October 22, 2020

Ashley Rhoades, MBS, RAC
Manager, Regulatory Affairs
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404

Dear Ms. Rhoades:

On February 4, 2020, pursuant to Section 564(b)(1)(C) of the Act, the Secretary of the Department of Health and Human Services (HHS) determined that there is a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad, and that involves the virus that causes COVID-19.[1] On the basis of such determination, the Secretary of HHS on March 27, 2020, declared that circumstances exist justifying the authorization of emergency use of drugs and biological products during the COVID-19 pandemic, pursuant to Section 564 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bbb-3), subject to terms of any authorization issued under that section.[2]

On May 1, 2020, the Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for emergency use of Veklury® (remdesivir) for the treatment of hospitalized patients with severe 2019 coronavirus disease (COVID-19)[3], pursuant to Section 564 of the Act. Veklury is a direct acting antiviral drug that inhibits viral RNA synthesis. At that time, Veklury was an investigational drug and not approved for any indication.

On August 28, 2020, having concluded that revising this EUA was appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA reissued the May 1, 2020, letter in its entirety with revisions incorporated to expand the authorized use of Veklury by no longer limiting its use to the treatment of patients with severe disease. In addition, the Fact Sheet for Health Care Providers was revised to provide updated clinical trial results and supporting data.[4]

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[1] U.S. Department of Health and Human Services, *Determination of a Public Health Emergency and Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*. February 4, 2020.

[2] U.S. Department of Health and Human Services, *Declaration that Circumstances Exist Justifying Authorizations Pursuant to Section 564(b) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 360bbb-3*, 85 FR 18250 (April 1, 2020).

[3] For purposes of the May 1, 2020, EUA, patients with severe disease were defined as patients with oxygen saturation (SpO2) ≤94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).

[4] Prior to the reissuance of the EUA on August 28, 2020, and pursuant to the conditions of authorization, Gilead had requested, and FDA had concurred with, other changes to the Fact Sheets, including but not limited to: (1) clarified dosing and administration recommendations; (2) added sponsor's recommended formula to be used in calculating eGFR (this formula was removed in the August 28, 2020, reissuance); (3) added hypersensitivity reaction and drug interaction information; (4) added safety information from randomized, clinical trials; (5) removed information

On October 1, 2020, having concluded that revising this EUA was appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA reissued the August 28, 2020, letter in its entirety with revisions incorporated to the scope and conditions of authorization designating Gilead Sciences, Inc. and its authorized distributors[5] as the responsible parties for the distribution of Velkury. On October 16, 2020, FDA reissued the October 1, 2020, letter in its entirety with revisions to clarify that an alternate care site (ACS) meeting certain criteria was considered an "inpatient hospital setting" for the purposes of the scope of the EUA, and as such, was within the terms and conditions of FDA's authorization.

On October 22, 2020, FDA approved NDA 214787 for Veklury (remdesivir), which is indicated for adults and pediatric patients (12 years and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization. Under its approval, Veklury should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care. Having concluded that revising this EUA is appropriate to protect the public health or safety under Section 564(g)(2) of the Act, FDA is reissuing the October 16, 2020, letter in its entirety with revisions to remove uses previously authorized that are now the subject of the approved NDA 214787 for Veklury, and to continue authorizing Veklury for emergency use to treat suspected or laboratory-confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg.

Veklury has activity in cell culture and animal models against SARS-CoV, MERS-CoV, and SARS-CoV-2. Based on review of the data from the randomized, double-blinded, placebo-controlled trial conducted by NIAID (NCT04280705), from the Gilead-sponsored open-label trial that evaluated different durations of Veklury (NCT04292899), and from the Gilead-sponsored open-label trial that evaluated different durations of Veklury as compared to standard of care (NCT04292730), it is reasonable to believe that Veklury may be effective and the known and potential benefits of Veklury outweigh the known and potential risks of the drug for the treatment of suspected or laboratory-confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg.

Having concluded that the criteria for issuance of this authorization under Section 564(c) of the Act are met, I am authorizing the emergency use of Veklury for treatment of COVID-19, as described in the Scope of Authorization section of this reissued letter (Section II) and subject to the terms of this authorization.

I. Criteria for Issuance of Authorization

I have concluded that the emergency use of Veklury for the treatment of COVID-19 when administered as described in the Scope of Authorization (Section II) meets the criteria for issuance of an authorization under Section 564(c) of the Act, because:

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related to the compassionate use program; and (6) added reference to remdesivir's trade name, Veklury.

[5] "Authorized Distributor(s)" are identified by Gilead as an entity or entities allowed to distribute authorized Veklury.

1. SARS-CoV-2 can cause a serious or life-threatening disease or condition, including severe respiratory illness, to humans infected by this virus;

2. Based on the totality of scientific evidence available to FDA, it is reasonable to believe that Veklury may be effective in treating suspected or laboratory-confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg and that, when used under the conditions described in this authorization, the known and potential benefits of Veklury when used to treat suspected or laboratory-confirmed COVID-19 outweigh the known and potential risks of such products; and

3. There is no adequate, approved, and available alternative to the emergency use of Veklury to treat suspected or laboratory-confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg.[6]

II. Scope of Authorization

I have concluded, pursuant to Section 564(d)(1) of the Act, that the scope of this authorization is limited as follows:

- The Veklury covered by this authorization will be used only to treat suspected or laboratory-confirmed COVID-19 in hospitalized[7] pediatric patients weighing 3.5 kg to less than 40 kg *or* hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg administered via intravenous (IV) infusion by a healthcare provider; and

- The use of Veklury covered by this authorization should be in accordance with the dosing regimens as detailed in the authorized Facts Sheets.

Product Description

Veklury is a nucleoside ribonucleic acid (RNA) polymerase inhibitor. Veklury for injection, 100 mg, is a sterile, preservative-free lyophilized solid that is to be reconstituted with 19mL of sterile water for injection and diluted into 0.9% saline prior to intravenous (IV) administration. Following reconstitution, each single-dose, clear glass vial contains a 5 mg/mL Veklury concentrated solution with sufficient volume to allow withdrawal of 20 mL.

The authorized product includes remdesivir for injection[8] with a vial label and/or carton labeling that is clearly marked for "emergency use authorization", Veklury for injection with a vial label

[6] No other criteria of issuance have been prescribed by regulation under Section 564(c)(4) of the Act.
[7] Individuals determined as being appropriate for acute inpatient hospitalization and who are admitted or transferred to an alternate care site (ACS) that is capable of providing acute care that is comparable to general inpatient hospital care are within the terms and conditions of this Letter of Authorization. An ACS is intended to provide additional hospital surge capacity and capability for communities overwhelmed by patients with COVID-19.
[8] FDA's authorization includes remdesivir for injection manufactured and labeled prior to Gilead's reference to remdesivir's trade name, "Veklury", in product labeling.

and/or carton labeling that is clearly marked for "emergency use authorization", and commercially available[9] Veklury for injection.

Veklury for injection, 100 mg, vials should be stored below 30 °C until time of use. Following reconstitution with sterile water and dilution with 0.9% saline, the solution can be stored for up to 24 hours at room temperature (20 °C to 25 °C) or 48 hours at refrigerated temperatures (2 °C to 8 °C).

Veklury is authorized for emergency use with the following product-specific information required to be made available to healthcare providers and patients, respectively, through Gilead's website at ***www.gilead.com/remdesivir***:

- Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of Veklury **(**remdesivir)
- Fact Sheet for Parents and Caregivers: Emergency Use Authorization (EUA) of Veklury **(**remdesivir**)** for Coronavirus Disease 2019 (COVID-19)

I have concluded, pursuant to Section 564(d)(2) of the Act, that it is reasonable to believe that the known and potential benefits of Veklury, when used for the treatment of COVID-19 and used in accordance with this Scope of Authorization (Section II), outweigh its known and potential risks.

I have concluded, pursuant to Section 564(d)(3) of the Act, based on the totality of scientific evidence available to FDA, that it is reasonable to believe that Veklury may be effective for the treatment of COVID-19 when used in accordance with this Scope of Authorization (Section II), pursuant to Section 564(c)(2)(A) of the Act.

Having reviewed the scientific information available to FDA, including the information supporting the conclusions described in Section I above, I have concluded that Veklury (as described in this Scope of Authorization (Section II)) meets the criteria set forth in Section 564(c) of the Act concerning safety and potential effectiveness.

The emergency use of your product under an EUA must be consistent with, and may not exceed, the terms of the Authorization, including the Scope of Authorization (Section II) and the Conditions of Authorization (Section III). Subject to the terms of this EUA and under the circumstances set forth in the Secretary of HHS's determination under Section 564(b)(1)(C) described above and the Secretary of HHS's corresponding declaration under Section 564(b)(1), Veklury is authorized to treat suspected or laboratory-confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg as described in the Scope of Authorization (Section II) under this EUA, despite the fact that it does not meet certain requirements otherwise required by applicable federal law.

[9] For the purposes of this Letter of Authorization, commercially available Veklury for injection refers to product in United States distribution under the approved New Drug Application 214787.

III. Conditions of Authorization

Pursuant to Section 564 of the Act, I am establishing the following conditions on this authorization:

Gilead Sciences, Inc. (Gilead) and Authorized Distributors

A. Gilead and authorized distributor(s) will ensure that the authorized Veklury is distributed and the authorized labeling (i.e., Fact Sheets) will be made available to hospitals and healthcare facilities consistent with the terms of this letter.

B. Gilead and authorized distributor(s) will ensure that appropriate storage is maintained until the product is delivered to hospitals and healthcare facilities.

C. Gilead and authorized distributor(s) will ensure that the terms of this EUA are made available to all relevant stakeholders (e.g., U.S. government agencies, state and local government authorities, authorized distributors, healthcare facilities, healthcare providers) involved in distributing or receiving authorized Veklury. Gilead will provide to all relevant stakeholders a copy of this letter of authorization and communicate any subsequent amendments that might be made to this letter of authorization and its authorized accompanying materials (i.e., Fact Sheets).

D. Gilead may request changes to this authorization, including to the authorized Fact Sheets for Veklury, and FDA may determine that such changes may be permitted without amendment of this EUA, upon concurrence of the Office of Infectious Diseases/Office of New Drugs/Center for Drug Evaluation and Research (CDER), the Counter-Terrorism and Emergency Coordination Staff/Office of the Center Director/CDER, and Office of Counterterrorism and Emerging Threats/Office of the Chief Scientist/Office of the Commissioner.

E. Gilead will report to FDA serious adverse events and all medication errors associated with the use of the authorized Veklury that are reported to Gilead using either of the following options.

   Option 1: Submit reports through the Safety Reporting Portal (SRP) as described on the FDA SRP web page.

   Option 2: Submit reports directly through the Electronic Submissions Gateway (ESG) as described on the FAERS electronic submissions web page.

   Submitted reports under both options should state: “use of Veklury (remdesivir) was under an EUA”. For reports submitted under Option 1, include this language at the beginning of the question “Describe Event” for further analysis. For reports submitted under Option 2, include this language at the beginning of the “Case Narrative” field.

F. Through a process of inventory control, Gilead and authorized distributor(s) will maintain records regarding distribution of the authorized Veklury (i.e., lot numbers, quantity, receiving site, receipt date).

G. Gilead and authorized distributor(s) will make available to FDA upon request any records maintained in connection with this EUA.

Hospitals and Other Healthcare Facilities to Whom the Authorized Veklury Is Distributed and Healthcare Providers Administering the Authorized Veklury

H. Healthcare facilities and healthcare providers will ensure that they are aware of the letter of authorization, and the terms herein, and that the authorized Fact Sheets are made available to healthcare providers and to patients and caregivers, respectively, through appropriate means.

I. Healthcare facilities and healthcare providers receiving Veklury will track serious adverse events that are considered to be potentially attributable to Veklury use and must report these to FDA in accordance with the Fact Sheet for Healthcare Providers. Complete and submit a MedWatch form (www.fda.gov/medwatch/report.htm), or Complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178) (these forms can be found via link above). Call 1-800-FDA-1088 for questions. Submitted reports should state, "use of Veklury (remdesivir) was under an EUA" at the beginning of the question "Describe Event" for further analysis.

J. Through a process of inventory control, healthcare facilities will maintain records regarding the dispensed authorized Veklury (i.e., lot numbers, quantity, receiving site, receipt date), product storage, and maintain patient information (e.g., patient name, age, disease manifestation, number of doses administered per patient, other drugs administered).

K. Healthcare facilities will ensure that any records associated with this EUA are maintained until notified by Gilead and/or FDA. Such records will be made available to Gilead, HHS, and FDA for inspection upon request.

Conditions Related to Printed Matter, Advertising and Promotion

L. All descriptive printed matter, including advertising and promotional material, relating to the use of the Veklury for the treatment of suspected or laboratory-confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg shall be consistent with the authorized labeling, as well as the terms set forth in this EUA and the applicable requirements set forth in the Act and FDA regulations.

M. No descriptive printed matter, including advertising or promotional material, relating to the use of the Veklury may represent or suggest that such products are safe or effective when used for the treatment of suspected or laboratory-confirmed COVID-19 in hospitalized

pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg.

N. All descriptive printed matter, including advertising and promotional material, relating to the use of the Veklury to treat suspected or laboratory-confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg or hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg shall clearly and conspicuously state that:

- the Veklury has not been approved, but has been authorized for emergency use by FDA to treat suspected or laboratory-confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg *or* hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg;

- the Veklury is authorized under an EUA for the treatment of suspected or laboratory-confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg *or* hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use of the 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.

IV. Duration of Authorization

This EUA will be effective until the declaration that circumstances exist justifying the authorization of the emergency use of drugs and biological products during the COVID-19 pandemic is terminated under Section 564(b)(2) of the Act or the EUA is revoked under Section 564(g) of the Act.

Sincerely,

Denise M. Hinton -S3

Digitally signed by Denise M. Hinton -S3
Date: 2020.10.22 13:53:29 -04'00'

RADM Denise M. Hinton
Chief Scientist
Food and Drug Administration

FACT SHEET FOR HEALTHCARE PROVIDERS
EMERGENCY USE AUTHORIZATION (EUA) OF VEKLURY® (remdesivir) FOR HOSPITALIZED PEDIATRIC PATIENTS WEIGHING 3.5 KG TO LESS THAN 40 KG *OR* HOSPITALIZED PEDIATRIC PATIENTS LESS THAN 12 YEARS OF AGE WEIGHING AT LEAST 3.5 KG

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of VEKLURY for treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg *or* hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg.

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 hospitalized pediatric patients weighing 3.5 kg to less than 40 kg *or* hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg. 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 (2.2)].*
  - 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.

- The recommended treatment duration for patients not requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (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.
- The recommended total treatment duration for patients requiring invasive mechanical ventilation and/or ECMO is 10 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 in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization. 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 treatment of hospitalized pediatric patients weighing 3.5 kg to less than 40 kg *or* hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg with suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) for whom use of an intravenous (IV) agent is clinically appropriate. **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

- Empiric treatment of hospitalized patients with suspected COVID-19 can be considered pending laboratory confirmation of SARS-CoV-2 infection.
- VEKLURY can be used at any time after onset of symptoms in hospitalized patients.
- Pediatric patients (greater than 28 days old) must have an estimated glomerular filtration rate (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 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 (2.2)].*

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 Only**	5 mg/kg	2.5 mg/kg
40 kg and higher		200 mg	100 mg

- The recommended treatment duration for patients not requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (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.
- The recommended total treatment duration for patients requiring invasive mechanical ventilation and/or ECMO is 10 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 patients weighing 3.5 kg to less than 40 kg or 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. 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 under close medical supervision for hypersensitivity reactions during and following administration of VEKLURY. 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 cell culture data demonstrating an 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, Clinical Trials Experience (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 treatment of suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg *or* hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg.
- 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 treatment of suspected or laboratory confirmed COVID-19 in hospitalized pediatric patients weighing 3.5 kg to less than 40 kg ***or*** hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg for whom use of an IV agent is clinically appropriate and who are under the care or consultation of a licensed clinician skilled in the diagnosis and management of patients with potentially life-threatening illness and medication-related adverse events.
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.
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 responses to requests from FDA for information about adverse events and medication errors following administration of VEKLURY.
8. The prescribing healthcare provider and/or the provider's designee are/is responsible for mandatory reporting of all medication errors and serious adverse events* considered to be potentially related to VEKLURY occurring during VEKLURY treatment within 7 calendar days from the onset of the event. The reports should include unique identifiers and the words "VEKLURY (remdesivir) under Emergency Use Authorization (EUA)" in the description section of the report.

- Submit adverse event reports to FDA MedWatch using one of the following methods:
  - Complete and submit the report online: www.fda.gov/medwatch/report.htm, or
  - By using a postage-paid Form FDA 3500 (available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf) and returning by mail (MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787), or by fax (1-800-FDA-0178), or
  - Call 1-800-FDA-1088 to request a reporting form
  - Submitted reports should include in the field name, "Describe Event, Problem, or Product Use/Medication Error" a statement **"VEKLURY (remdesivir) under Emergency Use Authorization (EUA)."**

*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.

[see Full EUA Prescribing Information, Adverse Reactions and Medication Errors Reporting Requirements and Instructions (8)]

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

APPROVED AVAILABLE ALTERNATIVES

There is no approved available alternative product for treating 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 hospitalized with COVID-19. 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 hospitalized pediatric patients weighing 3.5 kg to less than 40 kg *or* hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg with COVID-19[1]. 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.

[1] 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.

FULL EUA PRESCRIBING INFORMATION

FULL EUA PRESCRIBING INFORMATION: CONTENTS*

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

1. AUTHORIZED USE

VEKLURY is authorized for use under an EUA for treatment of hospitalized pediatric patients weighing 3.5 kg to less than 40 kg *or* hospitalized pediatric patients less than 12 years of age weighing at least 3.5 kg with suspected or laboratory confirmed coronavirus disease 2019 (COVID-19) for whom use of an intravenous (IV) agent is clinically appropriate.

2. DOSAGE AND ADMINISTRATION

2.1 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 (2.3), 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 Clinical Trials Experience (6.1)]*.

2.2 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 (2.4), 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 Only**	5 mg/kg	2.5 mg/kg
40 kg and higher		200 mg	100 mg

- The recommended treatment duration for patients not requiring invasive mechanical ventilation and/or extracorporeal membrane oxygenation (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.
- The recommended total treatment duration for patients requiring invasive mechanical ventilation and/or ECMO is 10 days.
- VEKLURY for injection must be reconstituted and further diluted prior to administration via intravenous infusion.

2.3 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.

2.4 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.

- 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. 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 solution should result.
- If the contents of the vial are not completely dissolved, shake the vial again for 30 seconds and allow the contents to settle for 2 to 3 minutes. Repeat this procedure as necessary until the contents of the vial are completely dissolved. 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.

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

2.5 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. 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 under close medical supervision for hypersensitivity reactions during and following administration of VEKLURY. 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 cell culture data demonstrating an 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, 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 (≥ 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 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 ≥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 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 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).

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 Patients with COVID-19

The following adverse reactions have been identified during use of VEKLURY primarily in adult patients 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 ≥3% of Adult Subjects Receiving VEKLURY 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 Adult Subjects Receiving VEKLURY 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 Adult Subjects Receiving VEKLURY 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.

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 (2.1)]*.

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 medication errors and the following selected serious adverse events occurring during VEKLURY use and considered to be potentially attributable to VEKLURY. These adverse events must be reported within 7 calendar days from the onset of the event:

- 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.

If a serious and unexpected adverse event occurs and appears to be associated with the use of VEKLURY, the prescribing healthcare provider and/or the provider's designee should complete and submit a MedWatch form to FDA using one of the following methods:

- Complete and submit the report online: www.fda.gov/medwatch/report.htm, or
- Use a postage-paid Form FDA 3500 (available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM163919.pdf) and returning by mail (MedWatch, 5600 Fishers Lane, Rockville, MD 20852-9787), or by fax (1-800-FDA-0178), or
- Call 1-800-FDA-1088 to request a reporting form

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) 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 antagonism observed in cell culture, 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

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*).

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

Pregnant women hospitalized with COVID-19 are at risk for serious morbidity and mortality.

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.

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) *[see Dosage and Administration (2.2, 2.3, 2.4, 2.5)]*.

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 (2.1, 2.3)].*

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 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 (2.1)].*

11.5 Hepatic Impairment

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

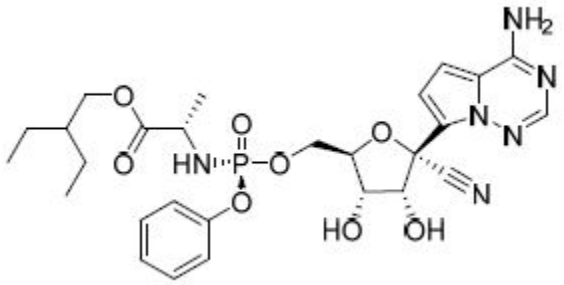
Perform hepatic laboratory testing in all patients before starting VEKLURY and during treatment as clinically appropriate *[see Dosage and Administration (2.1)]*.

12. OVERDOSAGE

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

13. PRODUCT DESCRIPTION

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



13.1 Physical Appearance

VEKLURY for injection contains 100 mg of remdesivir as a sterile, preservative-free lyophilized white to off-white to yellow powder in a single-dose clear glass vial. It requires reconstitution and then further dilution prior to administration by intravenous infusion *[see Dosage and Administration (2.4, 2.5)].*

13.2 Inactive Ingredients

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

14. CLINICAL PHARMACOLOGY

14.1 Mechanism of Action

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

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

14.2 Pharmacokinetics

The pharmacokinetic (PK) properties of remdesivir and metabolites have been evaluated in adults in several Phase 1 trials and are provided in Table 11. The multiple dose PK parameters of remdesivir and metabolites in healthy adults are provided in Table 12.

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

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

ND=not detected

a. Remdesivir administered as a 30-minute IV infusion (Study GS-US-399-5505); range of median observed on Day 1 and Day 5 or 10.

b. Range of protein binding for remdesivir from 2 independent experiments show no evidence of concentration-dependent protein binding for remdesivir.

c. Median (Study GS-US-399-4231).

d. Mean (Study GS-US-399-4231).

Table 12 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 (EC_{50}) of 9.9 nM after 48 hours of treatment. Remdesivir inhibited the replication of SARS-CoV-2 in the continuous human lung epithelial cell line Calu-3 with an EC_{50} value of 280 nM after 72 hours of treatment. The antiviral activity of remdesivir was antagonized by chloroquine phosphate in a dose-dependent manner when the two drugs were co-incubated at clinically relevant concentrations in HEp-2 cells infected with respiratory syncytial virus (RSV). Higher remdesivir EC_{50} values were observed with increasing concentrations of chloroquine phosphate. Increasing concentrations of chloroquine phosphate reduced formation of remdesivir triphosphate in normal human bronchial epithelial cells.

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

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. The combination of these two substitutions conferred a 5.6-fold reduction in susceptibility to remdesivir. The mutant viruses showed reduced viral fitness in cell culture, and 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.

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 (EC_{50} 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 EC_{50} 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 three 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 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 SpO_2 >94% and respiratory rate <24 breaths/minute without supplemental oxygen; severe disease was defined as an SpO_2 ≤94% on room air, a respiratory rate ≥24 breaths/minute, an oxygen requirement, or a requirement for mechanical ventilation. Subjects had to have at least one of the following to be enrolled in the trial: radiographic infiltrates by imaging, SpO_2 ≤94% on room air, a requirement for supplemental oxygen, or a requirement for mechanical ventilation. Subjects treated with VEKLURY received 200 mg on Day 1 and 100 mg once daily on subsequent days, for 10 days of treatment via intravenous infusion. Treatment with VEKLURY was stopped in subjects who were discharged from the hospital prior to the completion of 10 days of treatment.

At baseline, mean age was 59 years (with 36% of subjects aged 65 or older); 64% of subjects were male, 53% were White, 21% were Black, and 13% were Asian; 24% were Hispanic or Latino; 105 subjects had mild/moderate disease (10% in both treatment groups); 957 subjects had severe disease (90% in both treatment groups). 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 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 SpO_2 of ≤94% on room air, and radiological evidence of pneumonia compared 200 subjects who received VEKLURY for 5 days with 197 subjects who received VEKLURY for 10 days. Treatment with VEKLURY was stopped in subjects who were discharged from the hospital prior to completion of their protocol-defined duration of treatment. Subjects on mechanical ventilation at screening were excluded. All subjects received 200 mg of VEKLURY on Day 1 and 100 mg once daily on subsequent days via intravenous infusion, plus standard of care.

At baseline, the median age of subjects was 61 years (range, 20 to 98 years); 64% were male, 75% were White, 12% were Black, and 12% were Asian; 22% were Hispanic or Latino. More subjects in the 10-day group than the 5-day group required invasive mechanical ventilation or ECMO (5% vs 2%), or high-flow oxygen support (30% vs 25%) at baseline. 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 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, SpO_2 >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. 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.

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 (2.4)].*

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. This product contains no preservative; therefore, partially used vials should be discarded *[see Dosage and Administration (2.5)].*

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 (7), and Microbiology (12.4)].*

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

Revised: 10/2020

Fact Sheet for Parents and Caregivers
Emergency Use Authorization (EUA) of VEKLURY® (remdesivir) for Hospitalized Children Weighing 8 pounds (3.5 kg) to Less Than 88 pounds (40 kg) or Hospitalized Children Less Than 12 Years of Age Weighing at least 8 pounds (3.5 kg) with Coronavirus Disease 2019 (COVID-19)

Your child is being given a medicine called **VEKLURY.** VEKLURY is a medicine approved for adults and children 12 years of age and older and weighing at least 88 pounds (40 kg) for the treatment of coronavirus disease 2019 (COVID-19) requiring hospitalization. It is not known if VEKLURY is safe and effective for the treatment of COVID-19 in hospitalized children weighing 8 pounds (3.5 kg) to less than 88 pounds (40 kg) or hospitalized children less than 12 years of age weighing at least 8 pounds (3.5 kg), and VEKLURY is not FDA approved for this use. This Fact Sheet contains information to help you understand the potential risks and potential benefits of your child receiving VEKLURY.

Read this Fact Sheet for information about VEKLURY. Talk to your healthcare provider if you have questions. It is your choice for your child to receive VEKLURY or to stop it at any time.

What is COVID-19?
COVID-19 is caused by a virus called a coronavirus. People can get COVID-19 through contact with another person who has the virus.

COVID-19 illnesses have ranged from very mild (including some with no reported symptoms) to severe, including illness resulting in death. While information so far suggests that most COVID-19 illness is mild, serious illness can happen and may cause some of a child's other medical conditions to become worse. People of all ages with severe, long-lasting (chronic) medical conditions like heart disease, lung disease, and diabetes, for example, seem to be at higher risk of being hospitalized for COVID-19.

What are the symptoms of COVID-19?
The symptoms of COVID-19 are fever, cough, and shortness of breath, which may appear 2 to 14 days after exposure. Serious illness including breathing problems can occur and may cause your child's other medical conditions to become worse.

What is VEKLURY?
VEKLURY is an approved antiviral medicine for adults and children 12 years of age and older and weighing at least 88 pounds (40 kg) for the treatment of COVID-19 requiring hospitalization. VEKLURY was shown in clinical trials in adults to shorten the time to recovery in some people.

VEKLURY is still being studied in hospitalized children.

There are no medicines approved by the FDA as safe and effective to treat hospitalized children weighing 8 pounds (3.5 kg) to less than 88 pounds (40 kg) or hospitalized children younger than 12 years of age weighing at least 8 pounds (3.5 kg) who have COVID-19. Therefore, the FDA has authorized the emergency use of VEKLURY for this use under an Emergency Use Authorization (EUA). For more information on EUA, see the "**What is an Emergency Use Authorization (EUA)?**" section at the end of this Fact Sheet.

What should I tell my healthcare provider before my child receives VEKLURY?
Tell your healthcare provider about all of your child's medical conditions, including if your child:
- Has kidney problems
- Has liver problems
- Is taking any medicines (prescription, over-the-counter, vitamins, or herbal products). VEKLURY may interact with other medicines.
    - **Especially tell your healthcare provider if your child is taking the medicines chloroquine phosphate or hydroxychloroquine sulfate.**

How will my child receive VEKLURY?
VEKLURY is given to your child through a vein (intravenous or IV) one time each day for up to 10 days. Your healthcare provider will decide how many doses your child needs.

What are the important possible side effects of VEKLURY?
Possible side effects of VEKLURY are:

- Allergic reactions. Allergic reactions can happen during and after infusion with VEKLURY. Tell your healthcare provider right away if your child gets any of the following signs and symptoms of allergic reactions: changes to heart rate, fever, shortness of breath, wheezing, swelling of the lips, face, or throat, rash, nausea, sweating, or shivering.
- Increases in levels of 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 child's liver enzymes before receiving VEKLURY and as needed while receiving VEKLURY. Your healthcare provider may stop treatment with VEKLURY if your child develops new or worsening liver problems.

The most common side effect of VEKLURY is nausea.

These are not all the possible side effects of VEKLURY. VEKLURY is still being studied so it is possible that all of the risks are not known at this time.

The side effects of getting any medicine by vein may include brief pain, bleeding, bruising of the skin, soreness, swelling, and possible infection at the injection site.

What other treatment choices are there?
Like VEKLURY, FDA may allow for the emergency use of other medicines to treat hospitalized children weighing 8 pounds (3.5 kg) to less than 88 pounds (40 kg) or hospitalized children younger than 12 years of age weighing at least 8 pounds (3.5 kg) with COVID-19. Go to https://www.covid19treatmentguidelines.nih.gov/ for information on the emergency use of other medicines that are not approved by the FDA to treat people in the hospital with COVID-19. Your healthcare provider may talk with you about clinical trials your child may be eligible for.

It is your choice for your child to be treated or not to be treated with VEKLURY. Should you decide not to receive VEKLURY or to stop it at any time, it will not change your child's standard medical care.

How do I report side effects with VEKLURY?
Tell your healthcare provider right away if your child has any side effect that bothers them or does not go away.

Report side effects to **FDA MedWatch** at www.fda.gov/medwatch or call 1-800-FDA-1088 and to **Gilead** by calling 1-800-GILEAD-5.

How can I learn more?

- Ask your healthcare provider.
- Visit https://www.covid19treatmentguidelines.nih.gov/
- Contact your local or state public health department.

What is an Emergency Use Authorization (EUA)?
The United States FDA has made VEKLURY available to hospitalized children weighing 8 pounds (3.5 kg) to less than 88 pounds (40 kg) or hospitalized children less than 12 years of age weighing at least 8 pounds (3.5 kg) under an emergency access mechanism called an EUA. The EUA is supported by a Secretary of Health and Human Service (HHS) declaration that circumstances exist to justify the emergency use of drugs and biological products during the COVID-19 pandemic.

The FDA may issue an EUA when certain criteria are met, which includes that there are no adequate, approved, available alternatives. In addition, the FDA decision is based on the totality of scientific evidence available showing that it is reasonable to believe that the product meets certain criteria for safety, performance, and labeling and may be effective in treatment of patients during the COVID-19 pandemic. All of these criteria must

be met to allow for the product to be used in the treatment of hospitalized children weighing 8 pounds (3.5 kg) to less than 88 pounds (40 kg) or hospitalized children less than 12 years of age weighing at least 8 pounds (3.5 kg) during the COVID-19 pandemic, and that the known and potential benefits outweigh the known and potential risks for such use.

The EUA for VEKLURY is in effect for the duration of the COVID-19 declaration justifying emergency use of the product, unless terminated or revoked (after which the product may no longer be used).

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/s/

CHRISTINE KIM
10/22/2020 02:04:22 PM
See signature authority on page 7 of the letter.