

**Emergency Use Authorization (EUA) for remdesivir, an unapproved product  
Center for Drug Evaluation and Research (CDER) Memorandum**

**Identifying Information**

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| Application Type (EUA or Pre-EUA)<br>If EUA, designate whether pre-event or intra-event EUA request.                         | EUA  |
| EUA Application Number(s)  | 46   |
| Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address | Gilead Sciences, Inc.<br>Attention: Madelyn Low, MBS<br>Senior Manager, Regulatory Affairs<br>333 Lakeside Drive Foster City, CA 94404<br>(b) (6)  |
| Submission Date(s)   | January 14, 2022; January 20, 2022   |
| Receipt Date(s)  | January 14, 2022; January 20, 2022   |
| OND Division / Office  | Division of Antivirals (DAV)/Office of Infectious Diseases (OID)   |
| Proprietary Name   | Veklury  |
| Established Name/Other names used during development   | Remdesivir (RDV)   |
| Dosage Forms/Strengths   | Lyophilized formulation for injection, 100 mg  |
| Therapeutic Class  | Coronavirus nucleoside analog RNA polymerase inhibitor   |
| Intended Use or Need for EUA   | Treatment of coronavirus disease 2019 (COVID-19)   |
| Intended Population(s)*  | Pediatric patients weighing 3.5 kg to less than 40 kg <u>or</u> pediatric patients less than 12 years of age weighing at least 3.5 kg with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are:<br><ul style="list-style-type: none"> <li>• Hospitalized (current), or</li> <li>• Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death (revised)</li> </ul> |

**I. EUA Determination/Declaration**

On February 4, 2020, Secretary of Health and Human Services determined pursuant to section 564 of the Federal Food, Drug and Cosmetic (FD&C) Act 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.

On the basis of this determination, the Secretary of Health and Human Services declared that circumstances exist justifying the authorization of emergency use of drugs and biologics during the COVID-19 outbreak, pursuant to section 564 of the FD&C Act, subject to the terms of any authorization issued under that section.

## **II. Recommendations**

### **A. Recommend EUA Revision**

Veklury (remdesivir, RDV) is currently authorized 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.

Based on review and extrapolation of efficacy data from adequate and well-controlled studies in adults (comprising the randomized clinical trials submitted to support the original NDA approval) and the results of Study GS-US-540-9012 (submitted to support the supplemental NDA approval and summarized below), the Division of Antivirals, Office of Infectious Diseases, Office of New Drugs, CDER recommends issuance of a revision to EUA 46 to include use for the treatment of coronavirus disease 2019 (COVID-19) in pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg, with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death. The pediatric population age and weight range for whom RDV is authorized remains the same, i.e. 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg.

The Omicron variant of concern (VOC) has become the dominant variant in the US and is predicted to have reduced susceptibility to several anti-SARS-CoV-2 monoclonal antibodies (mAbs); it is anticipated there will be a limited supply of other therapeutic agents that are active against the Omicron variant for patients, including children, who are at high risk of progression to severe COVID-19 and who might benefit from these therapies. We considered this therapeutic context as part of our recommendation to revise this EUA for Veklury.

Based on cell culture antiviral activity data, RDV is expected to be active against SARS-CoV-2 variants that have circulated at a high frequency to date, including against the Omicron (B.1.1.529) VOC. Preliminary antiviral activity of RDV and its active form GS-441524 against a representative of the Omicron variant has been evaluated along with representative Alpha, Beta, Gamma, and Delta variants in an authentic virus inhibition assay in Vero E6 cells. The preliminary data indicate that RDV and GS-441524 retain activity against each variant evaluated (EC<sub>50</sub>

value range: 0.048-0.077  $\mu$ M). While a wild type control virus was not included in the reported results, EC<sub>50</sub> values against Omicron were within 2-fold those of variants previously evaluated, which have been shown to be susceptible relative to wild type (WA1). The nsp12 gene of Omicron is commonly distinguished from wild type virus (WA1) by a single substitution, P323L, which is also shared by other variants that have been evaluated and which does not appear to impact RDV activity in cell culture. Together, these data indicate that RDV is not expected to have reduced activity against the evaluated variants in cell culture, including Delta and Omicron variants.

## **B. Summary of Regulatory Actions for EUA and NDA**

On May 1, 2020, the Agency granted emergency use authorization (EUA) for the investigational antiviral RDV to treat adults and children hospitalized with severe COVID-19. Based on review of the topline data from the randomized, double-blinded, placebo-controlled trial conducted by NIAID (ACTT-1; NCT04280705) and from the Gilead-sponsored open-label trial that evaluated different durations of RDV (Study 5773 [Part A]; NCT04292899), the Agency concluded that, based on the totality of scientific evidence available, including information from adequate and well-controlled clinical trials, it is reasonable to believe that RDV may be effective for the treatment of adults and children with suspected or laboratory confirmed COVID-19 hospitalized with severe COVID-19 (defined as SpO<sub>2</sub>  $\leq$  94% on room air, or requiring supplemental oxygen, or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation), and that the known and potential benefits of RDV, when used for the treatment of COVID-19 as authorized, outweighed the known and potential risks of the product. Please refer to the June 15, 2020, July 27, 2020 and August 28, 2020 EUA revisions for additional details.

On October 22, 2020, FDA approved Veklury for use in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization. The October 22, 2020 NDA indication does not include those 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 requiring hospitalization.

At the time of the October 22, 2020 NDA approval, the Agency issued a Pediatric Research Equity Act (PREA) post-marketing requirement (PMR) for the conduct of a clinical trial in pediatric patients and the submission of the results from that trial to the Agency; the aforementioned pediatric trial is currently ongoing and, once completed, the data may support revising the indication to include use in a broader pediatric patient population.

Concurrent with the October 22, 2020 approval of NDA 214787, FDA also revised the EUA for Veklury to remove the previously authorized uses (use in adults and certain pediatric patients) covered under the approved NDA. FDA

continued to authorize 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. This assessment was based on review and extrapolation of efficacy data from the three aforementioned randomized clinical trials in hospitalized adults that supported the October 22, 2020 approval of NDA 214787. FDA determined that retaining this authorized use is appropriate to protect public health or safety under section 564(g)(2) of the Federal Food, Drug and Cosmetic Act. The Agency believed that maintaining the EUA will ensure that important information about the recommended use (e.g., dosing recommendations) for pediatric patients not covered under the USPI will continue to be available to health care providers. As noted above, FDA revised the EUA concurrent with the approval of RDV.

### **III. Proposed Use and Dosing of the Product Under the EUA**

#### Proposed Use Under EUA:

We recommend that EUA 46 should be revised to authorize RDV for emergency 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 with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

#### New Authorized Dosage Under EUA:

Non-hospitalized patients:

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

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

### Recommended Dosage Form and Dosage in Pediatric Patients

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

The dose preparation, administration, how supplied and storage and handling instructions remain unchanged.

#### Rationale for Dose in Pediatrics:

The recommended dose for RDV for use in non-hospitalized pediatric patients with mild-to-moderate COVID-19 was based on the following:

- Based on pharmacokinetic modeling and simulation, exposures in pediatric patients after administration of the authorized pediatric dose(s) are expected to be comparable to the exposures observed in adults after administration of the authorized adult dose(s).
- The recommended dosing in hospitalized and non-hospitalized adult and pediatric patients for the approved product is the same except for the duration of therapy (5-10 days for hospitalized and 3 days for non-hospitalized). Therefore, the same principle was used for the pediatric patients 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg. The same dosing under the EUA for hospitalized pediatric patients was used for the revised EUA for non-hospitalized pediatric patients except for the duration (5-10 days for hospitalized and 3 days for non-hospitalized).
- Robust clinical data are available in hospitalized and non-hospitalized adults. Because exposures in pediatric patients are expected to be comparable to the exposures observed in adults, the EUA revision for non-hospitalized pediatric patients with mild-to-moderate COVID-19 is supported through extrapolation of efficacy from adequate and well-controlled studies in adults.

#### IV. Summary of Data

Detailed Rationale for Revision of the Authorized Use for Symptomatic COVID-19 for Pediatric Patients who are Not hospitalized and have Mild-to-Moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death

There is statistical evidence for the efficacy of RDV for the treatment of patients who are not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death:

- Study GS-US-540-9012: Randomized, double-blind trial comparing RDV for 3 days versus placebo (PBO) in 562 non-hospitalized patients with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death. Results for the primary efficacy analysis in the overall study population strongly favored RDV.

Study GS-US-540-9012, a Phase 3 randomized, double-blind, placebo-controlled, clinical trial (NCT04501952) evaluated RDV 200 mg once daily for 1 day followed by RDV 100 mg once daily for 2 days (for a total of 3 days of intravenously administered therapy) in 554 adult and 8 pediatric subjects (12 years of age and older and weighing at least 40 kg) who were non-hospitalized, had mild-to-moderate COVID-19, were symptomatic for COVID-19 for  $\leq 7$  days, had confirmed SARS-CoV-2 infection, and had at least one risk factor for progression to hospitalization. Risk factors for progression to hospitalization included age  $\geq 60$  years, obesity (BMI  $\geq 30$ ), chronic lung disease, hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, immunocompromised state, chronic mild or moderate kidney disease, chronic liver disease, current cancer, and sickle cell disease. Subjects who received, required, or were expected to require supplemental oxygen were excluded from the trial. Subjects were randomized in a 1:1 manner, stratified by residence in a skilled nursing facility (yes/no), age ( $<60$  vs  $\geq 60$  years), and region (US vs ex-US) to receive RDV (n=279) or PBO (n=283), plus standard of care.

At baseline, mean age was 50 years (with 30% of subjects aged 60 or older); 52% were male, 80% were White, 8% were Black, and 2% were Asian; 44% were Hispanic or Latino; median body mass index was 30.7 kg/m<sup>2</sup>. Subjects in this trial were unvaccinated. Subjects initiated treatment with RDV or placebo in outpatient facilities (84%), home healthcare settings (13%), or skilled nursing facilities (3%). The most common comorbidities were diabetes mellitus (62%), obesity (56%), and hypertension (48%). Median (Q1, Q3) duration of symptoms prior to treatment was 5 (3, 6) days; median viral load was 6.3 log<sub>10</sub> copies/mL at baseline. The baseline demographics and disease characteristics were well balanced across the RDV and PBO treatment groups.

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

The overall safety profile for the 3-day course of IV RDV in non-hospitalized subjects is consistent with the known safety profile of IV RDV administered to hospitalized subjects for 5 or 10 days.

Of the 562 subjects in Study GS-US-540-9012, 279 (276 adults and 3 pediatric subjects) were treated with RDV for 3 days, and 283 (278 adults and 5 pediatric subjects) were treated with placebo for 3 days.

Of the 279 subjects treated with RDV, 227 subjects received at least one dose of RDV at an outpatient facility, 44 subjects received at least one dose of RDV in a home healthcare setting, and 8 subjects received at least one dose of VEKLURY at a skilled nursing facility. Subjects treated with RDV received 200 mg on Day 1 and 100 mg once daily on subsequent days. Adverse reactions (all grades) were reported in 34 (12%) subjects in the RDV group and 25 (9%) subjects in the placebo group. The most common adverse reaction occurring in at least 5% of subjects in the RDV group was nausea (6%). There were no serious adverse reactions or adverse reactions leading to treatment discontinuation in either treatment group. The safety of RDV in subjects who received RDV in a home healthcare setting was comparable to that observed in the overall GS-US-540-9012 study population, but this conclusion is based on limited data. Laboratory abnormalities (Grades 3 and 4) reported in  $\geq 2\%$  of subjects (RDV vs PBO) were creatinine clearance decreased (6% vs 2%), creatinine increased (3% vs 1%), glucose increased (6% vs 6%), lymphocytes decreased (2% vs 1%) and prothrombin time increased 1% vs 2%).

## V. Summary of Revisions to EUA Fact Sheets

- Authorized Use (Section 1):
  - Expanding the scope of the authorized use to include the treatment of COVID-19 in pediatric patients with positive results of direct SARS-CoV-2 viral testing, who are not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.

The authorized age and/or weight range remain unchanged: 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.

- Dosing (Section 2):
  - Added dosing recommendations for non-hospitalized pediatric patients with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19, including hospitalization or death. Dosing recommendations are identical to those for hospitalized pediatric patients except the duration is 3 days instead of 5-10 days.
  - Updated the recommendations for monitoring (during infusion and post-infusion).

- Warnings and Precautions (Section 5):
  - Section 5.1 of the Warnings and Precautions section (hypersensitivity reactions including infusion-related and anaphylactic reactions) was revised with the recommendations for monitoring (during infusion and at least one-hour post-infusion) that were added to Section 2. The additional wording for post-infusion monitoring is based on the totality of data from hospitalized and non-hospitalized settings, and the finding that the majority of these reactions, including those that resulted in the Warnings and Precautions, occurred within one-hour post-infusion.
- Overall Safety Summary (Section 6):
  - Updated with the Study GS-US-540-9012 safety data that will be described in the USPI.
- Use in Specific Populations (Section 11):
  - The Pediatric subsection was revised for consistency with the revised pediatric population cover under this EUA revision.
  - Information regarding the pregnancy exposure registry was added.
- Clinical Trial Results and Supporting Data for EUA (Section 18):
  - Updated with the Study GS-US-540-9012 efficacy data that will be described in the USPI.
- Editorial revisions to the Fact Sheets for consistency with the pediatric EUA and to avoid redundancy.

## **VI. Risk-Benefit Assessment and Recommendations for Emergency Use**

Based on the totality of scientific evidence available, it is reasonable to believe that Veklury may be effective for the treatment of COVID-19 in pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg, with positive results of direct SARS-CoV-2 viral testing, who are not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death, and that, the known and potential benefits of Veklury, when administered for the treatment of COVID-19 as described above, outweigh the known and potential risks of the product.

As such, concurrent with the approval of NDA 214787/S-10, CDER recommends that EUA 046 be revised to expand the scope of authorized uses consistent with the above. In effect, the recommended revision to EUA 046 would authorize Veklury (remdesivir) for emergency use for the treatment of COVID-19 in pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg, with positive results of direct SARS-CoV-2 viral testing, who are:

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



The EUA is specifically 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.

Although the available data have limitations, it is plausible that the impact of a direct-acting antiviral drug (such as remdesivir) for the treatment of COVID-19 may be greater if administered earlier in the disease course when viral replication, as opposed to immunopathological processes, may be playing a greater role.

FDA has determined that expanding this authorized use is appropriate to protect public health or safety under section 564(g)(2) of the Federal Food, Drug and Cosmetic Act. The Agency believes that expanding the EUA will ensure that important information about the recommended use (e.g., dosing recommendations) for pediatric patients not covered under the USPI will continue to be available to health care providers. As noted above, FDA will revise the EUA concurrent with the approval of NDA 214787/S-10.

**FACT SHEET FOR HEALTHCARE PROVIDERS  
EMERGENCY USE AUTHORIZATION (EUA) OF VEKLURY® (remdesivir) FOR  
THE TREATMENT OF CORONAVIRUS DISEASE 2019 (COVID-19) IN  
PEDIATRIC PATIENTS WEIGHING 3.5 KG TO LESS THAN 40 KG OR  
PEDIATRIC PATIENTS LESS THAN 12 YEARS OF AGE WEIGHING AT  
LEAST 3.5 KG, WITH POSITIVE RESULTS OF DIRECT SARS-CoV-2 VIRAL  
TESTING WHO ARE:  
HOSPITALIZED, OR  
NOT HOSPITALIZED AND HAVE MILD-TO-MODERATE COVID-19, AND ARE  
AT HIGH RISK FOR PROGRESSION TO SEVERE COVID-19, INCLUDING  
HOSPITALIZATION OR DEATH**

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to permit the emergency use of VEKLURY for the treatment of coronavirus disease 2019 (COVID-19) in pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg, with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are:

- Hospitalized, or
- Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death. Refer to CDC website<sup>1</sup> for additional details.

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

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

**This EUA is for the use of VEKLURY to treat COVID-19 in pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg, with positive results of direct SARS-CoV-2 viral testing who are:  
Hospitalized, or  
Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.**

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



**VEKLURY must be administered by intravenous (IV) infusion.**

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

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

**Hospitalized patients:**

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

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

**Non-hospitalized patients:**

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

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

Administer VEKLURY via intravenous infusion over 30 to 120 minutes.

For information on clinical trials that are testing the use of VEKLURY in COVID-19, please see [www.clinicaltrials.gov](https://www.clinicaltrials.gov).

## AUTHORIZED USE

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

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

VEKLURY is not approved to treat pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg.

VEKLURY is authorized for use under an EUA for the treatment of COVID-19 in pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg, with positive results of direct SARS-CoV-2 viral testing, who are:

- Hospitalized, or
- Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death. Refer to CDC website<sup>2</sup> for additional details.

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

## Contraindications

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

## Dosing

### Patient Selection and Treatment Initiation

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

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

- least 7 days to less than or equal to 28 days old) must have serum creatinine determined before starting VEKLURY and be monitored during treatment as clinically appropriate.
- Perform hepatic laboratory testing in all patients before starting VEKLURY and during treatment as clinically appropriate.
  - Determine prothrombin time in all patients before starting VEKLURY and monitor during treatment as clinically appropriate.
  - **The only authorized dosage form of VEKLURY for pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg is VEKLURY for injection (supplied as 100 mg lyophilized powder in vial).**
  - For pediatric patients weighing 3.5 kg to less than 40 kg, administer a body weight-based dosing regimen of VEKLURY.
  - For pediatric patients less than 12 years of age and weighing 40 kg and higher, administer a single loading dose of VEKLURY 200 mg on Day 1 followed by once-daily maintenance doses of VEKLURY 100 mg from Day 2.
  - Table 1 below provides the recommended dosage and dosage form in pediatric patients under this EUA [see *Full EUA Prescribing Information, Recommended Dosage in Pediatric Patients (2.3)*].

**Table 1 Recommended Dosage Form and Dosage in Pediatric Patients**

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

Hospitalized patients:

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

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

#### Non-hospitalized patients:

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

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

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

#### Renal Impairment

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

#### Dose Preparation

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

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

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

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

#### **Important Preparation and Administration Instructions**

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

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

#### Storage and Handling of Reconstituted Vial and Diluted Solution

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

Store diluted VEKLURY solution for infusion for no more than 24 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) prior to administration.

#### **Warnings**

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

#### Hypersensitivity Including Infusion-Related and Anaphylactic Reactions

Hypersensitivity reactions, including infusion-related and anaphylactic reactions, have been observed during and following administration of VEKLURY; most occurred within one hour. Signs and symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, diaphoresis, and shivering. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. Monitor patients during infusion and observe patients for at least one hour after infusion is complete for signs and symptoms of hypersensitivity as clinically appropriate. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration of VEKLURY and initiate appropriate treatment. The use of VEKLURY is contraindicated in patients with known hypersensitivity to VEKLURY or any components of the product [see *Full EUA Prescribing Information, Contraindications (4), Warnings and Precautions (5.1)*].

#### Increased Risk of Transaminase Elevations

Transaminase elevations have been observed in healthy volunteers who received 200 mg of VEKLURY followed by 100 mg doses up to 10 days; the transaminase elevations were mild (Grade 1) to moderate (Grade 2) in severity and resolved upon discontinuation of VEKLURY. Transaminase elevations have

also been reported in patients with COVID-19 who received VEKLURY. Because transaminase elevations have been reported as a clinical feature of COVID-19, and the incidence was similar in patients receiving placebo versus VEKLURY in clinical trials of VEKLURY, discerning the contribution of VEKLURY to transaminase elevations in patients with COVID-19 can be challenging [see *Full EUA Prescribing Information, Warnings and Precautions (5.2)*].

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

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

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

Coadministration of VEKLURY and chloroquine phosphate or hydroxychloroquine sulfate is not recommended based on data from cell culture experiments demonstrating a potential antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of VEKLURY [see *Full EUA Prescribing Information, Warnings and Precautions (5.3), Drug Interactions (10), Microbiology/Resistance Information (15)*].

### **Serious Side Effects**

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

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

### **INSTRUCTIONS FOR HEALTHCARE PROVIDERS**

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

- That FDA has authorized the emergency use of VEKLURY for the treatment of coronavirus disease 2019 (COVID-19) in pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg, with positive results of direct SARS-CoV-2 viral testing, who are:
  - Hospitalized, or
  - Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death.



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

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

For information on clinical trials that are testing the use of VEKLURY for COVID-19, please see [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

### **MANDATORY REQUIREMENTS FOR VEKLURY ADMINISTRATION UNDER EMERGENCY USE AUTHORIZATION:**

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

1. VEKLURY is authorized for the treatment of COVID-19 in pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg, with positive results of direct SARS-CoV-2 viral testing, who are:
  - Hospitalized, or
  - Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death. Please refer to CDC website<sup>3</sup> for additional details.
2. As the healthcare provider, communicate to the parent/caregiver and your patient, as age appropriate, information consistent with the “Fact Sheet for Parents and Caregivers” prior to the patient receiving VEKLURY. Healthcare providers (to the extent practicable given the circumstances of the emergency) must document in the patient’s medical record that the parent/caregiver has been:
  - Given the “Fact Sheet for Parents and Caregivers,”
  - Informed of alternatives to receiving VEKLURY, and
  - Informed that VEKLURY is an approved drug that is authorized for this unapproved use under EUA.
3. Pediatric patients (greater than 28 days old) must have an eGFR determined and full-term neonates (at least 7 days to less than or equal to 28 days old) must have serum creatinine determined before starting VEKLURY and monitored during treatment as clinically appropriate.

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

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

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

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

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

Gilead Global Patient Safety

Fax: 1-650-522-5477

E-mail: [Safety\\_fc@gilead.com](mailto:Safety_fc@gilead.com)

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

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

\*Serious Adverse Events are defined as:

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

## **APPROVED AVAILABLE ALTERNATIVES**

There is no approved available alternative product for the treatment of COVID-19 in pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg, with positive results of direct SARS-CoV-2 viral testing, and who are:

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

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

## **AUTHORITY FOR ISSUANCE OF THE EUA**

The Secretary of HHS has declared that circumstances exist that justify the emergency use of drugs and biological products during the COVID-19 pandemic. In response, the FDA has issued an EUA for the approved product, VEKLURY, for the unapproved use to treat COVID-19 in pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg, with positive results of direct SARS-CoV-2 viral testing, and who are<sup>4</sup>:

- Hospitalized, or

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

- Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death. Please refer to CDC website<sup>5</sup> for additional details.

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

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

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

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

# FULL EUA PRESCRIBING INFORMATION

## FULL EUA PRESCRIBING INFORMATION: CONTENTS\*

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

## 1. AUTHORIZED USE

VEKLURY is authorized for use under an EUA for the treatment of coronavirus disease 2019 (COVID-19) in pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg, with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are:

- Hospitalized, or
- Not hospitalized and have mild-to-moderate COVID-19, and are at high risk for progression to severe COVID-19, including hospitalization or death. Refer to CDC website<sup>6</sup> for additional details.

## 2. DOSAGE AND ADMINISTRATION

### 2.1 Dosage and Administration Overview

- VEKLURY may only be administered in settings in which healthcare providers have immediate access to medications to treat a severe infusion or hypersensitivity reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary [see *Warnings and Precautions* (5.1)].

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

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

## 2.2 Important Testing Before and During Treatment

- Pediatric patients (greater than 28 days old) must have an eGFR determined and full-term neonates (at least 7 days to less than or equal to 28 days old) must have serum creatinine determined before starting VEKLURY and during treatment as clinically appropriate [see *Dosage and Administration* (2.4), *Use in Specific Populations* (11.4)].
- Perform hepatic laboratory testing in all patients before starting VEKLURY and during treatment as clinically appropriate [see *Warnings and Precautions* (5.2), *Use in Specific Populations* (11.5)].
- Determine prothrombin time in all patients before starting VEKLURY and monitor during treatment as clinically appropriate [see *Overall Safety Summary* (6.1)].

## 2.3 Recommended Dosage in Pediatric Patients

**The only authorized dosage form of VEKLURY for pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg is VEKLURY for injection (supplied as 100 mg lyophilized powder in vial).**

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

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

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

**Table 1 Recommended Dosage Form and Dosage in Pediatric Patients**

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

Hospitalized patients:

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

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

#### Non-hospitalized patients:

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

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

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

## **2.4 Renal Impairment**

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

## **2.5 Dose Preparation and Administration, VEKLURY for Injection**

The authorized dosage form of VEKLURY for pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg is VEKLURY for injection (supplied as 100 mg lyophilized powder) only.

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard the vial if the lyophilized powder is discolored or contains particulate matter. Prior to dilution in 0.9% sodium chloride, reconstituted VEKLURY for injection should be a clear, colorless to yellow solution, free of visible particles.
- **Care should be taken during admixture to prevent inadvertent microbial contamination.** As there is no preservative or bacteriostatic agent present in this product, aseptic technique must be used in preparation of the final parenteral solution. It is always recommended to

administer intravenous medication immediately after preparation when possible.

#### Reconstitution Instructions

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

- Aseptically reconstitute VEKLURY lyophilized powder by addition of 19 mL of Sterile Water for Injection using a suitably sized syringe and needle per vial.
- Only use Sterile Water for Injection to reconstitute VEKLURY lyophilized powder.
- Discard the vial if a vacuum does not pull the Sterile Water for Injection into the vial.
- Immediately shake the vial for 30 seconds.
- Allow the contents of the vial to settle for 2 to 3 minutes. A clear, colorless to yellow solution, free of visible particles, should result.
- If the contents of the vial are not completely dissolved, shake the vial again for 30 seconds and allow the contents to settle for 2 to 3 minutes. Repeat this procedure as necessary until the contents of the vial are completely dissolved. Discard the vial if the contents are not completely dissolved.
- Following reconstitution, each vial contains 100 mg/20 mL (5 mg/mL) of remdesivir solution.
- Use reconstituted VEKLURY for injection immediately to prepare the diluted solution.

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

##### *Dilution Instructions*

- For pediatric patients weighing 3.5 kg to less than 40 kg, the 100 mg/20 mL (5 mg/mL) remdesivir reconstituted solution should be further diluted to a fixed concentration of 1.25 mg/mL using 0.9% sodium chloride.
- The final required infusion volume concentration of 1.25 mg/mL remdesivir diluted solution for infusion is based on the pediatric weight-based dosing regimens of 5 mg/kg for the Loading Dose and 2.5 mg/kg for each Maintenance Dose.
- Small 0.9% sodium chloride infusion bags (e.g., 25, 50, or 100 mL) or an appropriately sized syringe should be used for pediatric dosing. The recommended dose is administered via intravenous infusion in a total volume dependent on the dose to yield the target remdesivir concentration of 1.25 mg/mL.
- A syringe and syringe pump may be used for infusion volumes less than 50 mL.
- Refer to Table 2 for recommended rate of infusion.

##### Infusion with IV Bag



- Determine the total infusion volume needed to achieve a final infusion volume concentration of 1.25 mg/mL of remdesivir diluted solution based on the patient's calculated dose.
- Select an appropriately sized infusion bag (either prefilled with 0.9% sodium chloride or empty) to prepare VEKLURY diluted solution.
- If using a prefilled 0.9% sodium chloride infusion bag, withdraw and discard the amount of diluent equal to the volume of reconstituted VEKLURY solution needed per patient's dose plus a quantity sufficient to achieve a 1.25 mg/mL final volume concentration of remdesivir diluted solution.
- Withdraw the required volume of reconstituted VEKLURY solution into an appropriately sized syringe.
- Transfer the required volume of reconstituted VEKLURY solution to the 0.9% sodium chloride infusion bag.
- Gently invert the bag 20 times to mix the solution in the bag. Do not shake.
- If using an empty infusion bag, transfer the required volume of reconstituted VEKLURY solution to the bag, followed by a volume of 0.9% sodium chloride sufficient to achieve a 1.25 mg/mL final volume concentration of remdesivir diluted solution.
- The prepared infusion solution is stable for 24 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

#### Infusion with Syringe

- Determine the total infusion volume needed to achieve a final infusion volume concentration of 1.25 mg/mL of remdesivir diluted solution based on patient's calculated dose.
- Select an appropriately sized syringe equal to or larger than the calculated total infusion volume of 1.25 mg/mL remdesivir solution needed.
- Withdraw the required volume of reconstituted VEKLURY solution from the vial into the syringe based on patient's calculated dose, followed by the required volume of 0.9% sodium chloride needed to achieve a 1.25 mg/mL final volume concentration of remdesivir diluted solution.
- Gently invert the syringe 20 times to mix the solution in the syringe. Do not shake.

The prepared diluted solution should be used immediately.

#### Administration Instructions

The prepared diluted solution should not be administered simultaneously with any other medication. The compatibility of VEKLURY with IV solutions and medications other than 0.9% sodium chloride injection, USP is not known.

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

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

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

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

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

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

*Dilution Instructions*

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

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

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

- Withdraw and discard the required volume of 0.9% sodium chloride from the infusion bag following instructions in Table 3, using an appropriately sized syringe and needle.
- Withdraw the required volume of reconstituted VEKLURY for injection from the VEKLURY vial following instructions in Table 3. Discard any unused portion remaining in the reconstituted vial.
- Transfer the required volume of reconstituted VEKLURY for injection to the selected infusion bag.
- Gently invert the bag 20 times to mix the solution in the bag. Do not shake.
- The prepared diluted solution is stable for 24 hours at room temperature (20°C to 25°C [68°F to 77°F]) or 48 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]).

#### *Administration Instructions*

The prepared diluted solution should not be administered simultaneously with any other medication. The compatibility of VEKLURY with IV solutions and medications other than 0.9% sodium chloride injection, USP is not known.

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

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

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

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

## 2.6 Storage of Prepared Dosages

After reconstitution, use vials immediately to prepare diluted solution.

The diluted VEKLURY solution in syringe should be used immediately.

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

### IMPORTANT:

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

## 3. DOSAGE FORMS AND STRENGTHS

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

## 4. CONTRAINDICATIONS

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

## 5. WARNINGS AND PRECAUTIONS

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

### 5.1 Hypersensitivity Including Infusion-Related and Anaphylactic Reactions

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

### 5.2 Increased Risk of Transaminase Elevations

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

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

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

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

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

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

## 6. OVERALL SAFETY SUMMARY

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

### 6.1 Clinical Trials Experience

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

NIAID ACTT-1 was a randomized, double-blind, placebo-controlled clinical trial in hospitalized adult subjects with mild, moderate, and severe COVID-19 treated with VEKLURY (n=532) or placebo (n=516) for up to 10 days. Subjects treated with VEKLURY received 200 mg on Day 1 and 100 mg once daily on subsequent days. The collection of adverse event data in this trial was limited to severe (Grade 3) or potentially life-threatening (Grade 4) adverse events, serious adverse events, adverse events leading to study drug discontinuation, and moderate (Grade 2) severity or higher hypersensitivity reactions. Rates of adverse reactions ( $\geq$  Grade 3), serious adverse reactions, and adverse reactions leading to treatment discontinuation are presented in Table 5.

**Table 5 Summary of Adverse Reaction Rates in Hospitalized Adult Subjects with Mild, Moderate, or Severe COVID-19 in NIAID ACTT-1**

| <b>Types of Adverse Reactions</b>                      | <b>VEKLURY<br/>N=532<br/>n (%)</b> | <b>Placebo<br/>N=516<br/>n (%)</b> |
|--|------------------------------------|------------------------------------|
| Adverse reactions, Grades $\geq 3$                     | 41 (8%)                            | 46 (9%)                            |
| Serious adverse reactions                              | 2 (0.4%) <sup>a</sup>              | 3 (0.6%)                           |
| Adverse reactions leading to treatment discontinuation | 11 (2%) <sup>b</sup>               | 15 (3%)                            |

a. Seizure (n=1), infusion-related reaction (n=1).

b. Seizure (n=1), infusion-related reaction (n=1), transaminases increased (n=3), ALT increased and AST increased (n=1), GFR decreased (n=2), acute kidney injury (n=3).

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

**Table 6 Summary of Adverse Reaction Rates in Hospitalized Adult Subjects with Severe COVID-19 in Study 5773**

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

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<sup>a</sup> Rates in Hospitalized Adult Subjects with Moderate COVID-19 in Study 5774**

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

a. Attribution of events to study drug was not performed for the SOC group.

b. Heart rate decreased.

c. ALT increased (n=2), ALT increased and AST increased (n=1), hypertransaminasaemia (n=1), blood alkaline phosphatase increased (n=1), rash (n=2), heart rate decreased (n=1).

Study GS-US-540-9012 was a randomized, double-blind, placebo-controlled clinical trial in subjects who were non-hospitalized, were symptomatic for COVID-19 for ≤7 days, had confirmed SARS-CoV-2 infection, and had at least one risk factor for progression to hospitalization treated with VEKLURY (n=279; 276 adults and 3 pediatric subjects 12 years of age and older weighing at least 40 kg) or placebo (n=283; 278 adults and 5 pediatric subjects 12 years of age and older weighing at least 40 kg) for 3 days. Of the 279 subjects treated with VEKLURY, 227 subjects received at least one dose of VEKLURY at an outpatient facility, 44 subjects received at least one dose of VEKLURY in a home healthcare setting, and 8 subjects received at least one dose of VEKLURY at a skilled nursing facility. Subjects treated with VEKLURY received 200 mg on Day 1 and 100 mg once daily on subsequent days [see *Clinical Trial Results and Supporting Data for EUA (18)*]. Adverse reactions (all grades) were reported in 34 (12%) subjects in the VEKLURY group and 25 (9%) subjects in the placebo group. The most common adverse reaction occurring in at least 5% of subjects in the VEKLURY group was nausea (6%). There were no serious adverse reactions or adverse reactions leading to treatment discontinuation in either treatment group. Safety in subjects who received VEKLURY in a home healthcare setting was comparable to that observed in the overall GS-US-540-9012 study population, but these findings are based on limited data.

#### Less Common Adverse Reactions

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

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



## Emergency Use Authorization Experience in Subjects with COVID-19

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

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

### Laboratory Abnormalities

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

The frequencies of laboratory abnormalities (Grades 3-4) occurring in at least 3% of adult subjects with COVID-19 receiving VEKLURY in Trials NIAID ACTT-1, 5773, and 5774 are presented in Table 8, Table 9, and Table 10, respectively.

**Table 8 Laboratory Abnormalities (Grades 3-4) Reported in ≥3% of Hospitalized Adult Subjects with Mild, Moderate, or Severe COVID-19 in NIAID ACTT-1**

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

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

b. Based on the Cockcroft-Gault formula.

**Table 9 Laboratory Abnormalities (Grades 3-4) Reported in ≥3% of Hospitalized Adult Subjects with Severe COVID-19 in Trial 5773**

| <b>Laboratory Parameter Abnormality<sup>a</sup></b> | <b>VEKLURY<br/>5 Days<br/>N=200</b> | <b>VEKLURY<br/>10 Days<br/>N=197</b> |
|---|-------------------------------------|--------------------------------------|
| ALT increased                                       | 6%                                  | 8%                                   |
| AST increased                                       | 7%                                  | 6%                                   |
| Creatinine clearance decreased <sup>b</sup>         | 10%                                 | 19%                                  |
| Creatinine increased                                | 5%                                  | 15%                                  |
| Glucose increased                                   | 11%                                 | 8%                                   |
| Hemoglobin decreased                                | 6%                                  | 8%                                   |

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

b. Based on the Cockcroft-Gault formula.

**Table 10 Laboratory Abnormalities (Grades 3-4) Reported in ≥3% of Hospitalized Adult Subjects with Moderate COVID-19 in Trial 5774**

| <b>Laboratory Parameter Abnormality<sup>a</sup></b> | <b>VEKLURY<br/>5 Days<br/>N=191</b> | <b>VEKLURY<br/>10 Days<br/>N=193</b> | <b>SOC<br/>N=200</b> |
|---|-------------------------------------|--------------------------------------|----------------------|
| ALT increased                                       | 2%                                  | 3%                                   | 8%                   |
| Creatinine clearance decreased <sup>b</sup>         | 2%                                  | 5%                                   | 8%                   |
| Glucose increased                                   | 4%                                  | 3%                                   | 2%                   |
| Hemoglobin decreased                                | 3%                                  | 1%                                   | 6%                   |

SOC=Standard of care.

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

b. Based on the Cockcroft-Gault formula.

The frequencies of laboratory abnormalities (Grades 3-4) occurring in at least 2% of subjects with COVID-19 receiving VEKLURY in Trial GS-US-540-9012 are presented in Table 11.

**Table 11 Laboratory Abnormalities (Grades 3-4) Reported in ≥2% of Non-Hospitalized Subjects in Trial 9012**

| <b>Laboratory Parameter Abnormality<sup>a</sup></b> | <b>VEKLURY 3 Days<br/>N=279</b> | <b>Placebo<br/>N=283</b> |
|---|---------------------------------|--------------------------|
| Creatinine clearance decreased <sup>b</sup>         | 6%                              | 2%                       |
| Creatinine increased                                | 3%                              | 1%                       |
| Glucose increased                                   | 6%                              | 6%                       |
| Lymphocytes decreased                               | 2%                              | 1%                       |
| Prothrombin time increased                          | 1%                              | 2%                       |

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

## **7. PATIENT MONITORING RECOMMENDATIONS**

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

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

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

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

## **8. ADVERSE REACTIONS AND MEDICATION ERRORS REPORTING REQUIREMENTS AND INSTRUCTIONS**

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

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

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

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

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

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

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

\*Serious adverse events are defined as:

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

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

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

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

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

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

## 9. OTHER REPORTING REQUIREMENTS

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

Gilead Global Patient Safety

Fax: 1-650-522-5477

E-mail: [Safety\\_fc@gilead.com](mailto:Safety_fc@gilead.com)

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

## 10. DRUG INTERACTIONS

Due to potential antagonism based on data from cell culture experiments, concomitant use of VEKLURY with chloroquine phosphate or hydroxychloroquine sulfate is not recommended [see *Warnings and Precautions* (5.3), *Microbiology/Resistance Information* (15)].

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

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

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

## **11. USE IN SPECIFIC POPULATIONS**

### **11.1 Pregnancy**

#### Pregnancy Exposure Registry

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

#### Risk Summary

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

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

#### Clinical Considerations

##### *Disease-associated maternal and/or embryo-fetal risk*

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

##### Animal Data

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

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

## 11.2 Lactation

### Risk Summary

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

### Animal Data

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

## 11.3 Pediatric Use

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

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

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

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

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

#### **11.4 Renal Impairment**

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

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

#### **11.5 Hepatic Impairment**

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

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

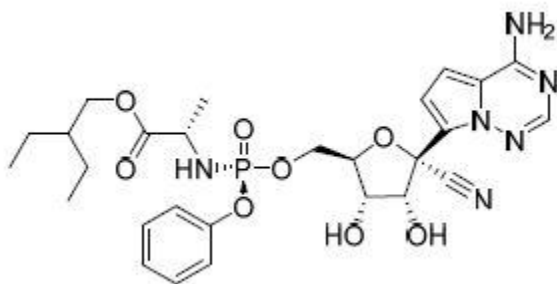
### **12. OVERDOSAGE**

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



### 13. PRODUCT DESCRIPTION

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



#### 13.1 Physical Appearance

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

#### 13.2 Inactive Ingredients

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

### 14. CLINICAL PHARMACOLOGY

#### 14.1 Mechanism of Action

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

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

#### 14.2 Pharmacokinetics

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

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

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

ND=not detected

- Remdesivir administered as a 30-minute IV infusion (Study GS-US-399-5505); range of median observed on Day 1 and Day 5 or 10.
- Range of protein binding for remdesivir from 2 independent experiments show no evidence of concentration-dependent protein binding for remdesivir.
- Median (Study GS-US-399-4231).
- Mean (Study GS-US-399-4231).

**Table 13 Multiple Dose PK Parameters<sup>a</sup> 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 <sub>max</sub><br>(nanogram per mL)     | 2229 (19.2) | 145 (19.3)  | 246 (33.9) |
| AUC <sub>tau</sub><br>(nanogram·h per mL) | 1585 (16.6) | 2229 (18.4) | 462 (31.4) |
| C <sub>trough</sub><br>(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<sub>50</sub>) of 9.9 nM after 48 hours of treatment. Remdesivir inhibited the replication of SARS-CoV-2 in the continuous human lung epithelial cell lines Calu-3 and A549-hACE2 with EC<sub>50</sub> values of 280 nM after 72 hours of treatment and 115 nM after 48 hours of treatment, respectively.

Remdesivir EC<sub>50</sub> values for SARS-CoV-2 in A549-hACE2 cells were not different when combined with chloroquine phosphate or hydroxychloroquine sulfate at concentrations up to 2.5 μM. In a separate study, the antiviral activity of remdesivir was antagonized by chloroquine phosphate in a dose-dependent manner when the two drugs were co-incubated at clinically relevant concentrations in HEp-2 cells infected with respiratory syncytial virus (RSV). Higher remdesivir EC<sub>50</sub> values were observed with increasing concentrations of chloroquine phosphate. Increasing concentrations of chloroquine phosphate or

hydroxychloroquine sulfate reduced formation of remdesivir triphosphate in A549-hACE2, HEp-2, and normal human bronchial epithelial cells.

Based on cell culture susceptibility testing by plaque assay and/or N protein ELISA assay, remdesivir retained similar antiviral activity ( $\leq 1.5$ -fold change) against clinical isolates of SARS-CoV-2 variants containing the P323L substitution in the viral polymerase including the Alpha (B.1.1.7), Beta (B.1.351), Delta (B.1.617.2), Gamma (P.1), and Epsilon (B.1.429) variants compared to earlier lineage SARS-CoV-2 (lineage A) isolates.

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

### *Resistance*

SARS-CoV-2 isolates with reduced susceptibility to remdesivir have been selected in cell culture. In a selection with GS-441524, the parent nucleoside of remdesivir, virus pools emerged expressing amino acid substitutions at V166A, N198S, S759A, V792I, C799F, and C799R in the viral RNA-dependent RNA polymerase (nsp12). When these substitutions were individually introduced into a wild-type recombinant virus by site-directed mutagenesis, 1.7- to 3.5-fold reductions in susceptibility to remdesivir were observed. In a cell culture resistance selection experiment with remdesivir, nsp12 amino acid substitution E802D emerged, resulting in a 2.5-fold reduction in susceptibility to remdesivir. In another selection with remdesivir using a SARS-CoV-2 isolate containing the P323L substitution in the viral polymerase, a single amino acid substitution at V166L emerged. Recombinant SARS-CoV-2 with substitutions at P323L alone or P323L+V166L in combination exhibited 1.3- and 1.5-fold reductions in remdesivir susceptibility, respectively.

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

SARS-CoV-2 nsp12 E802D substitution has emerged in one individual treated with remdesivir. The E802D substitution resulted in a 2.5-fold increase in the remdesivir EC<sub>50</sub> value.

## **16. NONCLINICAL TOXICOLOGY**

### Carcinogenesis

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

### Mutagenesis

Remdesivir was not genotoxic in a battery of assays, including bacterial mutagenicity, chromosome aberration using human peripheral blood lymphocytes, and in vivo rat micronucleus assays.

### Impairment of Fertility

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

Reproductive toxicity, including decreases in corpora lutea, numbers of implantation sites, and viable embryos, was seen when remdesivir was administered intravenous daily at a systemically toxic dose (10 mg/kg) in female rats 14 days prior to mating and during conception; exposures of the predominant circulating metabolite (GS-441524) were 1.3 times the exposure in humans at the RHD.

### Animal Toxicology and/or Pharmacology

Intravenous administration (slow bolus) of remdesivir to male rhesus monkeys at dosage levels of 5, 10, and 20 mg/kg/day for 7 days resulted, at all dose levels, in increased mean urea nitrogen and increased mean creatinine, renal tubular atrophy, and basophilia and casts.

Intravenous administration (slow bolus) of remdesivir to rats at dosage levels of  $\geq 3$  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 four randomized clinical trials in adult patients with COVID-19. VEKLURY is approved for use to treat COVID-19 in adults and pediatric patients 12 years of age and older and weighing at least 40 kg. VEKLURY is not approved for use in pediatric patients weighing 3.5 kg to less than 40 kg or pediatric patients less than 12 years of age weighing at least 3.5 kg.

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

A randomized, double-blind, placebo-controlled clinical trial (ACTT-1, NCT04280705) of hospitalized adult subjects with confirmed SARS-CoV-2 infection and mild, moderate, or severe COVID-19 compared treatment with VEKLURY for 10 days ( $n=541$ ) with placebo ( $n=521$ ). Mild/moderate disease was defined as  $SpO_2 >94\%$  and respiratory rate  $<24$  breaths/minute without supplemental oxygen; severe disease was defined as an  $SpO_2 \leq 94\%$  on room air, a respiratory rate  $\geq 24$  breaths/minute, an oxygen requirement, or a requirement for mechanical ventilation. Subjects had to have at least one of the following to be enrolled in the trial: radiographic infiltrates by imaging,  $SpO_2 \leq 94\%$  on room air, a requirement for supplemental oxygen, or a requirement for mechanical ventilation. Subjects treated with VEKLURY received 200 mg on Day 1 and 100 mg once daily on subsequent days, for 10 days of treatment via intravenous infusion. Treatment with VEKLURY was stopped in subjects who were discharged from the hospital prior to the completion of 10 days of treatment.

At baseline, mean age was 59 years (with 36% of subjects aged 65 or older); 64% of subjects were male, 53% were White, 21% were Black, and 13% were Asian; 24% were Hispanic or Latino; 105 subjects had mild/moderate disease (10% in both treatment groups); 957 subjects had severe disease (90% in both treatment groups). Subjects in this trial were unvaccinated. A total of 285 subjects (27%) ( $n=131$  received VEKLURY) were on invasive mechanical ventilation or ECMO. The most common comorbidities were hypertension (51%),

obesity (45%), and type 2 diabetes mellitus (31%); the distribution of comorbidities was similar between the two treatment groups.

The primary clinical endpoint was time to recovery within 29 days after randomization. Recovery was defined as discharged from the hospital without limitations on activities, discharged from the hospital with limitations on activities and/or requiring home oxygen, or hospitalized but not requiring supplemental oxygen and no longer requiring ongoing medical care. The median time to recovery was 10 days in the VEKLURY group compared to 15 days in the placebo group (recovery rate ratio 1.29 [95% CI 1.12 to 1.49],  $p < 0.001$ ). Among subjects with mild/moderate disease at enrollment ( $n=105$ ), the median time to recovery was 5 days in both the VEKLURY and placebo groups (recovery rate ratio 1.22 [95% CI 0.82 to 1.81]). Among subjects with severe disease at enrollment ( $n=957$ ), the median time to recovery was 11 days in the VEKLURY group compared to 18 days in the placebo group (recovery rate ratio 1.31 [95% CI 1.12 to 1.52]).

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

1. not hospitalized, no limitations on activities;
2. not hospitalized, limitation on activities and/or requiring home oxygen;
3. hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care;
4. hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);
5. hospitalized, requiring supplemental oxygen;
6. hospitalized, on noninvasive ventilation or high-flow oxygen devices;
7. hospitalized, on invasive mechanical ventilation or ECMO; and
8. death.

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

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

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

A randomized, open-label multi-center clinical trial (Study 5773, NCT04292899) in adult subjects with confirmed SARS-CoV-2 infection, an  $\text{SpO}_2$  of  $\leq 94\%$  on room air, and radiological evidence of pneumonia compared 200 subjects who received VEKLURY for 5 days with 197 subjects who received VEKLURY for 10 days. Treatment with VEKLURY was stopped in subjects who were discharged from the hospital prior to completion of their protocol-defined duration of treatment. Subjects on mechanical ventilation at screening were excluded. All subjects received 200 mg of VEKLURY on Day 1 and 100 mg once daily on subsequent days via intravenous infusion, plus standard of care.

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

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

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

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

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

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

At baseline, the median age of subjects was 57 years (range, 12 to 95 years); 61% were male, 61% were White, 19% were Black, and 19% were Asian; 18% were Hispanic or Latino. Subjects in this trial were unvaccinated. Baseline clinical status, oxygen support status, and median duration of symptoms and hospitalization prior to first dose of VEKLURY were similar across treatment groups.

The primary endpoint was clinical status on Day 11 assessed on a 7-point ordinal scale consisting of the following categories:



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

Overall, the odds of improvement in the ordinal scale were higher in the 5-day VEKLURY group at Day 11 when compared to those receiving only standard of care (odds ratio 1.65 [95% CI 1.09 to 2.48],  $p=0.017$ ). The odds of improvement in clinical status with the 10-day treatment group when compared to those receiving only standard of care were not statistically significant (odds ratio 1.31 [95% CI 0.88 to 1.95]). All-cause mortality at Day 28 was  $\leq 2\%$  in all treatment groups.

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

A randomized, double-blind, placebo-controlled, clinical trial (Study 9012, NCT04501952) evaluated VEKLURY 200 mg once daily for 1 day followed by VEKLURY 100 mg once daily for 2 days (for a total of 3 days of intravenously administered therapy) in 554 adult and 8 pediatric subjects (12 years of age and older and weighing at least 40 kg) who were non-hospitalized, had mild-to-moderate COVID-19, were symptomatic for COVID-19 for  $\leq 7$  days, had confirmed SARS-CoV-2 infection, and had at least one risk factor for progression to hospitalization. Risk factors for progression to hospitalization included age  $\geq 60$  years, obesity (BMI  $\geq 30$ ), chronic lung disease, hypertension, cardiovascular or cerebrovascular disease, diabetes mellitus, immunocompromised state, chronic mild or moderate kidney disease, chronic liver disease, current cancer, and sickle cell disease. Subjects who received, required, or were expected to require supplemental oxygen were excluded from the trial. Subjects were randomized in a 1:1 manner, stratified by residence in a skilled nursing facility (yes/no), age ( $<60$  vs  $\geq 60$  years), and region (US vs ex-US) to receive VEKLURY ( $n=279$ ) or placebo ( $n=283$ ), plus standard of care.

At baseline, mean age was 50 years (with 30% of subjects aged 60 or older); 52% were male, 80% were White, 8% were Black, and 2% were Asian; 44% were Hispanic or Latino; median body mass index was 30.7 kg/m<sup>2</sup>. Subjects in this trial were unvaccinated. VEKLURY or placebo was first administered to subjects in outpatient facilities (84%), home healthcare settings (13%), or skilled nursing facilities (3%). The most common comorbidities were diabetes mellitus (62%), obesity (56%), and hypertension (48%). Median (Q1, Q3) duration of symptoms prior to treatment was 5 (3, 6) days; median viral load was 6.3 log<sub>10</sub>

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

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

## **19. HOW SUPPLIED/STORAGE AND HANDLING**

### How Supplied

VEKLURY for injection, 100 mg, is supplied as a single-dose vial containing a sterile, preservative-free white to off-white to yellow lyophilized powder. It requires reconstitution and further dilution prior to administration by intravenous infusion [see *Dosage and Administration* (2.5)].

Discard unused portion.

The container closure is not made with natural rubber latex.

### Storage and Handling

Do not reuse or save reconstituted or diluted VEKLURY for future use. This product contains no preservative; therefore, partially used vials should be discarded [see *Dosage and Administration* (2.6)].

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

After reconstitution, use vials immediately to prepare diluted solution. Dilute the reconstituted solution in 0.9% sodium chloride injection, USP within the same day as administration.

The diluted VEKLURY solution in syringe should be used immediately.

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

## 20. PATIENT COUNSELING INFORMATION

### **SEE *Fact Sheet for Parents and Caregivers***

#### Hypersensitivity Reactions

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

#### Increased Risk of Transaminase Elevations

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

#### Drug Interactions

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

#### Pregnancy Registry

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

#### Pregnancy

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

#### Lactation

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

## 21. CONTACT INFORMATION

**If you have questions, please contact**

**[www.askgileadmedical.com](http://www.askgileadmedical.com)**

**1-866-633-4474**

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**Fact Sheet for Parents and Caregivers**  
**Emergency Use Authorization (EUA) of VEKLURY® (remdesivir) for**  
**Coronavirus Disease 2019 (COVID-19) for Children Weighing 8 pounds (3.5 kg) to**  
**Less Than 88 pounds (40 kg) or for Children Less Than 12 Years of Age Weighing**  
**at least 8 pounds (3.5 kg) who are: hospitalized, or not hospitalized and have mild-**  
**to-moderate COVID-19 and are at high risk for progression to severe COVID-19,**  
**including hospitalization or death**

You are being given this Fact Sheet because your healthcare provider believes it is necessary to provide your child with **VEKLURY** for use for the treatment of coronavirus disease 2019 (COVID-19). The United States Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for VEKLURY for use in children weighing 8 pounds (3.5 kg) to less than 88 pounds (40 kg) **or** children less than 12 years of age weighing at least 8 pounds (3.5 kg) with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are:

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

This Fact Sheet contains information to help you understand the risks and benefits of your child receiving VEKLURY.

The FDA has issued an EUA to make VEKLURY available for this use during the COVID-19 pandemic (for more details about an EUA please see “**What is an Emergency Use Authorization?**” at the end of this document). VEKLURY is not approved for use as treatment for COVID-19 for the pediatric population covered under this EUA. Read this Fact Sheet for information about VEKLURY. Talk to your healthcare provider about your options or if you have any questions. It is your choice for your child to receive VEKLURY or stop it at any time.

**What is COVID-19?**

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

COVID-19 illnesses have ranged from very mild to severe, including illness with no reported symptoms and 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. Older people and 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 is VEKLURY?**

VEKLURY is a prescription medicine that is investigational for use for the treatment of COVID-19 in children weighing 8 pounds (3.5 kg) to less than 88 pounds (40 kg) **or** children less than 12 years of age weighing at least 8 pounds (3.5 kg) with positive results of direct SARS-CoV-2 viral testing, who are:

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

VEKLURY is investigational for this use because it is still being studied and there is limited information about the safety and effectiveness of using VEKLURY for the treatment of COVID-19 in this population.

VEKLURY is an FDA-approved prescription medicine used to treat COVID-19 in adults and children (12 years of age and older and weighing at least 88 pounds (40 kg), with positive results of direct SARS-CoV-2 viral testing, who are:

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

### **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 any allergies
- Has kidney or liver disease
- Has any serious illnesses

**Tell your healthcare provider about all the medicines your child takes**, including prescription and over-the-counter medicines, vitamins, and herbal supplements. VEKLURY may interact with other medicines and may cause serious side effects.

**Especially tell your healthcare provider if your child is taking the medicines chloroquine phosphate or hydroxychloroquine sulfate.**

### **How will my child receive VEKLURY?**

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

### **Who should generally not receive VEKLURY?**

**Your child should not receive VEKLURY if** your child is allergic to remdesivir or any of the ingredients in VEKLURY.

### **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. Your healthcare provider will monitor your child for signs and symptoms of allergic reactions during their infusion and for at least 1 hour after their infusion. 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 or wheezing
  - shivering
  - swelling of the lips, face, or throat
  - rash
  - nausea
  - sweating
- **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 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.

### **What other treatment choices are there?**

Like VEKLURY, FDA may allow for the emergency use of other medicines to treat people with COVID-19. Go to <https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy->

framework/emergency-use-authorization for information on the emergency use of other medicines that are not approved by the FDA to treat people 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 for your child not to receive it, it will not change your child's standard medical care.

### **How do I report side effects with VEKLURY?**

Contact your healthcare provider 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](https://www.fda.gov/medwatch) or call 1-800-FDA-1088 and to **Gilead** by calling 1-800-445-3235.

### **How can I learn more about COVID-19?**

- Ask your healthcare provider.
- Visit <https://www.cdc.gov/COVID19>.
- Contact your local or state public health department.

### **What is an Emergency Use Authorization (EUA)?**

The United States FDA has made VEKLURY available under an emergency access mechanism called an Emergency Use Authorization (EUA) for the treatment of coronavirus disease 2019 (COVID-19) in children weighing 8 pounds (3.5 kg) to less than 88 pounds (40 kg) **or** children less than 12 years of age weighing at least 8 pounds (3.5 kg), with positive results of direct severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral testing, who are:

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

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.

VEKLURY for the authorized use has not undergone the same type of review as an FDA-approved product. In issuing an EUA under the COVID-19 public health emergency, the FDA has determined, among other things, that based on the total amount of scientific evidence available including data from adequate and well controlled clinical trials, it is reasonable to believe that the product may be effective for diagnosing, treating, or preventing COVID-19, or a serious or life threatening disease or condition caused by COVID-19; that the known and potential benefits of the product, when used to diagnose, treat, or prevent such disease or condition, outweigh the known and potential risks of such product; and that there are no adequate, approved, and available alternatives.

All of these criteria must be met to allow for the product to be used in the treatment of the authorized patient population during the COVID-19 pandemic. The EUA for VEKLURY is in effect for the duration of the COVID-19 declaration justifying emergency use of VEKLURY, unless terminated or revoked (after which VEKLURY may no longer be used under the EUA).

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