively. See full prescribing information for VEKLURY.

VEKLURY® (remdesivir) for injection, for intravenous use
VEKLURY® (remdesivir) injection, for intravenous use
Initial U.S. Approval: 2020

RECENT MAJOR CHANGES

Indications and Usage (1)	01/2022
Dosage and Administration	01/2022
Dosage and Administration Overview (2.1)	01/2022
Recommended Dosage in Adults and Pediatric Patients 12 Years of Age and Older and Weighing at Least 40 kg (2.3)	01/2022
Dosage Preparation and Administration (2.5)	01/2022
Warnings and Precautions, Hypersensitivity Including Infusion-related and Anaphylactic Reactions (5.1)	01/2022

INDICATIONS AND USAGE

VEKLURY is a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, 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. (1)

DOSAGE AND ADMINISTRATION

- Testing: In all patients, before starting VEKLURY and during treatment as clinically appropriate, perform renal and hepatic laboratory testing. Assess prothrombin time before starting VEKLURY and monitor as clinically appropriate. (2.2)
- Recommended dosage in adults and pediatric patients 12 years of age and older and weighing at least 40 kg: a single loading dose of VEKLURY 200 mg on Day 1 followed by once-daily maintenance doses of VEKLURY 100 mg from Day 2 via intravenous infusion. The treatment course of VEKLURY should be initiated as soon as possible after diagnosis of symptomatic COVID-19 has been made. (2.3)
- For hospitalized patients requiring invasive mechanical ventilation and/or ECMO, the recommended total treatment duration is 10 days. (2.3)
- For hospitalized patients not requiring invasive mechanical ventilation and/or ECMO, the recommended treatment duration is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days for a total treatment duration of up to 10 days. (2.3)
- For non-hospitalized patients diagnosed with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, the recommended total treatment duration is 3 days (2.3).
- Administer VEKLURY via intravenous (IV) infusion over 30 to 120 minutes. (2.5)
- Renal impairment: VEKLURY is not recommended in patients with eGFR less than 30 mL/min. (2.4)

- Dose preparation and administration: Refer to the full prescribing information for further details for both formulations. (2.5)
- Storage of prepared dosages: VEKLURY contains no preservative. (2.6)

DOSAGE FORMS AND STRENGTHS

- For injection: 100 mg of remdesivir as a lyophilized powder, in a single-dose vial. (3)
- Injection: 100 mg/20 mL (5 mg/mL) remdesivir, in a single-dose vial. (3)

CONTRAINDICATIONS

VEKLURY is contraindicated in patients with a history of clinically significant hypersensitivity reactions to VEKLURY or any components of the product. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity including infusion-related and anaphylactic reactions: Hypersensitivity reactions have been observed during and following administration of VEKLURY. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent signs and symptoms of hypersensitivity. 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. (5.1)
- Increased risk of transaminase elevations: Transaminase elevations have been observed in healthy volunteers and have also been reported in patients with COVID-19 who received VEKLURY. 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. (5.2)
- 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. (5.3)

ADVERSE REACTIONS

The most common adverse reactions (incidence greater than or equal to 5%, all grades) observed with treatment with VEKLURY are nausea, ALT increased, and AST increased. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 01/2022

FULL PRESCRIBING INFORMATION: CONTENTS***1 INDICATIONS AND USAGE****2 DOSAGE AND ADMINISTRATION**

- 2.1 Dosage and Administration Overview
- 2.2 Testing Before Starting and During Treatment with VEKLURY
- 2.3 Recommended Dosage in Adults and Pediatric Patients 12 Years of Age and Older and Weighing at Least 40 kg
- 2.4 Renal Impairment
- 2.5 Dosage Preparation and Administration
- 2.6 Storage of Prepared Dosages

3 DOSAGE FORMS AND STRENGTHS**4 CONTRAINDICATIONS****5 WARNINGS AND PRECAUTIONS**

- 5.1 Hypersensitivity Including Infusion-related and Anaphylactic Reactions
- 5.2 Increased Risk of Transaminase Elevations
- 5.3 Risk of Reduced Antiviral Activity When Coadministered with Chloroquine Phosphate or Hydroxychloroquine Sulfate

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience

7 DRUG INTERACTIONS**8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use

- 8.5 Geriatric Use

- 8.6 Renal Impairment

- 8.7 Hepatic Impairment

10 OVERDOSAGE**11 DESCRIPTION****12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.4 Microbiology

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

- 14.1 NIAID ACTT-1 Study in Hospitalized Subjects with Mild/Moderate and Severe COVID-19
- 14.2 Study GS-US-540-5773 in Hospitalized Subjects with Severe COVID-19
- 14.3 Study GS-US-540-5774 in Hospitalized Subjects with Moderate COVID-19
- 14.4 Study GS-US-540-9012 in Non-Hospitalized Subjects with Mild-to-Moderate COVID-19 and at High Risk for Progression to Severe Disease

16 HOW SUPPLIED/STORAGE AND HANDLING**17 PATIENT COUNSELING INFORMATION**

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

VEKLURY is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are [see *Clinical Studies (14)*]:

- 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.

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 *Warnings and Precautions (5.1)*].
- Administer VEKLURY for the treatment of COVID-19 in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) by intravenous infusion only. Do not administer by any other route.
- There are TWO different formulations of VEKLURY:
 - VEKLURY for injection (supplied as 100 mg lyophilized powder in vial) must be reconstituted with Sterile Water for Injection prior to diluting in a 100 mL or 250 mL 0.9% sodium chloride infusion bag.
 - VEKLURY injection (supplied as 100 mg/20 mL [5 mg/mL] solution in vial) must be diluted in a 250 mL 0.9% sodium chloride infusion bag.
- There are differences in the way the two formulations are prepared. Carefully follow the product-specific preparation instructions below [see *Dosage and Administration (2.5)*].

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 (8.4, 8.6)*].

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 (8.7)*].

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 and Pediatric Patients 12 Years of Age and Older and Weighing at Least 40 kg

The recommended dosage for adults and pediatric patients 12 years of age and older and 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.

Hospitalized patients:

The treatment course of VEKLURY should be initiated as soon as possible after diagnosis of symptomatic COVID-19 has been made.

- The recommended total treatment duration for hospitalized patients requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO) is 10 days.
- The recommended treatment duration for hospitalized patients not requiring invasive mechanical ventilation and/or ECMO is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days for a total treatment duration of up to 10 days.

Non-hospitalized patients:

The treatment course of VEKLURY should be initiated as soon as possible after diagnosis of symptomatic COVID-19 has been made and within 7 days of symptom onset.

- The recommended total treatment duration for non-hospitalized patients diagnosed with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death, is 3 days.

VEKLURY must be diluted prior to intravenous infusion. Refer to Dosage and Administration (2.5) 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 (8.6)*].

2.5 Dosage Preparation and Administration

There are differences in the way the two formulations are prepared. Carefully follow the product-specific preparation instructions below.

VEKLURY for Injection (Supplied as 100 mg Lyophilized Powder in Vial)

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 (2.5)*].

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 infusion bag. Refer to Table 1 for instructions.

Table 1 Recommended Dilution Instructions—Reconstituted VEKLURY for Injection Lyophilized Powder

VEKLURY dose	0.9% sodium chloride infusion bag volume to be used	Volume to be withdrawn and discarded from 0.9% sodium chloride 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 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 [68°F to 77°F]) or 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

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 2.

Table 2 Recommended Rate of Infusion—Diluted VEKLURY for Injection Lyophilized Powder in Adults and Pediatric Patients 12 Years of Age and Older and 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

VEKLURY Injection (Supplied as 100 mg/20 mL [5 mg/mL] Solution in Vial)

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.

- Remove the required number of single-dose vial(s) from storage. Each vial contains 100 mg/20 mL of remdesivir. For each vial:

- Equilibrate to room temperature (20°C to 25°C [68°F to 77°F]). Sealed vials can be stored up to 12 hours at room temperature prior to dilution.
- Inspect the vial to ensure the container closure is free from defects and the solution is free of particulate matter.
- VEKLURY injection must be diluted in an infusion bag containing 250 mL of 0.9% sodium chloride only. Refer to Table 3 for instructions.

Table 3 Recommended Dilution Instructions—VEKLURY Injection (Supplied as Solution in Vial)

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

- Withdraw and discard the required volume of 0.9% sodium chloride from the bag following instructions in Table 3, using an appropriately sized syringe and needle.
- Withdraw the required volume of VEKLURY injection from the VEKLURY vial following instructions in Table 3, using an appropriately sized syringe.
 - Pull the syringe plunger rod back to fill the syringe with approximately 10 mL of air.
 - Inject the air into the VEKLURY injection vial above the level of the solution.
 - Invert the vial and withdraw the required volume of VEKLURY injection solution into the syringe. The last 5 mL of solution requires more force to withdraw.
- Transfer the required volume of VEKLURY injection to the 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 [68°F to 77°F]) or 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

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 4.

Table 4 Recommended Rate of Infusion—Diluted VEKLURY Injection Solution in Adults and Pediatric Patients 12 Years of Age and Older and 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

2.6 Storage of Prepared Dosages

VEKLURY for Injection (Supplied as Lyophilized Powder in Vial)

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 [68°F to 77°F]) prior to administration or 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

VEKLURY Injection (Supplied as Solution in Vial)

Store VEKLURY injection after dilution in the infusion bags 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]).

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.
- VEKLURY injection, 100 mg/20 mL (5 mg/mL), available as a clear, colorless to yellow solution, free of visible particles in single-dose vial.

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 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 [see *Adverse Reactions (6.1)*]. Because transaminase elevations have been reported as a clinical feature of COVID-19, 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 [see *Dosage and Administration (2.1)* and *Use in Specific Populations (8.7)*].

- 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 on the intracellular metabolic activation and antiviral activity of VEKLURY [see *Drug Interactions (7)* and *Microbiology (12.4)*].

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)*]

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.

The safety of VEKLURY is based on data from three Phase 3 studies in 1,313 hospitalized adult subjects with COVID-19, one Phase 3 study in 279 non-hospitalized adult and pediatric subjects (12 years of age and older weighing at least 40 kg) with mild-to-moderate COVID-19, four Phase 1 studies in 131 healthy adults, and from patients with COVID-19 who received VEKLURY under the Emergency Use Authorization or in a compassionate use program.

Clinical Trials Experience in Subjects 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 (14.1)*]. 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 (\geq Grade 3), 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 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 \geq 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 (14.2)*]. 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 6.

Table 6 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 (14.3)*]. 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 7.

Table 7 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

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

Emergency Use Authorization Experience in Subjects with COVID-19

The following adverse reactions have been identified during use of VEKLURY under Emergency Use Authorization:

- 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

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 8, Table 9, and Table 10, respectively.

Table 8 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 9 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 10 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 11.

Table 11 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.

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 (12.4)*].

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 [see *Clinical Pharmacology (12.3)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in individuals exposed to VEKLURY during pregnancy. Pregnant and recently pregnant individuals can go to <https://covid-pr.registry.com> to enroll or call 1-800-616-3791 to obtain information about the registry.

Risk Summary

Available data from published case reports and compassionate use of remdesivir in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In nonclinical reproductive toxicity studies, remdesivir demonstrated no adverse effect on embryo-fetal development when administered to pregnant animals at systemic exposures (AUC) of the predominant circulating metabolite of remdesivir (GS-441524) that were 4 times (rats and rabbits) the exposure in humans at the recommended human dose (RHD) (*see Data*). There are maternal and fetal risks associated with untreated COVID-19 in pregnancy (*see Clinical Considerations*).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo-fetal risk

COVID-19 in pregnancy is associated with adverse maternal and fetal outcomes, including preeclampsia, eclampsia, preterm birth, premature rupture of membranes, venous thromboembolic disease, and fetal death.

Data

Animal Data

Remdesivir was administered via intravenous injection to pregnant rats and rabbits (up to 20 mg/kg/day) on Gestation Days 6 through 17, and 7 through 20, respectively, and also to rats from Gestation Day 6 to Lactation/Post-partum Day 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.

8.2 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 (see *Data*). 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.

Data

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.

8.4 Pediatric Use

The safety and effectiveness of VEKLURY for the treatment of COVID-19 have been established in pediatric patients 12 years and older and weighing at least 40 kg, 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.

Use in this age group is based on extrapolation of pediatric efficacy from adequate and well-controlled studies in adults [see *Adverse Reactions (6.1)*, *Clinical Pharmacology (12.3)*, and *Clinical Studies (14)*].

Clinical trials of VEKLURY in hospitalized subjects 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. Thirty-nine pediatric patients 12 years and older and weighing at least 40 kg received VEKLURY in a compassionate use program in hospitalized subjects; the available clinical data from these patients are limited.

All pediatric patients 12 years of age and older and weighing at least 40 kg must have eGFR determined before starting VEKLURY and while receiving VEKLURY as clinically appropriate [see *Dosage and Administration (2.2, 2.4)*].

The safety and effectiveness of VEKLURY have not been established in pediatric patients younger than 12 years of age or weighing less than 40 kg.

8.5 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 (14)*]. 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.

8.6 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 (14)*].

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)*].

8.7 Hepatic Impairment

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

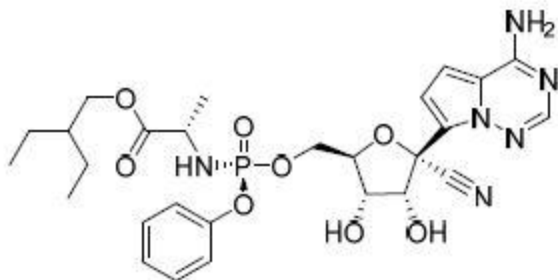
Perform hepatic laboratory testing in all patients before starting VEKLURY and while receiving VEKLURY as clinically appropriate [see *Dosage and Administration (2.2)* and *Warnings and Precautions (5.2)*].

10 OVERDOSAGE

There is no human experience of acute overdose 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.

11 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-altronitril-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 (2.4)*]. The inactive ingredients are 3 g betadex sulfobutyl ether sodium and may include hydrochloric acid and/or sodium hydroxide for pH adjustment.

VEKLURY injection contains 100 mg/20 mL (5 mg/mL) of remdesivir as a sterile, preservative-free, clear, colorless to yellow solution in a single-dose clear glass vial. It requires dilution prior to administration by intravenous infusion [see *Dosage and Administration (2.5)*]. The inactive ingredients are 6 g betadex sulfobutyl ether sodium, Water for Injection, USP, and may include hydrochloric acid and/or sodium hydroxide for pH adjustment.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Remdesivir is an antiviral drug with activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [see *Microbiology (12.4)*].

12.2 Pharmacodynamics

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

12.3. Pharmacokinetics

The pharmacokinetic (PK) properties of remdesivir and metabolites 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)

	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

- 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.
- Range of protein binding for remdesivir from 2 independent experiments show no evidence of concentration-dependent protein binding for remdesivir.
- Median (Study GS-US-399-4231).
- Mean (Study GS-US-399-4231).

Table 13 Multiple Dose PK Parameters^a of Remdesivir and Metabolites (GS-441524 and GS-704277) Following IV Administration of VEKLURY 100 mg to Healthy Adults

Parameter Mean (CV%)	Remdesivir	GS-441524	GS-704277
C _{max} (nanogram per mL)	2229 (19.2)	145 (19.3)	246 (33.9)
AUC _{tau} (nanogram·h per mL)	1585 (16.6)	2229 (18.4)	462 (31.4)
C _{trough} (nanogram per mL)	ND	69.2 (18.2)	ND

CV=Coefficient of Variation; ND=Not detectable (at 24 hours post-dose)

a. Remdesivir administered as a 30-minute IV infusion (Study GS-US-399-5505).

Specific Populations

Pharmacokinetic differences based on sex, race, age, renal function, and hepatic function on the exposures of remdesivir have not been evaluated.

Pediatric Patients

The pharmacokinetics of VEKLURY in pediatric patients have not been evaluated.

Using modeling and simulation, the recommended dosing regimen is expected to result in comparable steady-state plasma exposures of remdesivir and metabolites in patients 12 years of age and older and weighing at least 40 kg as observed in healthy adults [see *Use in Specific Populations (8.4)*].

Drug Interaction Studies

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

In vitro, remdesivir is a substrate for drug metabolizing enzyme CYP3A4, and is a substrate for Organic Anion Transporting Polypeptides 1B1 (OATP1B1) and P-glycoprotein (P-gp) transporters. In vitro, remdesivir is an inhibitor of CYP3A4, OATP1B1, OATP1B3, and MATE1. GS-704277 is a substrate for OATP1B1 and OATP1B3. The clinical relevance of these in vitro assessments has not been established.

Remdesivir is not a substrate for CYP1A1, 1A2, 2B6, 2C9, 2C19, or OATP1B3. GS-704277 and GS-441524 are not substrates for CYP1A1, 1A2, 2B6, 2C8, 2C9, 2D6, or 3A5. GS-441524 is also not a substrate for CYP2C19 or 3A4. GS-704277 and GS-441524 are not substrates for OAT1, OAT3, OCT1, OCT2, MATE1, or MATE2k. GS-441524 is also not a substrate for OATP1B1 or OATP1B3.

12.4 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 carboxylesterase 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 μ M. 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

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 μ M. 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 plaque assay and/or N protein ELISA assay, remdesivir retained similar antiviral activity (≤ 1.5 -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), Delta (B.1.617.2), Gamma (P.1), and Epsilon (B.1.429) variants compared to earlier lineage SARS-CoV-2 (lineage A) isolates.

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

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, S759A, 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 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.

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 EC₅₀ value.

13 NONCLINICAL TOXICOLOGY

13.1 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.

13.2 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.

14 CLINICAL STUDIES

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

A randomized, double-blind, placebo-controlled clinical trial (ACTT-1, NCT04280705) 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 SpO₂ >94% and respiratory rate <24 breaths/minute without supplemental oxygen; severe disease was defined as an SpO₂ \leq 94% on room air, a respiratory rate \geq 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, SpO₂ \leq 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). Subjects in this trial were unvaccinated. 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.

Overall, the odds of improvement in the ordinal scale were higher in the VEKLURY group at Day 15 when compared to the placebo group (odds ratio 1.54 [95% CI 1.25 to 1.91]).

Overall, 29-day mortality was 11% for the VEKLURY group vs 15% for the placebo group (hazard ratio 0.73 [95% CI 0.52 to 1.03]).

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

A randomized, open-label multi-center clinical trial (Study 5773, NCT04292899) in adult subjects with confirmed SARS-CoV-2 infection, an SpO₂ 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.

14.3 Study GS-US-540-5774 in Hospitalized Subjects with Moderate COVID-19

A randomized, open-label multi-center clinical trial (Study 5774, NCT04292730) of hospitalized adult subjects with confirmed SARS-CoV-2 infection, SpO₂ >94% and radiological evidence of pneumonia compared treatment with VEKLURY for 5 days (n=191) and treatment with VEKLURY for 10 days (n=193) with standard of care (n=200). Treatment with VEKLURY was stopped in subjects who were discharged from the hospital prior to completion of their protocol-defined duration of treatment. Subjects treated with VEKLURY received 200 mg on Day 1 and 100 mg once daily on subsequent days via intravenous infusion.

At baseline, the median age of subjects was 57 years (range, 12 to 95 years); 61% were male, 61% were White, 19% were Black, and 19% were Asian; 18% were Hispanic or Latino. Subjects in this trial were unvaccinated. Baseline clinical status, oxygen support status, and 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 11 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, the odds of improvement in the ordinal scale were higher in the 5-day VEKLURY group at Day 11 when compared to those receiving only standard of care (odds ratio 1.65 [95% CI 1.09 to 2.48], p=0.017). The odds of improvement in clinical status with the 10-day treatment group when compared to those receiving only standard of care were not statistically significant (odds ratio 1.31 [95% CI 0.88 to 1.95]). All-cause mortality at Day 28 was ≤2% in all treatment groups.

14.4 Study GS-US-540-9012 in Non-Hospitalized Subjects with Mild-to-Moderate COVID-19 and at High Risk for Progression to Severe Disease

A randomized, double-blind, placebo-controlled, clinical trial (Study 9012, NCT04501952) evaluated VEKLURY 200 mg once daily for 1 day followed by VEKLURY 100 mg once daily for 2 days (for a total of 3 days of intravenously administered therapy) in 554 adult and 8 pediatric subjects (12 years of age and older and weighing at least 40 kg) who were non-hospitalized, had mild-to-moderate COVID-19, 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. Risk factors for progression to hospitalization included age ≥ 60 years, obesity (BMI ≥ 30), chronic lung disease, hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, immunocompromised state, chronic mild or moderate kidney disease, chronic liver disease, current cancer, and sickle cell disease. Subjects who received, required, or were expected to require supplemental oxygen were excluded from the trial. Subjects were randomized in a 1:1 manner, stratified by residence in a skilled nursing facility (yes/no), age (<60 vs ≥ 60 years), and region (US vs ex-US) to receive VEKLURY (n=279) or placebo (n=283), plus standard of care.

At baseline, mean age was 50 years (with 30% of 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/m². Subjects in this trial were unvaccinated. VEKLURY or placebo was first administered to subjects in outpatient facilities (84%), home healthcare settings (13%), or skilled nursing facilities (3%). 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 log₁₀ copies/mL at baseline. The baseline demographics and disease characteristics were well balanced across the VEKLURY and placebo treatment groups.

The primary endpoint was the proportion of subjects with COVID-19 related hospitalization (defined as at least 24 hours of acute care) or all-cause mortality through Day 28. Events occurred in 2 (0.7%) subjects treated with VEKLURY compared to 15 (5.3%) subjects concurrently randomized to placebo (hazard ratio 0.134 [95% CI 0.031 to 0.586]; p=0.0076). No deaths were observed through Day 28.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

VEKLURY for injection: 100 mg (NDC 61958-2901-2), 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 (2.4)*]. Discard unused portion. The container closure is not made with natural rubber latex.

VEKLURY injection: 100 mg/20 mL (5 mg/mL) (NDC 61958-2902-2), is supplied as a single-dose vial containing a sterile, preservative-free, clear, colorless to yellow aqueous-based solution. It requires dilution prior to administration by intravenous infusion [see *Dosage and Administration (2.4)*]. 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. These products contain no preservative; therefore, partially used vials should be discarded [see *Dosage and Administration (2.5)*].

VEKLURY for Injection

Store VEKLURY for injection, 100 mg vials below 30°C (below 86°F) 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 [68°F to 77°F]) prior to administration or 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

VEKLURY Injection

Store VEKLURY injection vials at refrigerated temperature (2°C to 8°C [36°F to 46°F]) until required for use.

Dilute within the same day as administration. Prior to dilution, equilibrate VEKLURY injection to room temperature (20°C to 25°C [68°F to 77°F]). Sealed vials can be stored up to 12 hours at room temperature prior to dilution. Store VEKLURY injection after dilution in the infusion bags for no more than 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]).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient 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 (12.4)]*.

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 (8.1)]*.

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)]*.

VEKLURY is a trademark of Gilead Sciences, Inc., or its related companies. All other trademarks referenced herein are the property of their respective owners.

© 2022 Gilead Sciences, Inc. All rights reserved

PATIENT INFORMATION

VEKLURY® (VEK-lur-ee)
(remdesivir)
for injection

VEKLURY® (VEK-lur-ee)
(remdesivir)
injection

What is VEKLURY?

VEKLURY is a prescription medicine used for the treatment of coronavirus disease 2019 (COVID-19) in adults and children 12 years of age and older and weighing at least 88 pounds (40 kg) 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.

It is not known if VEKLURY is safe and effective in children under 12 years of age or weighing less than 88 pounds (40 kg).

Do not take VEKLURY if you are allergic to remdesivir or any of the ingredients in VEKLURY. See the end of this leaflet for a complete list of ingredients in VEKLURY.

Before receiving VEKLURY, tell your healthcare provider about all of your medical conditions, including if you:

- have kidney problems
- have liver problems
- are pregnant or plan to become pregnant. It is not known if VEKLURY can harm your unborn baby. **Tell your healthcare provider right away if you are or if you become pregnant.**
Pregnancy Registry: There is a pregnancy registry for individuals who receive VEKLURY during pregnancy. The purpose of this registry is to collect information about the health of you and your baby. Talk with your healthcare provider about how you can take part in this registry.
- are breastfeeding or plan to breastfeed. It is not known if VEKLURY can pass into your breast milk. Talk to your healthcare provider about the best way to feed your baby.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. VEKLURY may interact with other medicines.

Especially tell your healthcare provider if you are taking the medicines chloroquine phosphate or hydroxychloroquine sulfate.

How will I receive VEKLURY?

- **Hospitalized:** VEKLURY is given to you through a vein by intravenous (IV) infusion one time each day for up to 10 days. Your healthcare provider will decide how many doses you need.
- **Not hospitalized:** VEKLURY is given to you through a vein by intravenous (IV) infusion one time each day for 3 days.
- Your healthcare provider will do certain blood tests before starting and during treatment with VEKLURY.

What are the possible side effects of VEKLURY?

VEKLURY may cause serious side effects, including:

- **Allergic reactions.** Allergic reactions can happen during or after infusion with VEKLURY. Your healthcare provider will monitor you for signs and symptoms of allergic reactions during your infusion and for at least 1 hour after your infusion. Tell your healthcare provider right away if you get any of the following signs and symptoms of an allergic reaction:
 - changes in your heart rate
 - fever
 - shortness of breath, wheezing
 - swelling of the lips, face, or throat
 - rash
 - nausea
 - sweating
 - shivering
- **Increase in liver enzymes.** Increases in liver enzymes are common in people who have received VEKLURY and may be a sign of liver injury. Your healthcare provider will do blood tests to check your liver enzymes before and during treatment with VEKLURY as needed. Your healthcare provider may stop treatment with VEKLURY if you develop liver problems.

The most common side effect of VEKLURY is nausea.

These are not all of the possible side effects of VEKLURY.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of VEKLURY.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about VEKLURY that is written for healthcare professionals.

What are the ingredients in VEKLURY?

Active ingredient: remdesivir

Inactive ingredients:

VEKLURY for injection: betadex sulfobutyl ether sodium and may include hydrochloric acid and/or sodium hydroxide for pH adjustment.

VEKLURY injection: betadex sulfobutyl ether sodium, Water for Injection, USP, and may include hydrochloric acid and/or sodium hydroxide for pH adjustment.

Manufactured and distributed by: Gilead Sciences, Inc., Foster City, CA 94404

VEKLURY is a trademark of Gilead Sciences, Inc., or its related companies. All other trademarks referenced herein are the property of their respective owners.

© 2022 Gilead Sciences, Inc. All rights reserved.

214787-GS-003

For more information, call 1-800-445-3235 or go to www.VEKLURY.com.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: January/2022