CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214787Orig1s000

OTHER REVIEW(S)

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: **September 29, 2020**

To: Christine Kim
Senior Regulatory Health Project Manager
Division of Antiviral Products (DAVP)

From: Nima Ossareh, PharmD, RAC
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for VEKLURY (remdesivir) for injection, for intravenous use

NDA: 214787

In response to DAVP's consult request dated June 5, 2020, OPDP has reviewed the proposed product labeling (PI) and patient package insert (PPI) for VEKLURY (remdesivir) for injection, for intravenous use. The proposed indication is fo (b) (4)

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DAVP on September 23, 2020, and are provided below.

PPI: A combined OPDP and Division of Medical Policy Programs (DMPP) review of the PPI will be completed under a separate cover.

Thank you for your consult. If you have any questions, please contact Nima Ossareh at (240) 402-2769 or nima.ossareh@fda.hhs.gov.

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/s/

SAMUEL M SKARIAH
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Signing for Nima Ossareh

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 29, 2020
To:	Christine Kim, PharmD Regulatory Project Manager **Division of Antivirals (DAV)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Morgan Walker, PharmD, MBA, CPH Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nima Ossareh, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	VEKLURY (remdesivir)
Dosage Form and Route:	for injection, for intravenous use injection, for intravenous use
Application Type/Number:	NDA 214787
Applicant:	Gilead Sciences, Inc.

1 INTRODUCTION

On August 7, 2020, Gilead Sciences, Inc. submitted for the Agency's review an original New Drug Application (NDA) 214787 for VEKLURY (remdesivir) for injection. This application is a rolling submission. The proposed indication for this application is (b) (4)

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Antivirals (DAV) on June 5, 2020 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for VEKLURY (remdesivir) for injection.

2 MATERIAL REVIEWED

- Draft VEKLURY (remdesivir) for injection PPI received on August 7, 2020, and received by DMPP and OPDP on September 23, 2020.
- Draft VEKLURY (remdesivir) for injection Prescribing Information (PI) received on August 7, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 23, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

MORGAN A WALKER
09/29/2020 03:33:21 PM

SAMUEL M SKARIAH
09/29/2020 03:48:12 PM

LASHAWN M GRIFFITHS
09/29/2020 03:49:27 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	September 29, 2020
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 214787
Product Name and Strength:	Veklury (remdesivir) for injection, 100 mg per vial; Veklury (remdesivir) injection, 100 mg/20 mL (5 mg/mL)
Applicant/Sponsor Name:	Gilead Sciences, Inc
OSE RCM #:	2020-1161-1
DMEPA Safety Evaluator:	Valerie S. Vaughan, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on September 18, 2020 and September 25, 2020 for Veklury. The Division of Antivirals (DAV) requested that we review the revised container labels and carton labeling for Veklury (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review[a] and information request[b].

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a]Vaughan V. Label and Labeling Review for Veklury (NDA 214787). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 SEP 12. RCM No.: 2020-1161.
[b]Kim, C. FDA Communication: [External] NDA 214787 – RDV – Information Request. Silver Spring (MD): FDA, CDER, OND, DAV(US); 2020 SEP 22. NDA 214787.

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/s/

VALERIE S VAUGHAN
09/29/2020 07:42:24 PM

SEVAN H KOLEJIAN
09/29/2020 10:42:34 PM

Clinical Inspection Summary

Date	09/25/2020
From	Jenn Sellers, M.D., Ph.D., Medical Officer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Christine Kim, Pharm.D., Regulatory Project Manager Kirk Chan-Tack, M.D., Clinical Reviewer Adam Sherwat, M.D., Clinical Team Leader Division of Antiviral Products (DAVP)
NDA #	214787
Applicant	Gilead Sciences, Inc. (Gilead)
Drug	Remdesivir
NME	Yes
Therapeutic Classification	RNA-dependent RNA Polymerase Inhibitor
Proposed Indication	Treatment of Coronavirus Disease 2019 (COVID-19)
Consultation Request Dates	05/29/2020 for NIAID Study 06/09/2020 for Gilead Studies
Summary Goal Date	09/18/2020
Updated Summary Goal Date	09/25/2020
Action Goal Date	10/02/2020
PDUFA Date	04/21/2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMEBLATIONS

The clinical investigators Drs. Mehta, Zingman, Hohmann, Diaz, and Mullane as well as the sponsors, the National Institute of Allergy and Infectious Diseases (NIAID) and Gilead Sciences, Inc. were inspected in support of this application. Despite some regulatory deviations found at the sites of Drs. Mullane and Diaz, based on the results of these inspections, the studies (Protocols 20-0006, GS-US-540-5773, and GS-US-540-5774) appear to have been conducted adequately, and the data generated by the clinical investigator sites and submitted by the applicant (Gilead) appear acceptable in support of the respective indication.

II. BACKGROUND

NIAID conducted a randomized, double-blind, placebo-controlled Adaptive COVID-19 Treatment Trial (ACTT-1, Protocol 20-0006). Gilead conducted two randomized, open-label, multi-center clinical trials (Protocols GS-US-540-5773 and GS-US-540-5774). The applicant, Gilead, submitted data from these three studies to support the indication of remdesivir in the treatment of COVID-19. The FDA conducted clinical investigator inspections of Drs. Mehta, Zingman, and Hohmann for ACTT-1 (Protocol 20-0006); Drs. Diaz and Mullane for Protocols GS-US-540-5773 and GS-US-540-5774; as well as sponsor inspections of NIAID and Gilead.

The following briefly describes the Protocols 20-0006, GS-US-540-5773 and GS-US-540-5774.

Protocol 20-0006 (ACTT-1)

Title: "A Multicenter, Adaptive, Randomized Blinded Controlled Trial of the Safety and Efficacy of Investigational Therapeutics for the Treatment of COVID-19 in Hospitalized Adults"

The primary study objective was to evaluate the safety and efficacy of remdesivir in hospitalized adults diagnosed with COVID-19.

Subjects' clinical status was assessed and recorded daily during their hospitalization, from Day 1 through Day 29 using an eight-category ordinal scale. The 8 categories were as following:

1. Not hospitalized, no limitations of activities
2. Not hospitalized, limitation of activities, home oxygen requirement, or both
3. Hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control reasons)
4. Hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (COVID-19- related or other medical conditions)
5. Hospitalized, requiring any supplemental oxygen
6. Hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices
7. Hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
8. Death.

The primary efficacy endpoint was the time to recovery, defined as the first day, during the 28 days after enrollment, on which a subject satisfied categories 1, 2, or 3 on the eight-category ordinal scale.

The key secondary efficacy endpoint was the difference in clinical status in the eight-category ordinal scale among subjects treated with remdesivir as compared with placebo at Day 15.

Protocol GS-US-540-5773

Title: "A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants with Severe COVID-19"

The primary study objective was to evaluate the efficacy of two remdesivir regimens with respect to clinical status assessed by a 7-point ordinal scale on Day 14. Part A of this study was a randomized, open-label, multicenter study of remdesivir in subjects with severe COVID-19 infection.

The primary efficacy endpoint was clinical status assessed by a 7-point ordinal scale on Day 14. The ordinal scale was an assessment of the clinical status at a given study day. The scale was as follows:

1. Death
2. Hospitalized, on invasive mechanical ventilation or Extracorporeal membrane oxygenation (ECMO)
3. Hospitalized, on non-invasive ventilation or high flow oxygen devices
4. Hospitalized, requiring low flow supplemental oxygen
5. Hospitalized, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise)

6. Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per protocol remdesivir administration)
7. Not hospitalized

Protocol GS-US-540-5774

Title: "A Phase 3 Randomized Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734TM) in Participants with Moderate COVID-19 Compared to Standard of Care Treatment"

The primary study objective was to evaluate the efficacy of two remdesivir regimens compared to standard of care with respect to clinical status assessed by a 7-point ordinal scale on Day 11. Part A of this study was a randomized, open-label, multicenter study of remdesivir in subjects with moderate COVID-19 infection.

The primary efficacy endpoint was clinical status assessed by the 7-point ordinal scale (as described above for Protocol -5773) on Day 11.

Rationale for Site Selection

The clinical investigator (CI) sites were selected for inspection due to large enrollment and prior inspection history. Drs. Diaz and Mullane also participated in both Gilead studies.

III. RESULTS

1. **Aneesh Mehta, M.D.**
   Site #15
   1364 Clifton Road
   Northeast Atlanta, GA 30322
   Inspection dates: 13-21 July 2020

At this site for Protocol 20-0006 (ACTT-1), a total of 96 subjects were screened, 92 were enrolled, and 74 subjects completed the study. Eighteen subjects discontinued the study. There were 13 deaths (7 in remdesivir group and 6 in placebo group). Three subjects withdrew consent. Two subjects were transferred to hospice care and discontinued the study.

Records reviewed during the inspection included the following documents: 1) all informed consent forms for the 96 screened subjects; 2) all the primary and key secondary efficacy endpoint data for the 92 enrolled subjects; and 3) a full audit of the subject records for 20 enrolled subjects, which included, but were not limited to, study eligibility, subject disposition, adverse events, concomitant medications, and protocol deviations. The regulatory records reviewed included FDA Form 1572, financial disclosures, Independent Review Board (IRB) approvals, delegation logs, training records, drug accountability records, and monitoring reports.

The primary and key secondary efficacy endpoint data were verified against the data line listings provided by the sponsor; no discrepancies were noted. There was no evidence of underreporting of adverse events.

2. **Barry S. Zingman, M.D.**
   Site #29
   111 East 210th Street
   Bronx, NY 10467
   Inspection dates: 6-15 July 2020

At this site for Protocol 20-0006 (ACTT-1), 91 subjects were screened, all of whom were enrolled. A total of 67 subjects completed the study. Twenty-four subjects discontinued the study. There were 22 deaths (12 in placebo group and 10 in remdesivir group). Two withdrew consent.

Records reviewed during the inspection included, but were not limited to, subject electronic medical records (EMRs), vital flowsheets, medication administration reports, progress notes, research notes, and labs. Regulatory documents reviewed included informed consent forms, monitor logs, study personnel signature/responsibility list, Institutional Review Board (IRB) correspondence and approvals, drug accountability, subject-specific binder source documentation, unblinding log, and electronic case report forms (eCRFs) via the electronic data capture (EDC) system, e-Clinical.

Based on email communication from ORA, the primary and key secondary efficacy endpoint data were verified against the data line listings provided by the sponsor for all 91 enrolled subjects; no discrepancies were noted. Adverse events were also verified for all subjects, and there was no evidence of underreporting of adverse events.

3. **Elizabeth L. Hohmann, M.D.**
   Site #16
   55 Fruit St.
   Boston MA 02114
   Inspection dates: 14-17 July 2020

At this site for Protocol 20-0006 (ACTT-1), 49 subjects were screened and enrolled, and 46 subjects completed the study. Three subjects discontinued the study. There was one death (Subject #031 in the remdesivir group), which was reported appropriately to the sponsor according to the protocol. Two subjects withdrew consent, one prior to receiving any study drug.

Records reviewed during the inspection included all the informed consent forms (ICFs) and all the primary and key secondary efficacy endpoint data. Other subject records were audited and included, but were not limited to, study eligibility; vital signs and physical examinations; concomitant medications; and protocol deviations. Regulatory documents reviewed included investigator agreements, financial disclosure forms, Institutional Review Board (IRB) approvals, delegation log, screening and enrollment log, monitoring log, monitoring reports, and study drug records.

The primary and key secondary efficacy endpoint data were verified against the data line listings provided by the sponsor for all 48 subjects who received study drug; no discrepancies were noted. Adverse events were also verified for all subjects, and there was no evidence of underreporting of adverse events.

4. **George A. Diaz, M.D.**
   Site # 17359
   1330 Rockefeller Avenue, Suite 440
   Everett, Washington 98201
   Inspection dates: 9-17 July 2020

At this site for Part A of Protocol GS-US-540-5773, 72 subjects were screened, 69 were enrolled, and 50 subjects completed the study. Among the 19 subjects who did not complete the study, 14 discontinued due to death (6 in the 5-day remdesivir group and 8 in the10-day remdesivir group); 5 were considered lost to follow-up as these subjects were discharged but did not answer Day 28 follow-up phone calls. The deaths were reported appropriately to the sponsor according to the protocol.

At this site for Part A of Protocol GS-US-540-5774, 3 subjects were screened and enrolled, and 2 subjects completed the study. One subject was considered lost to follow-up, as the subject was discharged but did not answer the Day 28 follow-up phone call.

Informed consent forms for all enrolled subjects were reviewed. Other subject records reviewed included, but were not limited to, screening and study eligibility, COVID-19 testing, concomitant medications, protocol deviations, individual drug dispensing logs, and provider notes as well as hospitalization, discharge, and death reports. Regulatory documents reviewed included FDA Form 1572, financial disclosures, IRB approvals, and monitoring reports.

According to email communication from ORA, the primary efficacy endpoint data were verified against the data line listings provided by the sponsor for all Part A subjects at the site in Study GS-US-540-5773 and all three enrolled subjects in Study GS-US-540-5774. Adverse events were also verified for all subjects in both studies, and there was no evidence of underreporting of adverse events.

There was one discrepancy noted for the primary efficacy endpoint. Specifically, Subject # (b) (6) (in the remdesivir 5-day treatment group) in Study GS-US-540-5773 was on O2 via nasal cannula until Study Day 15. Therefore, the ordinal scale on Day 14 (the primary efficacy endpoint day) should have been “4” (hospitalized, requiring low flow supplemental oxygen), but the ordinal scale in the line listing was “5” (hospitalized, not requiring supplemental oxygen).

Reviewer’s comment: This isolated discrepancy for this subject in the ordinal scale on Day 14 is unlikely to have a significant impact on the overall efficacy results from this site for Study GS-US-540-5773.

There was one observation during this inspection. For protocol GS-US-540-5773, the CI did not report a serious adverse event (SAE) within 24 hours as required by protocol. Specifically, Subject # (b) (6) (in the remdesivir 10-day group) after several doses of study drug, had a grade 4, potentially life threatening estimated glomerular filtration rate (GFR) value of 23 ml/min (reference range ≥60 ml/min). On Study Day 7, the remdesivir was withdrawn due to worsening renal function. However, this SAE of grade 4 decreased GFR was not reported to the sponsor until eight days later.

Reviewer’s comment: The CI acknowledged the late reporting of this SAE and has implemented a corrective and preventive action plan. Late reporting (by more than a week) of this SAE was a protocol deviation, but there is no evidence that the safety of this or other study subjects was compromised by the late reporting.

5. **Kathleen M. Mullane, M.D.**
   Site # 2709
   5841 S. Maryland Avenue
   Chicago, Illinois 60637
   Inspection dates: 06-20 July 2020

At this site for Part A of Protocol GS-US-540-5773, 24 subjects were screened, 22 were enrolled, and 21 subjects completed the study. One subject was lost to follow up.

At this site for Part A of Protocol GS-US-540-5774, 11 subjects were screened and enrolled, and 10 subjects completed the study. One subject (# (b) (6) in the remdesivir 5-day group) died of respiratory failure; this death was reported appropriately to the sponsor according to the protocol.

Records reviewed during the inspection included a full audit of the study records for all enrolled subjects for Part A of both protocols. The subject-specific records included, but were not limited to, study eligibility criteria, vital signs, physical examinations, progress notes, concomitant medications, the primary efficacy endpoint data, adverse events, and protocol deviations. The inspection also reviewed the regulatory binder for both protocols, which included Independent Review Board (IRB) approvals, delegation of authority logs, financial disclosures, test article accountability records, correspondence between the sponsor and the clinical investigator, and correspondence between monitors and the clinical investigator.

The primary efficacy data were verified against the data line listings provided by the sponsor for all Part A subjects in both studies; no discrepancies were noted. There was no evidence of underreporting of adverse events.

The FDA CI inspection of Dr. Mullane had five observations. The followings are details of each observation, a review of Dr. Mullane's response (dated July 30, 2020), and OSI reviewer's comments.

A. For Protocol GS-US-540-5773, it was noted that any elevations in ALT >5 times upper limit of normal (5x ULN) was a criterion for discontinuing the administration of the study drug. However, Subject # (b) (6) was dosed from Study Days 2 to 5 despite having an ALT >5x ULN.

   Dr. Mullane, in her response, noted that the protocol states that if a participant experiences elevations in ALT >5x ULN, the study drug dosing for the individual subject will be placed on hold and may be discontinued, following a review of all available clinical data by the medical monitor and discussion with the investigator. However, such a discussion did not occur.

   Table 1 lists the subject's ALT levels during the hospitalization according to Dr. Mullane's response. The CI stated that she followed up the subject after discharge and noted that the subject did not have any signs or symptoms of hepatitis.

Table 1: ALT (U/L) Levels (Subject # (b) (6))

Hospitalization Day	ALT (U/L) 5 x ULN = 175 U/L	Study Day	Remdesivir Treatment
Admission	226	Not enrolled	No
Hospitalization Day 2	173	Not enrolled	No
Hospitalization Day 3	165 (Baseline)	Study Day 1 (Enrolled)	Yes
Hospitalization Day 4	176	Study Day 2	Yes
Hospitalization Day 5	190	Study Day 3	Yes
Hospitalization Day 6	178	Study Day 4	Yes
Hospitalization Day 7	221	Study Day 5 (Discharged)	Yes

Reviewer's comment: According to the protocol, consideration to discontinue remdesivir when a subject's ALT was >5x ULN was to be discussed with the medical monitor based on review of all available medical data. Such a discussion did not occur. That said, it should be noted that the subject's ALT at the end of the 5-day remdesivir treatment period was slightly lower than at admission. This observation neither impacted data reliability nor compromised the safety of the subject. The CI's noncompliance with regard to this study subject was reported in the NDA submission.

B. For Protocol GS-US-540-5773, it was noted that concurrent treatment with other agents with actual or possible direct acting antiviral activity against SAR-CoV-2 was prohibited less than 24 hours prior to study drug dosing. However, on admission, Subject # (b) (6) received hydroxychloroquine (HCQ) at 8:09pm. On Study Day 1, this subject received remdesivir at 3:27pm while also receiving HCQ at 8:03am and 8:58pm

In her response, Dr. Mullane noted that the subject was enrolled into the institutional "confirmed COVID-19 treatment pathway" on admission. The institutional "confirmed COVID-19 treatment pathway" recommended that, unless contraindicated, COVID-19 positive individuals be started on HCQ 400mg administered at every 12 hours intervals. The subject was enrolled into this pathway upon admission, before being enrolled into the study. On Study Day 2, the CI reportedly informed the sponsor that the subject inadvertently received two doses of HCQ 200 mg <24 hours prior to remdesivir dosing. The sponsor responded that the subject may continue study participation.

Reviewer's comment: Since this subject received 2 doses of HCQ <24 hours prior to study drug dosing, it could be considered that this subject met one of the exclusion criteria. However, the CI reported this deviation to the sponsor and received permission to continue this subject in the study. This isolated deviation is unlikely to affect the overall efficacy results from this site for the study. This deviation was not reported in the NDA submission.

C. For Protocol GS-US-540-5774, it was noted that subjects had to have a pulse oximetry (SpO2) of >94% on room air for inclusion into the study. (Note: otherwise the subject should be considered for the severe COVID study, -5773). Subject # (b) (6)'s SpO2 on room air was 93% approximately one hour prior to the subject signing the informed consent, and the subject's SpO2 on room air was documented at 93% after the subject received the first dose of study medication.

In her response, Dr. Mullane stated that O2 saturations varied in COVID-19 patients. In the case of this subject, in the 24 hours prior to enrollment, the subject reportedly had room air O2 saturations documented mostly as >94%. The CI contacted the Clinical Research Associate (CRA) and was reportedly advised that subjects should be "randomized to the study in which the propensity of the O2 saturations lay". In this case, in the opinion of the investigator, the propensity of O2 saturations classified the subject as having moderate COVID-19.

Reviewer's comment: It should be noted that according to the data line listings provided by the sponsor, this subject (in the 10-day treatment group) did not require any supplemental oxygen during the entire hospital stay and was able to be discharged on Day 5. While it appears that the subject was not enrolled in accordance with the investigational plan, this observation is unlikely to impact data reliability. The CI's noncompliance with regard to this study subject was not reported in the NDA submission.

D. For Protocol GS-US-540-5774, the protocol states that all serious adverse events (SAEs) will be transmitted to the sponsor within 24 hours of the clinical investigator's knowledge of the event. It was noted that Subject # (b) (6) experienced a SAE of febrile neutropenia. This SAE was evaluated by a sub-investigator who had been delegated to review, assess, and report SAEs, but this SAE was not reported to the sponsor until approximately 48 hours later.

In her response, Dr. Mullane stated that this subject, who had myelodysplastic syndrome and was chronically neutropenic, was initially admitted for febrile neutropenia and was found to be COVID-19 positive. The subject was enrolled, received 2 doses of remdesivir, deemed stable and discharged. The patient was readmitted 6 days later, and the SAE of febrile neutropenia was not reported within 24 hours.

Reviewer's comment: Late reporting (by 24 hours) of this SAE was a protocol deviation, but there is no evidence that the safety of this study subject was compromised by the late reporting. The finding was isolated, and it is unlikely to impact the overall reliability of the safety and efficacy data from the site. This noncompliance in SAE reporting was not reported in the NDA submission.

E. For Protocol GS-US-540-5773, the protocol lists a creatinine clearance of <50 mL/min as an exclusion criterion. For Subject # (b) (6), at the time of screening and informed consent, it was noted that there was no documented creatinine clearance (including the calculation method) in the subject's source documents or electronic medical record for the purpose of demonstrating that this exclusion criterion was not met.

In her response, Dr. Mullane stated that the calculation of creatinine clearance by the Cockcroft-Gault equation is embedded for therapeutic drug monitoring within the institution's EMR, and this calculation is easily obtained and reproducible on recalculation. The creatinine clearance (as calculated by the Cockcroft-Gault equation by the system) at the time of eligibility determination for this subject was 51.7 ml/min, demonstrating that this subject did not meet this exclusion criterion for baseline renal function. The CI stated that it was an oversight not to have included the calculated creatinine clearance in the source documentation for subject # (b) (6)

Reviewer's comment: The CI's response is acceptable.

6. NIAID/NIH
Division of Microbiology & Infectious Diseases
5601 Fishers Lane, Room 7F50
Bethesda, MD 20892-9826
Inspection dates: 10-14 August 2020

For this sponsor inspection for Protocol 20-0006 (ACTT-1), the FDA field investigators reviewed documents including, but not limited to, organizational charts, study protocol, financial disclosures, Form FDA 1572s, Transfer of Regulatory Obligation (TORO) contracts, standard operating procedures, monitoring reports, qualification of clinical investigators, medical monitor selection records, training records, adverse event reports, data collection and management records, operational manuals, and test article accountability records. The inspection focused particularly on the selection of clinical investigators, trial monitoring, randomization and blinding, the interim analysis, safety reporting, and data management. No significant issues were noted.

7. Gilead Sciences
333 Lakeside Drive
Foster City, CA 94404
Inspection dates: 06-18 August 2020

For this sponsor inspection for Protocols GS-US-540-5773 and GS-US-540-5774, the FDA field investigator reviewed documents including, but not limited to, signed investigator and sub-investigator agreements; financial disclosures; training records; monitoring reports and correspondence; serious adverse events (SAEs); protocol deviations; Institutional Review Board (IRB) and Ethics Committee (EC) approvals and correspondence; selection of the clinical investigators; selection of the regulatory monitors; training for the regulatory monitors; data management systems; monitoring; standard operating procedures and plans; noncompliance at clinical sites; data collection and handling; electronic records and signatures; drug accountability; the data monitoring committee (DMC); sponsor meeting minutes; compassionate and emergency use of the investigational drug. No significant issues were noted.

The inspection also investigated two reports (complaint #'s 9673 and 9674) made by the central IRB for Protocol GS-US-540-5773 regarding the concomitant use of prohibited medications at two study sites. Specifically, for this study, the IRB reported that 20 subjects received concomitant convalescent plasma at Dr. Judith Aberg's clinical site, and 51 subjects received concomitant HCQ at Dr. William Towner's clinical site. This was despite exclusion criterion #2, which states: concurrent treatment with other agents with actual or possible direct acting antiviral activity again SARS-CoV-2 is prohibited <24 hours prior to study drug dosing.

During the inspection, Gilead provided a written statement that no subjects in Part A of Protocol GS-US-540-5773 received concomitant convalescent plasma. As part of that same document, the sponsor provided a long list of subjects who received concomitant HCQ in Part A. The sponsor also explained the following (listed verbatim below):

- Original protocol (dated 24-Feb-2020): HCQ is prohibited under exclusion #2 within 24 hours of dosing except when it is given as documented standard of care therapy or is given

as a non-investigational agent (i.e., consistent with the locally approved product information)

- Amendment 1 (dated 15-Mar-2020): HCQ for investigational use for COVID-19 is prohibited under exclusion #2 within 24 hours of dosing and during dosing (section 5.5)
- Amendment 3 (dated 12-Apr-2020): HCQ is prohibited under exclusion #2 for investigational use for COVID-19 within 24 hours of dosing but not disallowed as a medication if not dosed concurrently
- Amendment 3, administrative letter 4 (dated 23-Apr-2020): HCQ for investigational use for COVID-19 is prohibited for coadministration. Administrative letter 4 served to align the eligibility criteria with the intended changes to Section 5.5.

The sponsor pointed out in the document that for a vast majority of subjects who received concomitant HCQ, it was under the original protocol, under which they met the conditions to receive HCQ. For a few subjects, the concomitant use of HCQ was a protocol deviation, as the respective sites implemented Protocol Amendment 1 while the subject was receiving treatment.

- Subject # (b) (6), randomized to remdesivir for 5 days
- Subject # (b) (6), randomized to remdesivir for 5 days
- Subject # (b) (6), randomized to remdesivir for 10 days
- Subject # (b) (6), randomized to remdesivir for 10 days
- Subject # (b) (6), randomized to remdesivir for 10 days

Reviewer's comment: The sponsor stated in writing during the inspection that no subjects received convalescent plasma in Part A of Protocol GS-US-540-5773. For the five subjects listed above, we recommend the review division determine the potential impact, if any, of the concomitant use of HCQ.

{See appended electronic signature page}

Jenn W. Sellers, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

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cc:
Central Doc. Rm. NDA 214787
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DAVP/Medical Officer/Kirk Chan-Tack
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs, ORPURM
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
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MEMORANDUM TO FILE

Version Date:	September 14, 2020
From:	Ethan D. Hausman, MD, Medical Officer Division of Pediatric and Maternal Health (DPMH)
Through:	John J. Alexander, MD, MPH, Deputy Director DPMH
NDA Number:	214,787
Sponsor:	Gilead Sciences, Inc.
Drug:	Veklury (remdesivir; GS-5734)
Indication:	(b) (4) [redacted]
Dosage Form(s) and Route of Administration:	Lyophilized powder for reconstitution in sterile water for intravenous (IV) injection Injection for IV use (in pre-solubilized containers)
Proposed Dose Regimen:	200 mg IV x 1 on Day 1, followed by 100 mg IV x 1/day on Days 2 through 5. Patients who do not demonstrate clinical improvement may receive additional 100 mg doses on days 6 through 10 for a total of 10 days of treatment. Patients on mechanical ventilation or extracorporeal membrane oxygenation (ECMO) should receive a 10-day course.
Division Consult Request:	The Division of Antiviral Products (DAV) requests DPMH assistance in labeling this new product.

Background

Veklury [remdesivir (RDV); GS-5734] is a nucleotide analog which acts as a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) ribonucleic acid (RNA) polymerase inhibitor. SARS-CoV-2 is a positive sense single stranded RNA virus, which causes coronavirus disease 2019 (COVID-19).

Since COVID-19 was first recognized in late 2019, the total number of cases and pediatric cases, including recoveries and deaths, has been difficult to determine due to varying diagnostic methods (RNA test, antibody test, or both), clinical case definitions, and the definition of 'pediatric' or 'child' in different regions. As of September 1, 2020, the Johns Hopkins reported approximately 6,031,287 cases, 2,184,825 recoveries, and 183,602 deaths in the US.[1] As of August 27, 2020, the American Academy of Pediatrics (AAP) estimates 476,439 US 'child COVID-19 cases' (approximately 9.5% of all US cases), a child case rate of 631 per 100,000 children, and child death rates ranging from 0% to 0.7% depending on the reporting region.[2]

In adults and children, COVID-19 produces a range of clinical manifestations from no apparent clinical illness, mild to moderate upper and lower respiratory tract inflammation, mild to moderate influenza-like symptoms, severe pneumonia, multi-organ system failure (MOSF), coagulation disruption (hemorrhage or thrombosis), and death. Emerging data suggests that while many patients recover without major sequalae, some patients have a prolonged recovery phase with chronic cough, fibrotic lung disease, bronchiectasis, pulmonary vascular disease, and neurologic symptoms.[3,4,5]

Some patients, predominantly children, develop an immune-inflammatory response approximately 2 to 4 weeks after onset of other symptoms;[6] however, the syndrome may also occur in previously asymptomatic patients from 3 to 6 weeks after exposure to a known positive contact. This multisystem inflammatory syndrome in children (MIS-C) presents with symptoms which overlap substantially with Kawasaki disease (strawberry tongue, rash, injected conjunctiva, coronary artery dilatation, swollen hands/feet, and fever) and the response to treatments directed at KD (e.g., IV immunoglobin) yields similar responses as seen in patients with KD. While this syndrome occurs predominantly in children, similar cases are reported in adults as old as 45 years.[7,8,9]

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[1] The COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU): https://coronavirus.jhu.edu/map.html; website accessed, September 1, 2020. These data are collected from

[2] American Academy of Pediatrics. Children and COVID-19: State Data Report, A joint report from the American Academy of Pediatrics and the Children's Hospital Association. Version 8/27/2020. https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/children-and-covid-19-state-level-data-report/ , and https://downloads.aap.org/AAP/PDF/AAP%20and%20CHA%20-%20Children%20and%20COVID-19%20State%20Data%20Report%208.27.20%20FINAL.pdf. Website and report accessed September 1, 2020.

[3] Fraser A. Long term respiratory complications of covid-19. BMJ 2020;370:m3001.

[4] Troyer ER, John JN, Hong S. Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. Brain Behav Immun. 2020 Jul;87:34-39.

[5] Williams FMK, Muirhead N, Pariante C. Covid-19 and chronic fatigue. BMJ. 2020 Jul 30;370:m2922.

[6] COVID-19–Associated Multisystem Inflammatory Syndrome in Children — United States, March–July 2020. MMWR. Weekly / August 14, 2020 / 69(32);1074–1080.

[7] Shaigany S, Gnirke M, Guttmann A, et al. Correspondence: An adult with Kawasaki-like multisystem inflammatory syndrome associated with COVID-19. Lancet 2020 July 25. 396(10246):E8-E10.

While the proportion of adult and pediatric patients who experience pneumonia differs, FDA's current understanding of the pathophysiology is that the COVID -19 pneumonia presents similarly. Adult and pediatric patients likely would have similar responses to therapeutic intervention, including direct antiviral activity. These factors would support extrapolation of pediatric effectiveness. Therefore, should review of the two clinical trials support effectiveness and safety, DAV expects that the indication would be for adults and pediatric patients 12 years and older weighing at least 40 kg, since a) the disease manifestations and expected response to treatment should be similar, b) PK/exposure response (ER) for the majority of small molecule drugs is similar in adolescents and adults.[10]

No pediatric patients received RDV in the adequate and well-controlled trials submitted for review in this original NDA submission. However, 99 pediatric patients have received RDV under compassionate use; of these, 39 pediatric patients 12 years and older and weighing at least 40 kg received RDV in a compassionate use program. However, the available safety data from these patients are limited. DAV's performed a separate analysis of adult studies to evaluate adverse effects in lower weight patients. This analysis indicates 30 adults weighing 40-50 kg received RDV in the submitted clinical trials and safety in this group was comparable to adult subjects weighing greater than 50 kg.

On May 1, 2020, FDA issued an Emergency Use Authorization (EUA) for RDV for potential treatment of COVID-19. The EUA was issued based on preliminary results of the two clinical trials submitted in support of the NDA which strongly suggested that treated patients appeared to have shortened recovery times compared to patients not receiving RDV. DAV has informed DPMH that should RDV receive approval, the EUA would remain in effect for patients 0 to 12 years including neonates until FDA receives data establishing safety and effectiveness in younger patients.

In order to gather additional pediatric information to support pediatric approval in younger patients, the sponsor has an agreed upon initial pediatric study plan wherein they commit to conducting a study of safety, tolerability, and pharmacokinetics (PK) in pediatric patients 0 to less than 18 years old including neonates. This pediatric trial is ongoing.

The most notable safety issues in the preclinical program and early clinical program include hepatotoxicity (manifested as transaminase elevations), and renal toxicity which may be attributed to the sulfobutylether-β-cyclodextrin sodium salt (SBECD) which is an excipient. Because SARS-CoV-2 is hepatotropic and renal tropic and because hepatotoxicity and nephrotoxicity are both reported in COVID-19 disease without RDV exposure, no conclusions can be made at this time regarding hepatotoxicity or nephrotoxicity. DAV intends to recommend postmarket studies to further explore these issues.

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[8] Jones I, Bell LCK, Manson JJ, Last A. Correspondence: An adult presentation consistent with PIMS-TS. Lancet Rheumatology 2020 July 10.
[9] Sokolovsky S, Soni P, Horrman T, et al. COVID-19 associated Kawasaki-like multisystem inflammatory disease in an adult. Am J Emerg Med. 2020 Jun 25;S0735-6757(20)30542-8
[10] Momper JD, Mulugeta Y, Green DJ, et al. Adolescent Dosing and Labeling Since the Food and Drug Administration Amendments Act of 2007. JAMA Pediatr. 2013;167(10):926-932.

Labeling Review

Comments in this review are taken from draft labeling as of August 19, 2020; however, draft labeling has undergoing substantial revisions time and the recommendations in this review reflect internally agreed upon labeling as of September 14, 2020.

DPMH labeling comments and recommendations focus on sections 1 (Indications and Usage), 4 (Contraindications), 5 (Warnings and Precautions), and 8.4 (Pediatric Usage). Section 2 (Dosage and Administration) will be summarized only since multiple disciplines have already provided comments and the section is in flux.

For this review, text which DPMH recommends deleting is noted by ~~strike-out~~, and text which DPMH recommends adding is noted in **bold red**. The reader is directed to the final negotiated label which may reflect changes not discussed in this document (e.g., agreed upon trade name of the drug), and to the approval letter which will include the text of any required postmarket studies.

1 Indication

(b) (4)

Reviewer comment: DPMH agrees with the indication.

2 Dosage and Administration

This section will summarize dosing issues related specific biochemical monitoring for renal and hepatic function only (preclinical testing [section 2.1] and dosing in renal impairment [section 2.3]).

2.1 Testing (b) (4) Initiating and During Treatment with Veklury

Determine eGFR in all patients before starting Veklury and monitor while receiving Veklury as clinically appropriate *[see Dosage and Administration (2.3) and Use in Specific Populations (8.4, 8.6)]*.

Perform hepatic laboratory testing in all patients (b) (4) starting Veklury and while receiving Veklury as clinically appropriate *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.4, 8.7)]*.

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

(b) (4) Renal Impairment

Veklury is not recommended (b) (4) patients with eGFR less than 30 mL/min *[see Dosage and Administration (2.1) and Use in Specific Populations (8.6)]*.

Reviewer comment: The units for eGFR should be mL/min/1.73 m^2

4 Contraindications

Reviewer comment: There will be no contraindications in labeling.

5 Warnings and Precautions

5.1. Hypersensitivity Including Infusion-related and Anaphylactic Reactions

Hypersensitivity reactions including infusion-related and anaphylactic reactions have been observed following administration of Veklury. Signs and symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, diaphoresis, and shivering. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration of Veklury and initiate appropriate treatment (b) (4)

Reviewer comment: DPMH agrees with this statement.

The following two issues have been added to labeling by DAV and Clinical Pharmacology. The language is currently under discussion with the sponsor and the reader is directed to final labeling for additional edits and clarifications.

5.2 Increased Risk of Transaminase Elevations

Transaminase elevations have been observed in healthy volunteers who received 200 mg of Veklury followed by 100 mg doses for up to 10 days; the transaminase elevations were mild (Grade 1) to moderate (Grade 2) in severity and resolved upon discontinuation of Veklury. Transaminase elevations have also been reported in patients with COVID-19 who received Veklury *[see Adverse Reactions (6.1)]*. Because transaminase elevations have been reported as a clinical feature of COVID-19, and the incidence was similar in patients receiving placebo versus Veklury in clinical trials of Veklury, discerning the contribution of Veklury to transaminase elevations in patients with COVID-19 can be challenging.

Perform hepatic laboratory testing in all patients (b) (4) starting Veklury and while receiving Veklury as clinically appropriate *[see Dosage and Administration (2.1) and Use in Specific Populations (8.7)]*.

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

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

Coadministration of Veklury and chloroquine phosphate or hydroxychloroquine sulfate is not recommended based on cell culture data demonstrating an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of Veklury *[see Drug Interactions (7) and Microbiology (12.4)]*.

8 Use In Specific Populations

8.4 Pediatric Use

Reviewer comment: DPMH, DAV, and Clinical Pharmacology discussed section 8.4 of labeling agreed to the following edits to the sponsor's proposed language, which should not interfere with availability of the drug under EUA for younger pediatric patients.

The safety, **and** effectiveness, (b) (4) -of Veklury for treatment of COVID-19 have (b) (4) been **established** (b) (4) in pediatric patients **12 years and older and weighing at least 40 kg. Use in this age group is based on extrapolation of pediatric efficacy from adequate and well-controlled studies in adults *[see Clinical Pharmacology (12.3) and Clinical Studies (14)]***. (b) (4)

Clinical trials of Veklury included 30 adult subjects weighing 40-50 kg. The safety in this weight group was comparable to adult subjects weighing greater than 50 kg. Thirty-nine pediatric patients 12 years and older and weighing at least 40 kg received Veklury in a compassionate use program; the available clinical data from these patients are limited.

All pediatric patients 12 years of age and older and weighing at least 40 kg must have eGFR determined before starting Veklury and while receiving Veklury as clinically appropriate *[see Dosage and Administration (2.1, 2.3)]*.

(b) (4)

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

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/s/

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LABELING AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	September 12, 2020
Requesting Office or Division:	Division of Antivirals (DAV)
Application Type and Number:	NDA 214787
Product Name, Dosage Form, and Strength:	Veklury (remdesivir) for Injection, 100 mg per vial; Veklury (remdesivir) Injection, 100 mg/20 mL (5 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Gilead Sciences, Inc.
FDA Received Date:	August 7, 2020
OSE RCM #:	2020-1161
DMEPA Safety Evaluator:	Valerie S. Vaughan, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA, BCPPS

1 REASON FOR REVIEW

As part of the approval process for Veklury (remdesivir) for injection, 100 mg and Veklury (remdesivir) injection, 100 mg/20 mL, the Division of Antivirals (DAV) requested that we review the proposed labels and labeling for areas that may lead to medication errors.

2 REGULATORY HISTORY

Remdesivir was granted Fast Track designation on March 26, 2020, which allowed a rolling submission for NDA 214787. On August 7, 2020, the final tier of NDA 214787 was received.

NDA 214787 is being reviewed under priority review for the treatment of coronavirus disease 2019 (COVID-19).

3 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Labeling Comments	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 OVERALL ASSESSMENT, FINDINGS, AND RECOMMENDATIONS

Our evaluations of the Prescribing Information, container labels, and carton labeling are included in sections 4.1 and 4.2, respectively.

4.1 ASSESSMENT OF PRESCRIBING INFORMATION

Our evaluation of the Prescribing Information (PI) identified areas of vulnerability that could lead to confusion or medication error. Additionally, we considered reports of medication errors received under the Emergency Use Authorization for this product to help guide our assessment. Therefore, we collaborated with the review team to revise Sections 2, 3, and 16 of the PI to clarify dosing and administration recommendations, preparation instructions, and storage (see *Appendix F Labeling Comments*).

4.2 ASSESSMENT OF CONTAINER LABELS AND CARTON LABELING

Our evaluation of the container labels and carton labeling received on June 11, 2020 identified areas of vulnerability that could lead to medication error. Additionally, we considered reports of medication errors received under the Emergency Use Authorization for this product to help guide our assessment. Table 2 below includes the identified medication error issues with the submitted container labels and carton labeling, DMEPA's rationale for concern, the proposed recommendation to minimize the risk for medication error, and general comments for revisions.

Table 2: Identified Issues and Recommendations for Gilead Sciences, Inc. (entire table to be conveyed to Applicant)

Container Labels, Carton Labeling, and Packaging			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Veklury for Injection (lyophilized powder)			
Container Labels and Carton Labeling			
1.	The statement, (b) (4) could lead to administration errors, (b) (4) Additionally, the statement, (b) (4) is located on the side panel of the container label and carton labeling and may be missed.	According to the Prescribing Information, remdesivir is to be administered by intravenous infusion only. If dilution instructions are missed, it could lead to preparation or administration errors, for example, administration of undiluted remdesivir injection. Additional clarity is needed to highlight that the product requires further dilution.	a. Revise to state, "Must be reconstituted and further diluted prior to use. For Intravenous Infusion" to appear together on the principal display panel (PDP) of the container label and carton labeling. Consider using a different color font (e.g., red) or other means to increase prominence. b. To ensure there is sufficient spacing on the carton to promote readability, consider moving the "Each vial contains…" statement to the side panel and adjusting the font size of the proprietary name, establish name, and strength statements.
2.	The carton labeling includes reconstitution instructions but does not	We have received reports of medication error under the Emergency Use	Revise the diluent to state: "Sterile Water for Injection." Additionally, include dilution

	include instructions regarding the need to further dilute prior to use. Additionally, we note that the diluent is listed as (b) (4) which could lead to confusion.	Authorization (EUA) for this product that describes an incorrect diluent (e.g., 5% Dextrose injection, 0.9% sodium chloride injection) used to reconstitute remdesivir for injection. Therefore, it is important to highlight the difference between the diluent needed for reconstitution and the diluent needed to further dilute the product prior to use.	instructions on the side panel of the carton labeling. For example: "Refer to package insert for detailed preparation and administration instructions. Reconstitute with 19 mL Sterile Water for Injection. Further dilute in 100 mL or 250 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion."
Veklury Injection (concentrated solution)			
Container Labels and Carton Labeling			
1.	The statement, (b) (4) could lead to administration errors (b) (4) . Additionally, the statement (b) (4) is located on the side panel of the container label and carton labeling and may be missed.	According to the Prescribing Information, remdesivir is to be administered by intravenous infusion only. If dilution instructions are missed, it could lead to preparation or administration errors, for example, administration of undiluted remdesivir injection. Additional clarity is needed to highlight that the product requires further dilution.	a. Revise to state, "Must be further diluted prior to use. For Intravenous Infusion" to appear together on the PDP of the container label and carton labeling. Consider using a different color font (e.g., red) or other means to increase prominence. b. To ensure there is sufficient spacing on the carton to promote readability, consider moving the "Each vial contains…" statement to the side panel and adjusting the font size of the proprietary name, establish name, and strength statements.

2.	The carton labeling does not convey that remdesivir injection is intended for patients who weigh at least 40 kg only.	Veklury injection contains a higher amount of sulfobutylether-β-cyclodextrin sodium salt [SBECD] than Veklury for injection, which results in a higher tonicity of the prepared solution and therefore is recommended for use only in patients weighing at least 40 kg. Additionally, we have received reports of medication errors under the EUA that describe administration of the wrong dosage form (i.e., remdesivir injection) to patients weighing less than 40kg.	Consider including the statement, "For patients who weigh 40 kg or higher" on the side panel of the carton labeling to provide additional differentiation and clarity between the two dosage forms.
3.	The carton labeling does not include further dilution instruction.	Remdesivir injection is intended to be further diluted in 250 mL of 0.9% sodium chloride injection. We have received reports of medication errors describing dilution of remdesivir injection in 100 mL of 0.9% sodium chloride injection.	Include dilution instructions on the side panel of the carton labeling. For example, consider adding the statement: "Refer to package insert for detailed preparation and administration instructions. Further dilute in 250 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion."
4.	The principle display panel of the carton labeling does not differentiate the storage conditions prior to use between Veklury injection and Veklury for injection.	We have received reports of medication error under the EUA that describe wrong storage of Veklury injection. Improper storage could result in administration of deteriorated drug product or delay in therapy.	Include the statement "Store refrigerated" on the PDP of the carton labeling for Veklury injection to further differentiate between the two dosage forms and ensure proper storage.

5.	The statement, (b) (4) on PDP of the carton labeling may cause confusion or misinterpretation.	Healthcare providers could misinterpret the statement (b) (4)	Revise to state, "Each mL contains 5 mg of remdesivir."
General Comment for both Veklury Container Labels and Carton Labeling			
1.	To improve readability, include parenthesis around the established name. You may consider including the dosage form on a separate line. For example, revise to appear in either of the following formats: (b) (4) Veklury (remdesivir) for Injection 100 mg/vial Veklury (remdesivir) Injection 100 mg/20 mL (5 mg/mL)		
2.	The expiration date format is denoted as "MMYYYY." To prevent confusion, ensure that only numerical characters (e.g., 01, 02, etc.) are used to represent the month of the expiration date.		
3.	Ensure the final storage recommendations on the container labels and carton labeling align with storage recommendations described in the Prescribing Information. Consider including information on post-dilution storage if space permits.		
4.	We note that the product codes of the NDC numbers (middle 4 digits) are similar (-2901- and -2902-). Healthcare providers traditionally use the middle digits to check the correct product, strength, and formulation. Assignment of sequential numbers for the middle digits is not an effective differentiating feature. Consider revising the NDC numbers to be non-sequential between the two dosage forms.		

5 CONCLUSION

Our evaluation of the proposed container label and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Applicant. We ask that the Division convey Table 2 in its entirety to the applicant so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 1 presents relevant product information for Veklury received on August 11, 2020 from Gilead Sciences, Inc.

Table 1. Relevant Product Information for Veklury	
Initial Approval Date	N/A
Active Ingredient	remdesivir
Indication	(b) (4) [redacted]
Route of Administration	Intravenous
Dosage Form	For Injection; Injection
Strength	For Injection: 100 mg per vial Injection: 100 mg/20 mL (5 mg/mL)
Dose and Frequency	Loading dose of 200 mg on Day 1 followed by once-daily maintenance doses of 100 mg from Day 2
How Supplied	Veklury for Injection: single-dose vial containing 100 mg remdesivir lyophilized powder that is to be reconstituted with 19 mL Sterile Water for Injection and further diluted in 0.9% sodium chloride injection. Veklury Injection: single-dose vial containing 100 mg/20 mL (5 mg/5mL) remdesivir solution for further dilution in 0.9% sodium chloride injection.
Storage	Veklury for Injection: (b) (4) [redacted] Veklury Injection: (b) (4) [redacted] (b) (4) [redacted]

Container Closure	Veklury for Injection: [redacted] clear glass vial with 20 mm finish, 20 mm [redacted] rubber stopper, 20 mm aluminum seal with [redacted] flip-off cap Veklury Injection: [redacted] clear glass, 20 mL with 20 mm finish, 20 mm [redacted] rubber stopper, and 20 mm aluminum seal with [redacted] flip-off cap

APPENDIX F. LABELING COMMENTS

- Applicant's response to the Agency's labeling comments dated September 3, 2020, received on September 9, 2020, available at: \\CDSESUB1\evsprod\nda214787\0040\m1\us\114-labeling\draft\annotated\annotated-draft-labeling-text-20200903.pdf

- Agency labeling comments to the applicant dated September 3, 2020[a]

Agency labeling comments to the ap

[a] Kim, Christine. FDA Communication: Electronic Mail Correspondence: Information Request/Advice for remdesivir (RDV). Silver Spring (MD): FDA, CDER, DAV (US);2020 SEP 09. NDA 214787

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Veklury labels and labeling submitted by Gilead Sciences, Inc.

- Container label received on June 11, 2020
- Carton labeling received on June 11, 2020
- Prescribing Information (Image not shown) received on August 11, 2020, available from \\CDSESUB1\evsprod\nda214787\0022\m1\us\114-labeling\draft\annotated\annotated-draft-labeling-text.pdf

G.2 Label and Labeling Images

- Veklury for Injection
  - Container Label

(b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

VALERIE S VAUGHAN
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SEVAN H KOLEJIAN
09/12/2020 05:16:54 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
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Division of Pediatric and Maternal Health Memorandum

Date: September 1, 2020 **Date Consulted:** August 17, 2020

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Leyla Sahin, MD, Senior Medical Officer, Maternal Health
Division of Pediatric and Maternal Health

Lynne P. Yao, MD, Director
Division of Pediatric and Maternal Health

To: Christine Kim, Regulatory Project Manager (RPM)
Division of Antivirals (DAV)

Drug: Veklury (remdesivir)

NDA: 214787

Proposed Indication: (b) (4)

Applicant: Gilead Sciences, Inc.

Subject: Pregnancy and Lactation labeling as part of original NDA application

Materials Reviewed:

- NDA 214787 submitted August 7, 2020.
- Applicant's response to DPMH information request (IR) submitted August 20, 2020 and August 25, 2020.

Consult Question: DAV requests DPMH assistance with review of the proposed PLLR labeling. "Please review the risk/benefit language related to pregnancy and lactation."

INTRODUCTION

On August 7, 2020, the applicant, Gilead Sciences, Inc., submitted an original NDA (214787) for Veklury (remdesivir) for the treatment of coronavirus disease 2019 (COVID-19). On August 17, 2020, the Division of Antivirals (DAV) consulted the Division of Pediatric and Maternal Health (DPMH) to assist with the labeling review for the *Pregnancy, Lactation, and Females and Males of Reproductive Potential* subsections.

REGULATORY HISTORY

- Remdesivir is a nucleotide analog SARS-CoV-2 ribonucleic acid (RNA) polymerase inhibitor with a proposed indication (b) (4)
- On March 26, 2020, remdesivir was granted Fast Track designation for the treatment of COVID-19. On April 6, 2020, the Agency granted Gilead's proposal to allow for a rolling review of its new drug application for remdesivir.
- On May 1, 2020, the Agency issued an Emergency Use Authorization (EUA) for remdesivir use in adults and children hospitalized with severe COVID-19.
- On May 7, 2020, remdesivir was first approved for marketing authorization in Japan and has since been approved in other territories globally.
- On August 18, 2020, the Agency sent the applicant an information request (IR) for any reported cases of drug exposure in pregnancy or lactation during the clinical development program. On August 20, 2020, the applicant submitted their response.
- On August 21, 2020, the Agency sent the applicant a follow-up IR for clarification on the discrepancy between the reported number of pregnancy exposures under compassionate use for remdesivir versus the number of pregnancy cases identified during the applicant's search of their global pharmacovigilance database. Additionally, available maternal outcome data were requested.
- On August 25, 2020, the applicant submitted the requested information.

Reviewer's Comment
Severe COVID-19 under the EUA for remdesivir is defined as patients with an oxygen saturation (SpO2) ≤ 94% on room air or requiring supplemental oxygen, mechanical ventilation, extracorporeal membrane oxygenation (ECMO), or a heart-lung bypass machine.[1]

[1] Frequently asked questions on the emergency use authorization for remdesivir for certain hospitalized COVID-19 patients. https://fda.gov/media/137574/download

BACKGROUND

Drug Characteristics[2]

- *Description:* a nucleotide analog SARs-CoV-2 RNA polymerase inhibitor.
- *Mechanism of action (MOA):* an adenosine nucleotide prodrug that distributes into cells where it is metabolized to form the pharmacologically active nucleoside triphosphate metabolite. Remdesivir triphosphate acts as an analog of adenosine triphosphate (ATP) and competes with 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 during replication of the viral RNA.
- *Dosage and Administration:* a single loading dose of 200 mg administered intravenously (IV) on Day 1 followed by once-daily maintenance doses of 100 mg IV from Day 2.
    - For patients requiring invasive mechanical ventilation (IMV) and/or extracorporeal membrane oxygenation (ECMO), the recommended total treatment is 10 days.
    - For patients not requiring IMV and/or ECMO, the recommended total treatment is 5 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to an additional 5 days for a total treatment of 10 days.
- *Molecular weight:* 602.6 Daltons
- *Pharmacokinetics:* pharmacokinetic properties of remdesivir and the predominant circulating metabolite GS-441524 have only been evaluated in healthy adult subjects.
    - *Protein binding:* remdesivir: 88%, GS-441524: 2%
    - *Half-life:* remdesivir: 1 hour, GS-441524: 27 hours
- *Contraindications:* none
- *Warnings and Precautions*: infusion-related reactions
- *Adverse reactions:* nausea

Condition: COVID-19 and Pregnancy

The National Institutes of Health (NIH) issued Treatment Guidelines for COVID-19.[3] The summary section on *Special Populations* concludes the following:

> To date, the vast majority of data generated about the epidemiology, clinical course, prevention, and treatment of COVID-19 have come from studies of nonpregnant adults. More information is urgently needed for other populations, such as pediatric patients, pregnant patients, transplant patients, and other immunocompromised patients with COVID-19. Data are emerging on the clinical course of COVID-19 in pregnant patients, pregnancy outcomes in the setting of COVID-19, and vertical transmission, but further research is needed."

[2] Remdesivir (NDA 214787) proposed prescribing information.

[3] COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines nih.gov/. Accessed 8/20/20.

The section on *Special Considerations in Pregnancy and Post-Delivery* incorporates guidance from the Centers for Disease Control and Prevention (CDC),[4,5,6] the American College of Obstetricians and Gynecologist (ACOG)[7] and the Society for Maternal Fetal Medicine (SMFM)[8] on the management of pregnant patients with COVID-19 as summarized below:

- *Pregnancy outcomes:* limited information is available regarding the effect of COVID-19 on obstetric or neonatal outcomes.[9] Initial reports of COVID-19 disease acquired in the 3rd trimester were largely reassuring, but data are limited to case reports and series.[10,11]
    - In one of the larger series from Wuhan, China, pregnant women did not appear to be at risk for more severe disease.[12] Among 147 pregnant women with COVID-19 (64 confirmed, 82 suspected, and 1 asymptomatic infection), 8% had severe disease and 1% had critical disease. In comparison, in the general population of persons with COVID-19, 13.8% had severe disease and 6.1% had critical disease.[13] While data are still emerging, the US experience has been similar.[14]
    - However, a recent data analysis from CDC surveillance suggest that in women with COVID-19, pregnant women (n=8,207) appear to be at increased risk for certain manifestations of severe illness compared to non-pregnant peers (n=83,205) including: increased risk of ICU admission (1 in 68 pregnant versus 1 in 110 non-pregnant, crude risk ratio 1.6, 95% CI 1.3-1.9) and mechanical ventilation (1 in 195 of pregnant versus 1 in 370 non-pregnant, crude risk ratio 1.9, 95% CI 1.4-2.6). Yet no increase was noted in mortality (1 in 513 of pregnant versus 1 in 400 of non-pregnant, crude risk ratio 0.8, 95% CI 0.5-1.3).[15]
    - CDC guidance for "Inpatient Obstetric Healthcare Settings," states the following: based on what we know at this time, pregnant people might be at an increased risk for severe illness from COVID-19 compared to non-pregnant people. Additionally, there may be an increased risk of adverse pregnancy outcomes, such as preterm birth, among pregnant people with COVID-19.[4]

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[4] CDC. Interim considerations for infection prevention and control of coronavirus disease 2019 in inpatient obstetric healthcare settings. 2020. https://www.cdc.gov/coronavirus/2019-ncov/inpatient-obstetric-healthcare-guidance.html.
[5] CDC. Interim guidance on breastfeeding and breast milk feeds in the context of COVID-19. 2020. https://www.cdc.gov/coronavirus/2019-ncov/hcp/care-for-breastfeeding-women.html.
[6]CDC. Evaluation and management considerations for neonates at risk for COVID-19. 2020. https://www.cdc.gov/coronavirus/2019-ncov/hcp/caring-for-newborns.html.
[7] ACOG Practice advisory: novel coronavirus 2019 (COVID-19). https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2020/03-novel-coronavirus-2019.
[8] SMFM Coronavirus (COVID-19) and pregnancy: what maternal fetal medicine subspecialists need to know. 202. https://www.smfm.org/covid19.
[9] WHO Clinical Management of COVID-19. Interim guidance May 27, 2020.
[10] Chen H, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet*. 2020; 395 (10226):809-815.
[11] Liu Y, et al. Clinical manifestations and outcomes of SARS-CoV-2 infection during pregnancy. *J Infect.*2020.
[12] Breslin N, et al. COVID-19 in pregnancy: early lessons. *Am Journal of Obstetrics & Gynecology MFM*. 2020.
[13] World Health Organization. Report of the WHO-China joint mission on coronavirus disease 2019 (COVID-19). 2020. https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf
[14] Breslin N, et al. COVID-19 infection among asymptomatic and symptomatic pregnant women: Two weeks of confirmed presentations to an affiliated pair of New York City hospitals. *Am J Obstet Gynecol MFM*. 2020.
[15] Ellington S, et al. Characteristics of Women of Reproductive Age with Laboratory-Confirmed SARS-CoV-2 Infection by Pregnancy Status-United States, January 22-June 7, 2020. MMWR Morb Mortal Wkly Rep 2020 Jun 26:69 (25):769-75.

- *Timing of Delivery:*
  - In most cases, the timing of delivery should be dictated by obstetric indications rather than maternal diagnosis of COVID-19. For women with suspected or confirmed COVID-19 early in pregnancy who recover, no alteration to the usual timing of delivery is indicated.
  - For women with suspected or confirmed COVID-19 in the 3rd trimester, it is reasonable to attempt to postpone delivery (if no other medical indications arise) until a negative test result is obtained or quarantine restrictions are lifted in an attempt to avoid virus transmission to the neonate.
  - Based on limited data on primarily cesarean deliveries, there appears to be no clear evidence of vertical transmission of SARS-CoV-2 via the transplacental route, but this has not been definitively ruled out.[16]

- *Management of COVID-19 in the Setting of Pregnancy:*
  - There are no FDA approved drugs/biologics for the treatment of COVID-19.
  - Most clinical trials to date have excluded pregnant and lactating women, despite FDA advice[17].
  - Decisions regarding the use of drugs approved for other indications or investigational agents to treat COVID-19 must be made with shared decision-making, considering the safety of the medication and the risk and seriousness of the maternal disease.

- *Post-delivery*:
  - CDC recommends the determination of whether or not to separate a mother with known or suspected COVID-19 and her infant should be made on a case-by-case basis using shared decision-making between the mother and the clinical team.[6]
  - Both ACOG[7] and the American Academy of Pediatrics (AAP)[18] support breastfeeding for infants. In women who are suspected or confirmed to have SARS-CoV-2 infection, the decision about whether and how to start or continue breastfeeding should be made by the mother in coordination with her family and healthcare practitioners.[16]
  - CDC's interim guidance on breastfeeding recommends women who intend to breastfeed and who are temporarily separated from their infants express their breastmilk, ideally from a dedicated pump, practice good hygiene before and after pumping, and consider having a healthy person feed the infant.[5]
  - CDC advises that women with COVID-19 who choose to room-in with their infants and feed them at the breast should practice good hand hygiene and wear a facemask to prevent transmission of the virus to the infant via respiratory droplets

[16] ACOG COVID-19 frequently asked questions for obstetricians-gynecologists, obstetrics. 2020. https://www.acog.org/clinical-information/physicians-faqs/convid-19-faqs-for-ob-gyns-obstetrics.
[17] Constantine MM, Landon MB, Saade GR. Protection by Exclusion: Another Missed Opportunity to Include Pregnant Women in Research During the Coronavirus Disease 2019 (COVID-19) Pandemic. Obstet Gyn 2020 Jul;136(1):26-28.
[18] The American Academy of Pediatrics. Critical updates on Covid-19: "Breastfeeding Guidance Post Hospital Discharge for Mothers or Infants with Suspected or Confirmed SARS-CoV-2. https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections/clinical-guidance/breastfeeding-guidance-post-hospital-discharge/

during breastfeeding. It is unknown whether mothers with COVID-19 can transmit the virus via breast milk, but the limited data available suggest this is not likely to be a source of transmission.[5]

- The World Health Organization (WHO) recommends mothers with suspected or confirmed COVID-19 should be encouraged to continue breastfeeding.[9] "From the available evidence, mothers should be counseled that the benefits of breastfeeding substantially outweigh the potential risks of transmission. In infants, the risk of COVID-19 is low, the infection is typically mild or asymptomatic, and the consequences of not breastfeeding or separation of mother and child can be significant. At this point, it appears COVID-19 in infants and children represents much lower risk to survival and health than the other infections and conditions that breastfeeding is protective against."

REVIEW

PREGNANCY

Nonclinical Experience[2]

In animal reproductive toxicity studies, remdesivir demonstrated no adverse effect on embryofetal 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). For more details, refer to the Nonclinical Review by John Dubinion, PhD.

Clinical Trials

- Pregnant women were excluded from the clinical studies with remdesivir for COVID-19. The applicant stated no pregnancies were reported in the clinical studies for COVID-19.
- Pregnant women are included in the ongoing compassionate use program (IN-US-540-5755) and expanded access program (IN-US-540-5821) if they meet criteria for severe COVID-19, as outlined in the protocol. The applicant stated in the Clinical Summary of Safety that remdesivir has been shipped to over 300 pregnant women through the compassionate use program; however, no outcome information was included in the NDA submission.
    - In response to the DPMH IR, the applicant performed a search of the Gilead global safety database for pregnancy cases involving remdesivir exposure cumulative to August 18, 2020.
    - A total of 156 pregnancy reports were identified across the clinical development program for remdesivir including: COVID-19 (n=142), Ebola Virus Disease (EVD) (n=13), and indication not specified but administered through EUA (n=1) with the following reported pregnancy outcomes:
        - Unknown (n=110)
        - Livebirth (n=33)
            - Gestational timing of exposure included: 3rd trimester (n=26), 2nd trimester (n=1), 1st trimester (n=0), unknown (n=6).
            - 2 infants with major malformations (pulmonary artery stenosis (PAS); ventricular septal defect (VSD)/atrial septal defect (ASD)/patent ductus arteriosus (PDA) at 30 weeks gestation). Both infants were exposed in the 3rd trimester; therefore, the

malformations were not likely due to remdesivir as cardiovascular development occurs in the 1st 8 weeks of gestation.

- Induced abortion (n=2)
  - Maternal EVD infection in both cases.
- Spontaneous abortion (n=7)
  - Underlying maternal EVD in 5 cases which increases the risk of spontaneous abortion.
  - Underlying severe maternal COVID-19 in 2 cases both requiring invasive mechanical ventilation (IMV).
- Stillbirth (n=4)
  - Underlying maternal EVD in 2 cases which increases the risk of stillbirth.
  - Underlying severe maternal COVID-19 in 2 cases both requiring IMV.

Reviewer's Comment
DPMH sent a follow-up IR requesting the applicant explain the discrepancy between the 300 reported compassionate use pregnancy cases versus the 156 pregnancy cases retrieved from their global safety database search and to provide maternal outcome information. The applicant responded that "although remdesivir has been shipped to over 300 pregnant women, it is not known from the shipping information how many of these women were treated and how many remained pregnant at the time of treatment." Further, the applicant noted capturing pregnancy cases from compassionate use in their global safety database is dependent on receipt of the Pregnancy Report Form from the treating physician. Of the total 156 pregnancy cases reported in their global safety database, 122 cases were from the compassionate use program.

Clinical outcome data were only available for 86 of these compassionate use pregnancy cases, and 19 women delivered before their 1st dose of remdesivir and were reclassified as postpartum. Maternal outcomes included:

- *At baseline, 40% of pregnant women (median gestational age 28 weeks) required invasive ventilation, in contrast to 95% of postpartum women (median gestational age at delivery 30 weeks).*
- *By Day 28 of follow-up, the level of oxygen requirement decreased in 96% and 89% of pregnant and postpartum women, respectively.*
- *Among pregnant women, 93% of those on mechanical ventilation were extubated, 93% recovered, and 90% were discharged.*
- *Among postpartum women, 89% were extubated, 89% recovered, and 84% were discharged.*
- *There was one maternal death attributed to underlying disease and no neonatal deaths.*

Applicant's Review of Published Literature
The applicant did not perform a literature search related to remdesivir use and pregnancy.

DPMH's Review of Published Literature

This Reviewer performed a search in PubMed, Embase, Micromedex[19], TERIS[20], Reprotox[21], and Briggs[22] to find relevant articles related to the use of remdesivir during pregnancy. Search terms included "remdesivir" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," and "miscarriage." The following relevant articles were identified:

- **Micromedex** Pregnancy Rating: Fetal risk cannot be ruled out. "Available evidence is inconclusive or is inadequate for determining fetal risk when used in pregnant women or women of childbearing potential. Weigh the potential benefits of drug treatment against potentials risk before prescribing this drug during pregnancy."

- Published case series and reports describing pregnancy outcomes in women exposed to remdesivir (all occurred during the 2nd and 3rd trimester) are summarized below in Table 1.

Table 1: Published Cases of Pregnancy Exposure to Remdesivir (RDV) for COVID-19

Publication	Study Type	N	Timing	Exposure	Outcome	Author's conclusions
Pierce-Williams, et al (2020)[23] USA	Cohort Aim was to describe the clinical course of pregnant women hospitalized with severe or critical COVID-19 at 12 US institutions	64 total 16 RDV	Not reported (most exposures were 3rd trimester)	Majority of patients received hydroxy-chloroquine (88%) RDV (n=16)	*Maternal outcomes:* 1 patient with cardiac arrest who required tracheostomy, no cases of maternal death. 50% of patients (32/64) delivered during the hospitalization (88% with critical disease delivered preterm often iatrogenic due to worsening maternal status, 94% by C-section (C/S)). *Fetal outcomes:* No stillbirths, neonatal deaths, cases of vertical transmission.	In pregnant women severe or critical COVID-19, average duration of hospitalization was 6 days [severe] vs 12 days [critical]. Women with critical disease had a high rate of acute respiratory distress syndrome (ARDS).
McCoy et. al.[24] (2020) USA	Case series Pregnant women with PCR-confirmed severe	5	2nd trimester (n=1) 3rd trimester (n=4)	Hydroxy-chloroquine Remdesivir 200 mg IV x1, then 100 mg IV daily for up to 9 days:	*Maternal*: 2 women treated with O_2 by NC; 3 women required mechanical ventilation and ICU care due to ARDS. All 5 women recovered and were	The small number of patients and early experience did not allow conclusions to be drawn about

[19] Truven Health Analytics information, http://www.micromedexsolutions.com/Accessed 8/20/20.
[20] TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 8/20/20.
[21] Reprotox® Website: www.Reprotox.org. REPROTOX® system Accessed 8/20/20.
[22] Briggs, GG. Freeman, RK. & Yaffe, SJ. (2017). Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.
[23]Pierce-Williams R, et al. Clinical course of severe and critical coronavirus disease 2019 in hospitalized pregnancies: a United States cohort study. Am J Obstet Gynecol MFM 2020.
[24] McCoy J, et al. Compassionate use of remdesivir for treatment of severe coronavirus disease 2019 in pregnant women. AJOG [Epub ahead of print].

Publication	Study Type	N	Timing	Exposure	Outcome	Author's conclusions
	COVID-19 treated with compassionate use			2 patients completed 10 days of treatment, 2 were discharged before completion, 1 discontinued treatment because of elevated LFTs attributed to RDV.	discharged from hospital on room air. *Fetal outcomes:* 1 ongoing pregnancy 4 preterm births (3 C/S, 1 uncomplicated spontaneous vaginal delivery)	safety and efficacy. There is an urgent need for inclusion of pregnant women in clinical trials to evaluate remdesivir and other treatments for COVID-19.[25]
Igbinosa I, et al (2020)[26] USA	Case series 3 pregnant women hospitalized with confirmed COVID-19 who met criteria for compassionate use of remdesivir	3	2nd trimester (n=2) 3rd trimester (n=1)	RDV 200 mg IVx1, then 100 mg IV	*Maternal outcome:* Case 1: patient developed transaminitis and intrahepatic cholestasis of pregnancy. All 3 women were receiving supplemental oxygen and had resolution of this requirement after initiation of remdesivir. *Fetal outcome:* Case 1: term livebirth (uncomplicated spontaneous vaginal delivery) Case 2 and 3: ongoing pregnancies	As the COVID-19 pandemic continues, pregnant women remain at risk for adverse medical and obstetric outcomes. Having safe and effective therapies is crucial. In each case, the process to obtain RDV delayed treatment by 1-2 days. This case series highlights the importance of including pregnant women in trials and provision of rapid access to this drug, as pregnant women face increased risk for adverse outcomes [15]
Lucarelli E, et al (2020)[27] USA	Case series	1	3rd trimester	Ceftriaxone Azithromycin	*Maternal outcome:* after several days of ventilation, all 3 women were extubated,	Our experience suggests that the mortality in

[25]LaCourse SM, et al. Importance of inclusion of pregnant and breastfeeding women in COVID-19 therapeutic trials. Clin Infect Dis 2020 [Epub ahead of print].
[26] Igbinosa I, et al. Use of remdesivir for pregnant patients with severe novel 2019 coronavirus disease. American Journal of Obstetrics and Gynecology (2020).
[27] Lucarelli E, et al. Mechanical ventilation in pregnancy due to COVID-19: A cohort of three cases. Am J Perinatol 2020; 37:1066-1069.

Publication	Study Type	N	Timing	Exposure	Outcome	Author's conclusions
	3 pregnant women with COVID-19 who required mechanical ventilation due to respiratory failure and pneumonia (only 1 treated with RDV)			Hydroxy-chloroquine Methyl-prednisolone Remdesivir 200 mg IV bid, then 100 mg IV x 9 days	and continuing their pregnancies with no demonstrable adverse effects. *Fetal outcome:* Pregnancy ongoing	pregnant women with COVID-19 requiring mechanical ventilation is not necessarily as high as in nonpregnant patients.
Naqvi M, et al (2020)[28] USA	Case report Pregnant woman hospitalized with severe COVID-19	1	2nd trimester	Tocilizumab Remdesivir 200 mg IV x1, 100 mg x 4 days Lovenox	*Maternal outcome:* survival, discharged home at 23 weeks gestation after 9 days in the hospital *Fetal outcome:* Pregnancy ongoing	Definitive conclusions cannot be drawn. Urgent need to include pregnant women in studies of investigational therapies for the treatment of severe COVID-19.
Anderson J, et al (2020)[29] USA	Case report Critically ill pregnant woman with COVID-19 pneumonia and ARDS	1	2nd trimester	Remdesivir 200 mg IV x1, 100 mg x 9 days Convalescent plasma Ceftriaxone Azithromycin Hydroxy-chloroquine Hydrocortisone Low molecular weight heparin	*Maternal outcome:* survival, hospital discharge at 24 weeks gestation *Fetal outcome:* pregnancy ongoing	On admission an application was made for compassionate use of RDV. RDV was not initiated until hospital day 5, by which time the patient status deteriorated and she required mechanical ventilation. Following initiation of RDV the patient improved and was extubated on day 5, and discharged on day 10.

[28] Naqvi M, et al. Tocilizumab and Remdesivir in a pregnant patient with coronavirus disease 2019 (COVID-19). Obstet Gynecol 2020;00:1-5.

[29] Anderson J, et al. The use of convalescent plasma therapy and remdesivir in the successful management of a critically ill obstetric patient with novel coronavirus 2019 infection: A case report. Case reports in Women's Health 27 (2020) e00221.

Publication	Study Type	N	Timing	Exposure	Outcome	Author's conclusions
Easterlin M, et al. (2020)[30] USA	Case report Pregnant woman with severe COVID-19 pneumonia and history of tuberous sclerosis	1	2nd trimester	Remdesivir Hydroxy-chloroquine Azithromycin Tocilizumab Convalescent plasma Nitric oxide	*Maternal outcome:* following delivery, maternal status initially improved but was ultimately complicated by bilateral pneumothoraces requiring chest tube, multiple pulmonary emboli, sepsis, and failed extubation requiring tracheostomy at 27 days intubation. *Fetal outcome:* Preterm birth at 25wks, C-section for worsening maternal status, Apgars 0, 2, 5. Placenta with chorioamnionitis. Infant RT-PCR negative for SARS-CoV-2. At publication infant critically ill with severe respiratory failure on high frequency ventilation, inotropic support, pressor-resistant hypotension, severe persistent pulmonary hypertension.	Pregnant women should take precautions to minimize exposure to SARS-CoV-2 to decrease adverse perinatal outcomes.

Reviewer's Comment
Overall, the available data from published cases and pharmacovigilance reports of remdesivir use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. This Reviewer notes pregnancy outcome information was missing in 70% (110 out of 156) of the cases retrieved from the applicant's search of their global safety database. Further, there are no available data regarding the use of remdesivir during the first trimester. These data indicate pregnant women with COVID-19 are being exposed to remdesivir and highlight the need to capture additional pregnancy safety data.

DPMH is aware of three ongoing pregnancy registries enrolling pregnant women with COVID-19 that the applicant may consider collaborating with to facilitate the collection of pregnancy safety data in the postmarketing setting (PRIORITY: Pregnancy Coronavirus Outcomes Registry, OTIS COVID-19 Pregnancy Registry, and IRCEP: International Registry of Coronavirus Exposure in Pregnancy). In addition, DPMH notes the applicant's response to the DAV IR regarding their plans to collect additional data in pregnant and lactating women to inform safe and effective use of remdesivir, which indicates the applicant is planning a pregnancy pharmacokinetic study in collaboration with the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT).

[30] Easterlin M, et al. Extremely preterm infant born to a mother with severe COVID-19 Pneumonia. Journal of Investigative Medicine High Impact Case Reports. Volume 8:1-5. 2020.

LACTATION

Nonclinical Experience[2]

In animal studies, 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 mothers from Gestation Day 6 to Lactation Day 20. Exposures in nursing pups were approximately 1% that of maternal exposure on Lactation Day 10. For more details, refer to the Nonclinical Review by John Dubinion, PhD.

Clinical Trials

- Lactating women were excluded from clinical studies with remdesivir for COVID-19. The applicant stated no lactation cases were reported.
- In response to the DPMH IR, the applicant performed a search of the Gilead global safety database up to August 20, 2020, which revealed no reports of infants who were exposed to remdesivir through breastfeeding.

Applicant's Review of Published Literature

The applicant did not perform a literature search related to remdesivir use and lactation.

DPMH's Review of Published Literature

This Reviewer performed a search in PubMed, Embase, Micromedex[19], TERIS[20], Reprotox[21], and Briggs[22], *Medications and Mothers' Milk*[31], and LactMed[32] to find relevant articles related to the use of remdesivir during lactation. Search terms included "remdesivir" AND "breastfeeding" or "lactation." The following relevant articles were identified:

- **Micromedex** Lactation Rating: Infant risk cannot be ruled out. "Available evidence and/or expert consensus is inconclusive or is inadequate for determining infant risk when used during breastfeeding. Weigh the potential benefits of drug treatment against potential risk before prescribing thus drug during breastfeeding.

- The **LactMed** summary of use during lactation states, "remdesivir is an investigational antiviral drug that is being tested for use against the novel coronavirus disease, COVID-19. Remdesivir is given intravenously because it is poorly absorbed orally, so infants are not likely to absorb clinically important amounts of the drug from milk. In addition, newborn infants have received intravenous remdesivir therapy for Ebola with no serious adverse drug reactions.[33,34] Given this limited information, it does not appear that mothers receiving remdesivir need to avoid nursing, but until more data are available, remdesivir should be used with careful infant monitoring

[31] Hale, Thomas (2020) Medications and Mothers' Milk online

[32] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. LactMed is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare providers and nursing women. LactMed provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding.

[33] Dornemann J, Burzio C, Ronsse A, et al. First newborn baby to receive experimental therapies survives Ebola virus disease. J Infect Dis. 2017;215:171–4.

[34] Mulangu S, Dodd LE, Davey RT Jr, et al. A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med. 2019;381:2293–303.

during breastfeeding. The most common adverse effects reported after intravenous infusion include elevated aminotransferase and bilirubin levels and other liver function tests. Diarrhea, rash, renal impairment, and hypotension have also been reported." No relevant published information was found regarding maternal drug levels or infant drug levels, effects in breastfed infants, or effects on milk production.

- Published case reports were identified that describe the evaluation of breastmilk for the presence of SARS-CoV-2 in lactating women with COVID-19 infection.[35,36,37,38,39,40] Of the 24 total case reports on breast milk samples from women infected with SARS-CoV-2, viral RNA was detected in samples from 4 women. However, environmental contamination or retrograde flow from an infected infant could not be ruled out.

- In a recently published lactation study,[41] the authors noted that detection of viral RNA from RT-PCR described in the case reports above does not equate with infectivity. The authors also noted that to date, SARS-CoV-2 has not been isolated from breast milk, and there are no documented cases of transmission of infectious virus to the infant through breastmilk. In this study, a total of 18 lactating women with confirmed SARS-CoV-2 provided between 1 and 12 milk samples, with a total of 64 samples collected. One sample had detectable SARS-CoV-2 RNA; however, no replication-competent virus was detectable in any sample including the sample that tested positive for viral RNA. The authors concluded these data suggest SARS-CoV-2 RNA does not represent replication-competent virus and breast milk may not be a source of infection for the infant.

Reviewer's Comment
The primary author of the above ongoing lactation study, Dr. Christina Chambers, communicated by email with Dr. Leyla Sahin from DPMH, noting that to date approximately 300 lactating women with confirmed or suspected COVID-19 have been enrolled in the study.[42] Dr. Chambers stated that a few of these women were treated with remdesivir and have submitted breast milk samples; however, there is no existing assay available to measure remdesivir levels in breast milk. Dr. Chambers expressed the need for development of an assay for remdesivir.

[35] Chen H, et al. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. *Lancet* 2020:395 (10226):809-815.
[36] Wu Y, et al. Coronavirus disease 2019 among pregnant Chinese women: case series data on the safety of vaginal birth and breastfeeding. BJOG. Published online May 5, 2020.
[37] Costa S, et al. Excretion of SARS-CoV-2 in human breast milk. *Clin Microbiol Infect.* Published online June 2, 2020.
[38] GroB R, et al. Detection of SARS-CoV-2 in human breastmilk. *Lancet.* 2020; 395(10239):1757-1758.
[39] Tam PCK, et al. Detectable severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in human breast milk of a mildly symptomatic patient with coronavirus disease 2019 (COVID-19). *Clin Infect Dis.* Published online May 30, 2020.
[40] Liu W, et al. Clinical characteristics of 19 neonates born to mothers with COVID-19. *Front Med*. 2020;14(2):193-198.
[41] Chambers C, et al. Evaluation of SARS-CoV-2 in Breast Milk from 18 Infected Women. JAMA. Published online August 19, 2020. Doi:10.1001/jama.2020.15580.
[42] Personal Communication between Dr. Leyla Sahin and Dr. Christina Chambers, August 21, 2020.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience[2]

Nonclinical toxicology 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 recommended human dose (RHD). Reproductive toxicity, including decreases in corpus lutea, numbers of implantation sites, and viable embryos, was seen when remdesivir was administered by daily intravenous administration at a systemically toxic dose (10 mg/kg) in female rats 14 days prior to mating and during conception; exposures of the predominant circulating metabolite (GS-441524) were 1.3 times the exposure in humans at the RHD. For more details, refer to the Nonclinical Review by John Dubinion, PhD.

Applicant's Review of Published Literature

The applicant did not perform a literature search related to remdesivir use and fertility.

DPMH's Review of Published Literature

This Reviewer performed a search in PubMed, Embase, Reprotox[21] to find relevant articles related to the use of remdesivir and effects on fertility. Search terms included "remdesivir" AND "fertility," "infertility," "contraception," and "oral contraceptives." No relevant articles were identified.

DISCUSSION AND CONCLUSIONS

Pregnancy

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. Considering pregnant women requiring hospitalization for severe COVID-19 are at risk for serious morbidity and mortality, DPMH recommends including this Clinical Consideration in subsection 8.1 of labeling for remdesivir to clearly communicate the potential need for treatment with remdesivir in pregnant patients.

Recommended postmarketing studies:

DPMH considered whether a postmarketing requirement (PMR) for a pregnancy safety study should be issued for remdesivir. Considering the COVID-19 pandemic is an unprecedented public health emergency that may affect millions of females of reproductive potential, including pregnant individuals, there is an important need to collect data that can inform the safe use of drug therapies during pregnancy. Despite FDA advice, pregnant patients were excluded from clinical trials with remdesivir for COVID-19. The NDA submission noted that no pregnancies were reported in clinical trials; however, over 300 pregnant patients received remdesivir under the sponsor's compassionate use program. Importantly, the majority of the pregnancy outcomes were unknown (outcomes available for 33 live births; most exposed in the third trimester). Therefore, there are inadequate data at this time to evaluate the safety of the drug when used during pregnancy. Additionally, there is a need to collect pharmacokinetic data in pregnant patients to confirm the appropriate dose of remdesivir during pregnancy because there are significant physiologic changes that may affect dosing, especially in the second and third trimesters.

Therefore, DPMH recommends postmarketing studies for a pregnancy exposure registry and a pharmacokinetic study in pregnant patients exposed to remdesivir. We also recommend that the applicant consider collaborating with the COVID-19 pregnancy registries that are currently enrolling pregnant patients with COVID-19. The applicant also stated collaboration is underway with the IMPAACT Network to initiate a pharmacokinetic study in pregnant patients hospitalized with COVID-19 and treated with remdesivir.

Lactation

There are no available data on the presence of remdesivir or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies, remdesivir and its metabolites were detected in the plasma of nursing rat pups following daily intravenous administration of remdesivir to pregnant mothers from Gestation Day 6 to Lactation Day 20. Although the physio-chemical properties of remdesivir (such as the low molecular weight and protein-binding) suggest it may be present in human milk, because it is poorly absorbed orally, breastfed infants are not likely to absorb clinically important amounts of the drug from milk.

It is currently unknown if SARS-CoV-2 can be transmitted to infants by breastfeeding. To date, although SARS-CoV-2 viral RNA has been detected in some breast milk samples, no replication-competent virus has been detected. Further, there are no documented cases of transmission of infectious virus to the infant through breast milk. Multiple organizations, including WHO and AAP, recommend lactating individuals infected with SARS-CoV-2 should be encouraged to continue breastfeeding as the benefits outweigh the potential risks. Protections are recommended (such as wearing a mask, practicing hand hygiene, etc.) to prevent transmission of the virus to the infant via maternal respiratory droplets during breastfeeding.

Therefore, DPMH recommends subsection 8.2 of labeling for remdesivir contain the standard Pregnancy and Lactation Labeling Rule (PLLR) risk/benefit statement, “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.” In addition, a statement will be added that breastfeeding individuals with COVID-19 should follow practices according to clinical guidelines to avoid exposing the infant to COVID-19.

Recommended postmarketing studies:

DPMH considered whether a PMR for a lactation study should be issued for remdesivir. Considering the COVID-19 pandemic is an unprecedented public health emergency that may affect millions of females of reproductive potential, including lactating individuals, there is an important need to collect data that can inform the safe use of drug therapies during lactation. Despite FDA advice, lactating patients were excluded from clinical trials with remdesivir for COVID-19 and no lactation cases have been reported to the applicant’s global pharmacovigilance database. However, the published literature indicates lactating patients with COVID-19 are being treated with remdesivir and milk samples are being collected.[41] Further, DPMH has been in contact with one study author[42] who noted breastmilk samples from lactating patients treated with remdesivir for COVID-19 have been submitted, but there is currently no validated assay for remdesivir which precludes assessment of the drug levels in milk. Additionally, the CUDDLE (Pharmacokinetics and Safety of Commonly Used Drugs in

Lactating Women and Breastfed Infants) study, a multicenter lactation study funded through NICHD, is planning to collect remdesivir breast milk samples. Therefore, DPMH recommends a postmarketing study for a breast milk only study to assess concentrations of remdesivir and relevant metabolites in breast milk. We also recommend that the applicant consider collaborating with investigators already collecting lactation information on remdesivir.

Additional recommendations for postmarketing studies:
In considering whether postmarketing studies recommended above (i.e., pregnancy registry, pregnancy PK study, and breastmilk-only lactation study) should be issued as requirements (PMRs) or commitments (PMCs), DPMH recommends that these studies be issued as PMRs. Such pregnancy studies are intended to collect important safety information and may be issued as PMR studies based on the authorities provided under section 505(o)(3) of the FD&C Act.[43,44] DPMH has issued over 50 PMR studies since 2016, including for drugs used as short-term or intermittent therapies. Issuance of these studies as PMR studies will ensure formal and specific requirements for reporting of study data. Moreover, issuance of these studies as PMRs would also serve an important public acknowledgement that collection of safety data in COVID-19 drugs that may be used during pregnancy and/or lactation is an important objective for FDA.

Females and Males of Reproductive Potential
There are no available data on the effects of remdesivir on human fertility. There is also no evidence to suggest remdesivir is associated with embryo-fetal toxicity, so contraception and pregnancy testing subheading are also not indicated. Therefore, DPMH recommends omitting subsection 8.3 of remdesivir labeling.

RECOMMENDATIONS
DPMH recommends the following:
Proposed PMRs:

1. "Conduct a prospective pregnancy exposure registry cohort study to obtain maternal, fetal, and infant outcomes of patients with COVID-19 exposed to Veklury during pregnancy. The registry will identify and record pregnancy complications, adverse maternal outcomes, major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, preterm births, small-for-gestational age births, effects on postnatal growth and development, and adverse effects in breastfed infants will be assessed through at least the first year of life."

2. "Conduct a single-arm pharmacokinetic study in pregnant patients exposed to Veklury to determine the optimal dosing regimen during pregnancy."

3. "Conduct a breastmilk only study to assess concentrations of remdesivir and relevant metabolites in breast milk."

[43] Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act Guidance for Industry. Accessed at: https://www fda.gov/media/131980/download
[44] Clinical Lactation Studies: Considerations for Study Design Draft Guidance for Industry. Accessed at: https://www.fda.gov/media/124749/download

DPMH revised subsections 8.1 and 8.2 of labeling for compliance with the PLLR (see below). The labeling recommendations below were discussed with the DAV Review Team at the August 26, 2020 labeling meeting. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Veklury (remdesivir) Pregnancy and Lactation Labeling
FULL PRESCRIBING INFORMATION
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy

Risk Summary

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

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

Data

Animal Data

Remdesivir was administered via intravenous injection to pregnant rats and rabbits (up to 20 mg/kg/day) on Gestation Days 6 through 17, and 7 through 20, respectively, and also to rats from Gestation Day 6 to Lactation/Post-partum Day 20. No adverse effects on embryo-fetal (rats and rabbits) or pre/postnatal (rats) development were observed in rats and rabbits at nontoxic doses in pregnant animals. During organogenesis, exposures to the predominant circulating metabolite (GS-441524) were 4 (rats and rabbits) times higher than the exposure in humans at the RHD. In a pre/postnatal development study, exposures to the predominant circulating metabolite of remdesivir (GS-441524) were similar to the human exposures at the RHD.

8.2 Lactation

Risk Summary

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

Data

Animal Data

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

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Memorandum

Date:	August 28, 2020
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Product Name:	Remdesivir
Subject:	Hepatotoxicity
Application Type/Number:	IND 147753, NDA 214787, EUA 46
Applicant:	Gilead Sciences, Inc.
OSE RCM #:	2020-1726

1 INTRODUCTION

This Division of Pharmacovigilance II (DPV II) memorandum describes hepatotoxicity cases identified in the FDA Adverse Event Reporting System (FAERS) database with remdesivir use under both the Emergency Use Authorization (EUA) and compassionate use program in the setting of coronavirus disease 2019 (COVID-19) from June 4, 2020 through August 16, 2020.[a] The Division of Antivirals (DAV) consulted DPV II and requested a summary of compelling hepatotoxicity cases under the EUA for remdesivir. This data will be used by DAV during their New Drug Application (NDA) safety review of remdesivir.

The purpose of this DPV II memorandum is to provide DAV with a summary of hepatotoxicity cases with remdesivir to determine if a warning is appropriate in the remdesivir product label.

1.1 BACKGROUND

On May 1, 2020, the FDA issued an EUA to permit the use of remdesivir for the treatment of suspected or laboratory confirmed COVID-19 in hospitalized adult and pediatric patients with severe disease. Severe disease is defined as those patients with an oxygen saturation of ≤ 94% on room air, those requiring supplemental oxygen, those requiring mechanical ventilation, or those requiring extracorporeal membrane oxygenation (ECMO).[1,2]

On July 9, 2020, DPV II completed a pharmacovigilance memorandum that provided a summary of the available safety data in FAERS and the medical literature related to the use of remdesivir under the EUA in the setting of COVID-19 from December 1, 2019 through June 3, 2020.[3] Of the 402 cases identified, 114 (28%) reported transaminase elevations/increased liver function tests. Of those 114 cases, 55 (48%) reported an increase in alanine transaminase (ALT) or aspartate aminotransferase (AST) of ≥ 5 times the upper limit of normal (ULN), with 21 (19%) that reported an ALT or AST increase of ≥ 10 times the ULN. The majority of cases (57%) had both ALT and AST elevations. Twenty-seven cases (24%) reported resolution of increased transaminases/liver function tests after discontinuation of remdesivir. No cases reported signs and symptoms of liver inflammation or liver injury such as jaundice, ascites, weakness, nausea, and vomiting. The memorandum acknowledged that because liver injury is common in patients with COVID-19, especially in severe infection, determining the contribution of remdesivir to these events remains challenging.

On August 18, 2020, DAV consulted DPV II requesting an analysis for compelling hepatotoxicity cases reported to FAERS with remdesivir use under the EUA in the setting of COVID-19 to determine if a warning is warranted in the label. DAV requested categorizing the hepatotoxicity cases as follows:

Narrow: All cases without confounders (e.g., sepsis, biliary obstruction, significant hypotension requiring vasopressors) reporting any increase of AST or ALT above the ULN **and** laboratory parameters (e.g., elevated prothrombin time (PT), international normalized ratio (INR), total

[a] The data lock start date was selected based on a previous DPV II remdesivir memorandum (completed on July 9, 2020, DARRTS Reference ID: 4638219), which included data through June 3, 2020.

bilirubin, decreased platelets) or clinical signs/symptoms (e.g., jaundice, ascites, encephalopathy) suggestive of liver failure.

Broad: All cases without confounders[b] (e.g., sepsis, biliary obstruction, significant hypotension equiring vasopressors) reporting AST or ALT elevations 10 times or more the ULN, including those that do not report other relevant laboratory parameters (i.e., PT/INR, bilirubin, platelets) or clinical signs/symptoms suggestive of liver failure.

1.2 RELEVANT SECTIONS FROM THE REMDESIVIR FACT SHEET FOR HEALTHCARE PROVIDERS[2]

5 WARNINGS AND PRECAUTIONS
There are limited clinical data available for remdesivir. Serious and unexpected adverse events may occur that have not been previously reported with remdesivir use.

5.2 Increased Risk of Transaminase Elevations
Transaminase elevations have been observed in healthy volunteers who received 200 mg of remdesivir followed by 100 mg doses for 5-10 days. Transaminase elevations have also been reported in patients with COVID-19 who received remdesivir in clinical trials. As transaminase elevations have been reported as a component of COVID-19, including in patients receiving placebo in clinical trials of remdesivir, discerning the contribution of remdesivir to transaminase elevations in this patient population is challenging.

Hepatic laboratory testing should be performed in all patients prior to starting remdesivir and daily while receiving remdesivir.

- Remdesivir should not be initiated in patients with ALT greater than or equal to 5 times the upper limit of normal at baseline.
- Remdesivir should be discontinued in patients who develop:
  - ALT greater than or equal to 5 times the upper limit of normal during treatment with remdesivir. Remdesivir may be restarted when ALT is less than 5 times the upper limit of normal.
    OR
  - ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR.

2 METHODS AND MATERIALS

2.1 CASE SELECTION CRITERIA

We screened reports retrieved from the search strategy described in **Table 1** below for cases of hepatoxicity (e.g., increased transaminases, hepatic failure, increased liver function tests) reported with remdesivir use for the treatment of COVID-19. We removed duplicate reports during this process.

[b] DPV II acknowledges that COVID-19 infection, in itself, is a cofounding factor for increased transaminases.

Inclusion criteria:
We included cases if there was:

- Any increase of AST or ALT above the ULN **AND** at least one of the following:
  - A reported laboratory parameter suggestive of hepatic failure (e.g., decreased platelets, increased PT/INR, or increased total bilirubin levels).[4]
  - Clinical signs/symptoms of hepatic failure (e.g., jaundice, ascites)

- An increase in AST or ALT of at least 10 times the ULN[c] with or without reported laboratory parameters (e.g., decreased platelets, increased PT/INR, or increased total bilirubin levels) or clinical signs/symptoms (e.g., jaundice, ascites) suggestive of hepatic failure.

Exclusion criteria:
We excluded cases for any one of the following reasons:

- Another likely cause for hepatotoxicity, including biliary obstruction, sepsis, alcohol abuse, cardiac arrest, hypotension requiring vasopressor support, or concomitant medications labeled for hepatoxicity in the Warnings and Precautions section.[d]
- The event occurred prior to initiation of or after completion of remdesivir treatment.

2.2 FAERS SEARCH STRATEGY

DPV II searched the FAERS database with the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*	
Date of search	Recurring daily searches†
Time period of search	June 4, 2020‡ – August 16, 2020
Search type	Drug Safety Analytics Dashboard (DSAD)
Product terms	Product Active Ingredient (PAI): Remdesivir
MedDRA search terms (Version 23.0)	Preferred Terms (PTs): *Asymptomatic COVID-19, COVID-19, COVID-19 pneumonia, Suspected COVID-19, SARS-CoV-2 carrier, Exposure to SARS-CoV-2, Occupational exposure to SARS-CoV-2, SARS-CoV-2 test, SARS-CoV-2 test false negative, SARS-CoV-2 test positive, COVID-19 prophylaxis, COVID-19 treatment, Coronavirus test positive, Coronavirus infection*

[c] Not all cases included reference ranges for AST and ALT; We used an ULN of 55 U/L for ALT and 48 U/L for AST for those cases. We also included cases that reported elevations greater than 10 times the ULN even if the reference range used was not reported.
[d] We included cases if the concomitant medication was labeled for hepatotoxicity in the Adverse Reactions section.

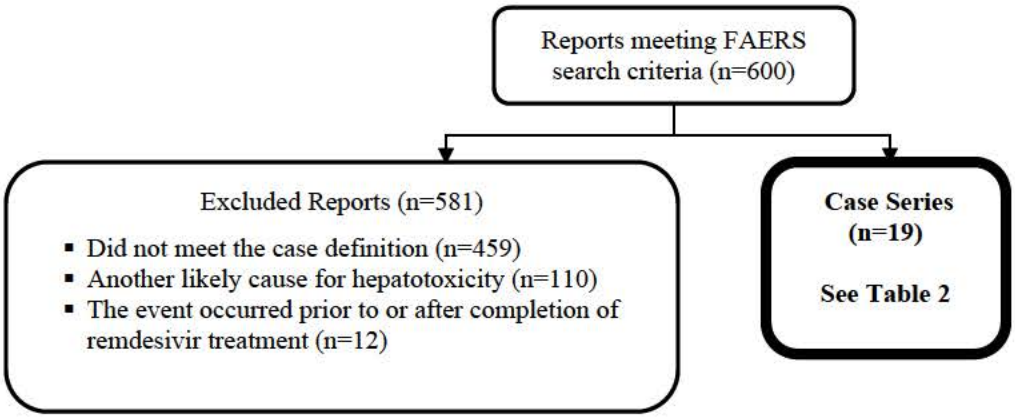
Table 1. FAERS Search Strategy*	
Other criteria (text string searches)	Reported Reason for Use: Coronavirus infection, Corona virus infection, Coronavirus test positive Reporter Narrative: Coronavirus, Corona virus, Novel coronavirus, ncov, 2019-ncov, 2019 ncov, Hubei, Wuhan, COVID, SARS-COV-2, SARS COV 2, T705, T-705, Emergency use authorization, EUA Medical History Comments: SARS-COV-2, SARS COV2, ncov, 2019-ncov, Corona virus, Coronavirus, COVID
* See **Appendix A** for a description of the FAERS database † Searches recurring daily on Tuesday-Friday with a 1-day prior completion date and on Monday with a 3-day prior completion date ‡ The data lock start date was selected based on a previous DPV II remdesivir memorandum (completed on July 9, 2020), which included data through June 3, 2020.	

3 RESULTS

3.1 FAERS CASE SELECTION

DPV II identified 600 cases reporting signs of hepatotoxicity (e.g., increased transaminases, increased liver function tests, hepatic failure) with remdesivir use for the treatment of COVID-19 in the FAERS database from June 4, 2020 through August 16, 2020. Of those 600 unique cases, 19 cases met the case definition described in **Section 2.1** (see **Figure 1**).

Figure 1. FAERS Case Selection



3.2 FINAL CASE SERIES

We excluded the majority of cases for not meeting the case definition of having an increase in transaminases of at least 10 times the ULN. Notably, several of these cases reported elevations

that while less than 10 times the ULN were still more than 5 times the ULN, the level at which the EUA Fact Sheet recommends to discontinue remdesivir. Of the 110 cases that reported another likely cause for hepatotoxicity, 74 reported concomitant medications labeled for hepatotoxicity in their respective WARNINGS AND PRECAUTIONS,[e] 33 reported hypotension and/or vasopressor requirement, 18 reported multi-organ failure, 17 reported cardiac arrest, 16 reported sepsis or septic shock, 2 reported a history of alcohol abuse, 1 reported a history of cirrhosis, and 1 reported biliary obstruction.[f] Of note, we excluded 38 cases solely for the reason of receiving a concomitant medication labeled for hepatotoxicity in WARNINGS AND PRECAUTIONS.

We identified 19 FAERS cases meeting the case definition described in **Section 2.1**. **Appendix B** contains narratives and a line listing of the 19 cases in this case series.

Table 2 provides the total number of cases identified that met the case selection criteria and describes the characteristics of these cases.

Table 2. Remdesivir Cases Reporting Hepatotoxicity in the Setting of COVID-19 under the EUA from June 4, 2020* through August 16, 2020 (n=19)

Sex	
Male	10
Female	9
Age (years)	
Range	25 – 88
Median	61
Mean	58
Report Type†	
Direct	19
Expedited (Gilead)	3
Serious outcomes (n=13)‡	
Other serious	10
Hospitalization	3
Life-threatening	1
Death	1

* The data lock start date was selected based on a previous DPV II remdesivir memorandum (completed on July 9, 2020), which included data through June 3, 2020.
† Three cases were submitted by both the Applicant and a healthcare provider.
‡ For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), and other serious important medical events. A case may report more than one serious outcome.

Key Findings:

[e] Concomitant medications included azithromycin (n=24), HMG-CoA reductase inhibitor (n=23), tocilizumab (n=16), amiodarone (n=15), acetaminophen (n=9), pantoprazole (n=9), hydroxychloroquine or chloroquine (n=5), methylprednisolone (n=4), levofloxacin (n=3), divaloproex (n=2), lopinavir/ritonavir (n=1), captopril (n=1), lisinopril (n=1), duloxetine (n=1), and carbamezapine (n=1).
[f] A case may report more than one reason for hepatotoxicity.

- All cases reported remdesivir use through the EUA.
- There were 10 males and 9 females in the case series. The average age of the patients in the cases was 58 years.
- All 19 cases had increased transaminases of at least 10 times the ULN and no other reported laboratory parameter suggestive of hepatic failure (e.g., decreased platelets, increased PT/INR, or increased total bilirubin levels) or clinical signs/symptoms of hepatic failure (e.g., jaundice, ascites).
- Eight cases reported either AST, ALT or both AST and ALT values greater than 20 times the ULN, including two cases that reported either AST or ALT values greater than 50 times the ULN. In addition, two cases also reported alkaline phosphatase levels at least 3 times ULN.
- The median time to onset of increased transaminases (n=18) was 3 days from the initiation of remdesivir.
- A positive dechallenge was reported in four of the cases, all of which required early discontinuation of remdesivir treatment. The majority of the cases did not report follow up AST/ALT values after discontinuation of remdesivir. None of the 19 cases reported a negative dechallenge.
- No cases reported clinical signs or symptoms suggestive of hepatic failure (e.g., jaundice, ascites).
- There was one fatal case; the patient died of cardiac arrest one day after the last remdesivir dose was given.

FAERS Case 17921943, Direct Report, Hospitalization

27-year-old female, gravida 2 para 1 (G2P1) at 35 weeks pregnant, diagnosed with COVID-19 and admitted with an initial presentation of tachypnea along with hypoxemia for which oxygen supplementation of 2 L was provided. The patient had abdominal pain on day 1 of hospitalization with elevated bilirubin and alkaline phosphatase levels only (lab values not provided). Abdominal ultrasound showed no evidence of biliary dilation and only mild right hydronephrosis felt to be secondary to pregnancy. The patient was treated with acetaminophen and had resolution of her pain the following day. Bilirubin elevation was felt to likely be secondary to COVID-19. On day 2 of hospitalization, the patient was pan-cultured and empirically started on piperacillin/tazobactam after developing fevers, tachycardia, elevated white blood cell count, elevated procalcitonin level, and elevated C-reactive protein (CRP) level. On day 3 of hospitalization, the patient had hypoxia (93-94% on room air) requiring 1-2 L oxygen, tachypnea, and fevers; remdesivir was started. The following day, piperacillin/tazobactam was discontinued after three days of treatment as all cultures had reported negative including blood cultures which were negative x 72 hours. On day five of remdesivir treatment, the patient had increased transaminases (ALT 312 U/L, AST 464 U/L) with downtrending total bilirubin (values not provided) and normal platelets (330 units not specified). Remdesivir was discontinued prior to receiving the fifth dose. Baseline ALT and AST had been 22 U/L and 25 U/L, respectively, prior to starting remdesivir (see **Table 3** below for ALT/AST trend). The patient was hemodynamically stable at the time of increased transaminases without abdominal pain, pruritus, jaundice or edema. No other factors were identified by the reporter that could have contributed to the increase in ALT and AST. Concomitant medications at time of increased transaminases were folic acid, thiamine, enoxaparin, heparin, and prenatal vitamins. All medications were held due to increased transaminases. ALT/AST continued to uptrend, plateauing to 583 U/L/623 U/L three

days after remdesivir was discontinued. Repeat abdominal ultrasound demonstrated no bile duct dilation, mild gallbladder sludge (no evidence of cholecystitis), and a well defined 0.9 cm hyperechoic lesion in right liver (consistent with hemangioma) without other liver changes. The patient had no hypertension, evidence of hemolysis, or low platelets throughout hospital stay; therefore, suspicion for pre-eclampsia or hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome was low. A gastroenterologist was consulted and suspected the increased transaminases were secondary to remdesivir treatment. The patient was able to be discharged and follow-up labs one week later revealed downtrending ALT of 391 U/L and AST of 268 U/L with alkaline phosphatase of 195 (units not specified).

Table 3. Patient's Transaminase and Platelet Levels During and After Remdesivir Treatment

	Prior to RDV	Day 2 of RDV	Day 3 of RDV	Day 4 of RDV	Day 5 of RDV *	Post-RDV Day 2	Post – RDV Day 3	Post-RDV Day 4	Post-RDV Day 12
ALT†	22	21	30	81	312	494	576	583	391
AST†	25	23	39	115	464	685	685	623	268
Platelets	NR	231	260	328	330	373	373	357	NR

* RDV discontinued prior to fifth dose. Abbreviations NR = not reported, RDV = remdesivir

† ALT and AST levels were measured in U/L. Units were not reported for platelet levels

Reviewer's comments: This case describes a pregnant female who experienced an increase in AST of 10 times the ULN and ALT 5 times the ULN on day 5 of remdesivir treatment. AST and ALT continued to rise to 14 times and 10 times the ULN, respectively, three days after the last remdesivir dose. Despite these elevations, the patient had no signs or symptoms suggesting hepatic failure. There was a slight decrease in AST four days after the last dose of remdesivir with a continued downward trend to 268 U/L by the twelfth day after the last dose of remdesivir. A decrease in ALT to 391 U/L was also observed by the twelfth day after the last dose of remdesivir. In addition to this positive dechallenge, no other likely causes of hepatotoxicity were identified. The patient was hemodynamically stable and not receiving any concomitant hepatotoxic medications at the time the transaminases increased. Additionally, both, abdominal ultrasounds were negative for biliary obstruction and unrevealing for other liver pathology to explain the elevated transaminases. Evaluation by an obstetrics specialist ruled out pregnancy-related causes of elevated transaminases like HELLP syndrome. Finally, the patient was also evaluated by a gastroenterology specialist who did not identify any other factors that could have contributed to the increase in AST and ALT and therefore suspected remdesivir as the cause of the transaminase level elevations.

FAERS Case 17874713, Direct Report, Other Serious

25-year-old obese male started on remdesivir and on day 4 of treatment had increased ALT levels in the "400s" and AST levels in the "300s"; remdesivir was discontinued at that time. ALT levels peaked in the "800s" and AST levels peaked in the "300s". Follow-up was received from the reporter 10 weeks after the initial FDA received date: Per the reporter, all baseline labs were within normal limits (WNL) prior to starting remdesivir. Additionally, the patient was hemodynamically stable, not on vasopressors, and not intubated at the time the transaminase levels increased. The patient's past medical history was positive only for obesity. Remdesivir was discontinued the day prior to discharge. On the day of discharge, the transaminases were still very elevated, however, they were trending down (values not provided).

Reviewer's comments: This case was notable for significant elevations in a young patient who had no significant past medical history and who was not intubated and was hemodynamically stable, not requiring any vasopressors, at the time of the increased transaminase levels (ALT of at least 15 times the ULN). In addition, a positive dechallenge was observed as transaminase levels started trending down after remdesivir was discontinued. Further assessment of this case is limited by missing information including concomitant medications, other laboratory parameters to evaluate hepatic function, and specific values to trend the AST and ALT levels during and after the remdesivir treatment course.

4 REVIEWER'S COMMENTS

Of the 600 hepatotoxicity cases reported with remdesivir use for the treatment of COVID-19, 19 cases met our case definition for significant hepatoxocity (at least 10 times the ULN) and did not have any identifiable, clinically relevant, risk factors for hepatotoxicity[g]. Of these 19 cases, none reported clinical signs or symptoms of hepatic failure or reported other laboratory parameters (e.g., increased PT or INR, increased bilirubin, decreased platelets) suggesting hepatic dysfunction. Only one case reported a fatal outcome; the patient died of cardiac arrest one day after receiving the last dose of remdesivir. Assessing causality with remdesivir in these cases is hindered by the limited information provided in spontaneous reporting. For example, only four of the cases reported a positive dechallenge with decreasing AST and ALT levels after discontinuation of remdesivir; the majority of the cases did not report an outcome of the adverse event. Additionally, several cases provided insufficient information about concomitant medications and clinical status at the time of the hepatobiliary laboratory abnormalities.

Importantly, 110 cases met the inclusion criteria of the case definition but we excluded these cases due to another reported likely cause for hepatotoxicity. A large number of these cases reported multi-organ failure, hypotenstion requiring vasopressor support, sepsis, or septic shock, all of which are not unusual findings in the COVID-19 patient population meeting criteria for remdesivir use through the EUA.[h] Also notable, 74 of the 110 excluded cases reported concomitant medications labeled for hepatotoxicity in WARNINGS AND PRECAUTIONS and of these 74 cases, we excluded 38 solely for this reason. It may be difficult to eliminate this confounder as several of these concomitant medications are common treatments used for COVID-19 patients including azithromycin, tocilizumab, hydroxychloroquine or chloroquine, lopinavir/ritonavir, and methylprednisolone.Pantoprazole, a commonly used treatment in intensive care unit (ICU) patients was frequently reported as well. The current version of the remdesivir fact sheet[2] acknowledges, "As transaminase elevations have been reported as a component of COVID-19, including in patients receiving placebo in clinical trials of remdesivir, discerning the contribution of remdesivir to transaminase elevations in this patient population is challenging."

[g] These risk factors include biliary obstruction, sepsis, alcohol abuse, cardiac arrest, hypotension requiring vasopressor support, or concomitant medications labeled for hepatoxicity in the Warnings and Precautions section.
[h] At the time these cases were reported, the EUA criteria for remdesivir was for use in adults and pediatric patients hospitalized with severe disease. Severe disease is defined as patients with an oxygen saturation $\leq$94% on room air or requiring supplemental oxygen or requiring mechanical ventilation or requiring extracorporeal membrane oxygenation (ECMO).

At this time we have identified a limited number of compelling hepatotoxicity cases with remdesivir use in patients without significant risk factors for liver injury. While these cases did not describe any confounders, we recognize that many of these cases may lack complete details. Because of the complexity of COVID-19 and the current population being treated (e.g., the concomitant use of other hepatotoxic medications, the requirement of vasopressors, or the development of multi-organ failure and sepsis), our assessment of the potential involvement of remdesivir in causing these hepatobiliary adverse events is limited. However, we cannot exclude the contribution of remdesivir to these hepatotoxic events based on the temporal association (median time to onset: 3 days) and a positive dechallenge in some of the cases. As the treatment population for remdesivir expands, some of these confounders may be eliminated allowing for identification of greater numbers of compelling cases should a relationship between remdesivir and these events exist. We will continue to monitor for all hepatotoxic adverse events with remdesivir use for the treatment of COVID-19.

5 REFERENCES

[1] Emergency Use Authorization Letter for Remdesivir. Issued May 1, 2020. https://www.fda.gov/media/137564/download (Accessed on August 20, 2020)
[2] Remdesivir Fact Sheet for Health Care Providers Emergency Use Authorization. Gilead Sciences, Inc; Revised July 2020. https://www fda.gov/media/137566/download (Accessed on August 20, 2020)
[3] McCartan K, Swank K, Chehab M, Fanti P. Office of Surveillance and Epidemiology Pharmacovigilance Memorandum. All adverse events reported with remdesivir in the setting of COVID-19 under the EUA. July 9, 2020. DARRTS Reference ID: 4638219.
[4] Liver Function Tests. Mayo Clinic. https://www mayoclinic.org/tests-procedures/liver-function-tests/about/pac-20394595 (Accessed on August 24, 2020)

6 APPENDICES

6.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

6.2 APPENDIX B. FAERS LINE LISTING OF HEPATOTOXICITY CASES WITH REMDESIVIR CASE SERIES (N=19)

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
1	06/02/2020	17854534	1	N/A	Direct	61	M	US	NR
	61 yo male with baseline ALT 76/AST 67 (day prior to starting remdesivir). Patient was given loading dose of remdesivir and the next day, ALT 412 IU/L/AST 590 IU/L. Remdesivir was discontinued on day 2. No significant past medical history except for anorexia, but weight was WNL. Outcome of events was not reported.								
2	06/03/2020	17859043	1	N/A	Direct	44	M	US	NR
	44 yo male with no reported past medical history (occasional alcohol use), started on remdesivir with a loading dose and the next morning the patient had elevated LFTs, repeated to confirm elevated (ALT 31 to 32 to 274 and AST 33 to 185 to 513). Remdesivir therapy was discontinued. Concomitant medication: enoxaparin. Outcome of events was not reported.								
3	06/04/2020	17861039	1	N/A	Direct	48	M	US	NR
	48 yo male started on remdesivir and less than 12 hours later, AST increased to 528 IU/L (baseline on admission was 131 IU/L). Remdesivir was stopped. Outcome of events was not reported.								
4	06/08/2020	17874713, 18180515	1	N/A	Direct	25	M	US	OT
	See section 3.2 for narrative.								
5	06/15/2020	17900509	1	N/A	Direct	65	M	US	HO, OT
	65 yo male admitted with pneumonia, fever, and diagnosed with COVID-19. The patient started on remdesivir with baseline LFTs WNL (Alk Phos 65 IU/L, ALT 21 IU/L, AST 31 IU/L). The following day, LFTs were significantly elevated (Alk Phos 485 IU/L, ALT 174 IU/L, AST 405 IU/L). Remdesivir was discontinued on day 2. Per report: no significant medical conditions. Outcome of events was not reported.								
6	06/17/2020	17910897	1	N/A	Direct	29	M	US	OT
	29 yo obese male started on remdesivir and on day 4 the patient had an increase in ALT 5 times ULN (453 IU/L). Remdesivir was discontinued on day 4. The following day, ALT increased to 756 IU/L. Patient received one dose of tocilizumab; however, it was four days prior to increased ALT level.								
7	06/19/2020	17921943†, 18180515	1	N/A	Direct	27	F	US	HO
	See Section 3.2 for narrative								
8	06/20/2020	17922014	1	N/A	Direct	66	M	US	OT

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
	66 yo male with a past medical history of HTN and DM. On admission, AST was 84 IU/L and ALT was 33 IU/L, alkaline phosphatase was 84 IU/L. Remdesivir was started day of admission. On day 3 of remdesivir, AST was 598 IU/L, ALT was 340 IU/L, and alkaline phosphatase was 93 IU/L. Per the report, LFTs improved after discontinuing remdesivir (values not provided).								
9	06/25/2020	17942965†	1	N/A	Direct	64	F	US	NR
	64 yo female with normal LFTs at baseline (values not reported), received 3 days of remdesivir and before day 4 of treatment, AST increased to 49 times (2360 IU/L) the ULN, ALT increased to 18 times (1021 IU/L) the ULN, and alkaline phosphatase increased to 249 IU/L. Remdesivir treatment was discontinued before the fourth dose. Outcome of the events was not reported.								
10	06/27/2020	17955146	1	N/A	Direct	67	F	US	OT
	67 yo female with a past medical history of HTN and DM. The patient received remdesivir, azithromycin, and ceftriaxone. On day 3 of remdesivir, AST increased to 2268 IU/L and ALT to 581 IU/L. Remdesivir was discontinued on day 3. Azithromycin was discontinued two days prior to increased transaminases. Outcome of the events was not reported.								
11	7/10/2020	18006887	1	N/A	Direct	54	M	US	NR
	54 yo obese male started on remdesivir for five days with no appreciable increases in LFTS. During the patient's first course of remdesivir, he also received azithromycin, ceftriaxone, and dexamethasone. Patient had worsening respiratory status and was restarted on remdesivir three days after the last dose. The following day (Day 2), AST increased to 705 (units not specified) and ALT to 739 (units not specified). Remdesivir was discontinued on day 2. Outcome of the events was not reported.								
12	7/11/2020	18012653	1	N/A	Direct	59	M	US	NR
	59 yo male with no significant past medical history presented with fever, chills, cough, SOB, body aches, and diarrhea for 6 days and was diagnosed with COVID. Baseline labs prior to starting remdesivir were: AST 187 IU/L, ALT 120 IU/L, Tbili 0.5 (units not specified), Alk Phos 279 (units not specified). Patient was given the loading dose of remdesivir at 18:19 and at 6:21 the next morning, labs showed AST 1663 IU/L, ALT 1027 IU/L, Tbili 1 (units not specified), Alk Phos 471 (units not specified). Remdesivir was held. Outcome of the events was not reported.								
13	7/13/2020	18018090	1	N/A	Direct	43	M	US	OT
	43 yo male treated with the loading dose of remdesivir. After this dose, ALT increased to 929 IU/L, AST to 905 IU/L, alkaline phosphatase to 254 IU/L, and ferritin to 7241 ng/ml. Action with remdesivir and outcome of the events was not reported.								
14	7/16/2020	18031365	1	N/A	Direct	88	F	US	OT
	88 yo female received 4 doses of remdesivir before treatment was stopped due to increased LFTs. ALT went from 30s-40s to 1093 and AST went from 50-70 to 3612. Outcome of the events was not reported.								
15	7/16/2020	18034929	1	N/A	Direct	69	F	US	OT

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
	69 yo female with no relevant medical history received remdesivir for 10 days and the following day had an increase in ALT to 2382 U/L and AST to 4558 U/L. Alkaline phosphatase was normal at 53 U/L and total bilirubin was normal at 0.7 mg/dL. No INR was completed on that date. Patient was also treated with azithromycin for 7 days but this was discontinued 8 days prior to the event. Outcome of the event was not reported.								
16	7/21/2020	18049743	1	N/A	Direct	79	F	US	HO
	79 yo female treated with remdesivir for 2 days. On day 2, AST was 21 U/L. The following day, AST increased to 1602 U/L. Outcome of the events was not reported.								
17	7/21/2020	18053368†	1	N/A	Direct	84	F	US	DE, HO, LT
	84 yo female with a past medical history of congestive heart failure, atrial fibrillation, diabetes mellitus, hypertension with baseline AST 34 and ALT 19 was started on remdesivir and had elevation of AST/ALT to 172/40 on day 3, 1816/311 and 1268/449 on day 4. Remdesivir was discontinued on day 5. The following day AST/ALT was 1450/435; on this day, she experienced cardiac arrest and died.								
18	8/3/2020	18104603	1	N/A	Direct	79	F	US	OT
	79 yo female treated with remdesivir for 2 days before remdesivir was discontinued due to ALT greater than 5 times the ULN. Baseline ALT was 47, increased to 124 after day 1 then up to 701 after day 2. Remdesivir was discontinued on day 3 prior to receiving dose. Concomitant medications included dexamethasone, aspirin, heparin. Outcome of the events was not reported.								
19	8/11/2020	18138512	1	N/A	Direct	51	F	US	NR
	51 yo female treated with remdesivir and had elevation of LFTs on day 3 requiring discontinuation of remdesivir. Baseline AST/ALT before starting remdesivir was 54 U/L/115 U/L. After receiving the loading dose and one maintenance dose, AST increased to 2371 U/L and ALT increased to 1375 U/L. After remdesivir was discontinued, the LFTs began to trend back down.								
	* As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events. A case can have more than one serious outcome. † Also received as an expedited report from Gilead. Abbreviations: NR = Not Reported, OT = other medically significant, HO=hospitalization, DE = death, LT= life-threatening								

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/s/

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08/28/2020 12:20:14 PM

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: August 20, 2020

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, PharmD
Clinical Analyst
Division of Cardiology and Nephrology

To: Christine Kim, RPM
DAV

Subject: QT Consult to NDA 214787 (SDN 022)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 8/11/2020 regarding the Division's QT related question. We reviewed the following materials:

- Previous IRT reviews for IND 147753 dated 05/22/2020 and 06/30/2020 in DARRTS;
- Summary of clinical pharmacology (Submission 0007); and
- Proposed label (Submission 0022).

1 Responses for the Division

Question: We are requesting your assistance with the following:

1) Proposed wording for the TQT study that will be conducted as a postmarketing requirement (PMR).
2) Review of Section 12.2 (Effect on QT Interval) of the Applicant's proposed labeling and provide any revisions as needed.

IRT's response:

1) We propose the following language for the PMR. Our proposal is for suggestions only and we defer the final decision to the Division.

   Conduct a thorough QT study to evaluate the effect of remdesivir on the QTc interval. Design and conduct the trial in accordance with the ICH E14 guidance entitled, "E14 Clinical

Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs", and its Questions and Answers (R3).

2) We do not recommend labeling language until the TQT study is completed.

(b) (4)

[redacted]

2 BACKGROUND

Remdesivir (RDV, GS-5734) is a nucleotide prodrug under clinical development (b) (4) [redacted] The recommended dosage is a single loading dose of 200 mg on Day 1 followed by once daily maintenance doses at 100 mg from Day 2; total duration of treatment is no more than 10 days based on disease condition.

Below is a summary of regulatory history related to QT assessment:

- The IRT reviewed the sponsor's QT assessment report based on study GS-US-399-1954 and concluded that available data were not adequate to conclude absence of small mean increases in the QTc interval (previous IRT review under IND 147753 dated 05/22/2020 in DARRTS).
- In response to the Agency's feedback on the QT assessment (Advice/Information Request letter under IND 147753 dated 05/22/2020 in DARRTS), the sponsor proposed to conduct the TQT study (b) (4) [redacted] The sponsor also proposed to conduct the TQT study following NDA submission.
- The Agency agreed with the sponsor's proposal to conduct the TQT study post-NDA filing (Advice/Information Request letter under IND 147753 dated 07/01/2020 in DARRTS). The Agency also recommended that the sponsor conducts the TQT study (b) (4) [redacted] and that the sponsor should provide anticipated approach for dose selection and anticipated timeline.
- In response to the Agency's feedback on 07/01/2020, the sponsor proposed to conduct the TQT study (b) (4) [redacted]

The sponsor does not have new QT data in this NDA submission.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov

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/s/

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08/21/2020 06:08:51 AM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Pharmacovigilance Memorandum

Date:	July 9, 2020
Reviewers:	Kate McCartan, MD, Medical Officer Kim Swank, PharmD, Safety Evaluator Miriam Chehab, PharmD, BCPPS, Safety Evaluator Division of Pharmacovigilance II Paolo Fanti, MD, Medical Officer Division of Pharmacovigilance I
Acting Team Leader:	Rachna Kapoor, PharmD, MBA Division of Pharmacovigilance II
Deputy Division Director:	Ida-Lina Diak, PharmD, MS Division of Pharmacovigilance II
Product Name:	Remdesivir
Subject:	All adverse events in the setting of COVID-19 under the EUA
Application Type/Number:	IND 147753, NDA 214787, EUA 46
Applicant:	Gilead Sciences, Inc.
OSE RCM #:	2020-1113

1 INTRODUCTION

This Division of Pharmacovigilance (DPV) II memorandum describes cases identified in the FDA Adverse Event Reporting System (FAERS) database and the medical literature with remdesivir use under the Emergency Use Authorization (EUA) in the setting of coronavirus disease 2019 (COVID-19) through June 3, 2020.[a] The Division of Antivirals (DAV) consulted DPV II and requested a summary of the adverse event data submitted under the EUA for remdesivir. This data will be used by DAV during their upcoming New Drug Application (NDA) review of remdesivir.

The purpose of this DPV II memorandum is to provide DAV with an overview of the available safety data in FAERS and the medical literature related to the use of remdesivir under the EUA in the setting of COVID-19.

1.1 BACKGROUND

Remdesivir is a nucleoside ribonucleic (RNA) polymerase inhibitor that is not currently FDA approved for any indication. Remdesivir has been found to have activity in both cell culture and animal models against Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV), Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and SARS-CoV-2.[1]

On May 1, 2020, the FDA issued an EUA to permit the use of remdesivir for the treatment of suspected or laboratory confirmed COVID-19 in hospitalized adult and pediatric patients with severe disease. Severe disease is defined as those patients with an oxygen saturation of ≤ 94% on room air, those requiring supplemental oxygen, those requiring mechanical ventilation, or those requiring extracorporeal membrane oxygenation (ECMO).[1, 2]

On May 27, 2020, DAV consulted DPV II requesting a safety summary of adverse events reported with remdesivir use under the EUA in the setting of COVID-19.

1.2 RELEVANT PRODUCT LABELING

The relevant sections from the remdesivir Fact Sheet are provided in **Appendix A**. Of note, the remdesivir Fact Sheet was updated on June 15, 2020. This update, which was discussed at a meeting with DAV on June 8, 2020, included the addition of language regarding the potential for hypersensitivity reactions, including anaphylaxis, and its associated adverse events.[2]

2 METHODS AND MATERIALS

2.1 CASE SELECTION CRITERIA

Reports retrieved from the search strategies described in **Tables 1 and 2** were screened for cases of adverse events reported with remdesivir use under the EUA for the treatment of COVID-19.

[a] See Section 4, Reviewer's Comments, for a summary of cases received from June 4, 2020 through July 1, 2020.

2.2 FAERS SEARCH STRATEGY

DPV II searched the FAERS database with the strategy described in **Table 1**.

Table 1. FAERS Search Strategy*	
Date of search	Recurring daily searches†
Time period of search	December 1, 2019 - June 3, 2020
Search type	Drug Safety Analytics Dashboard (DSAD)
Product terms	Product Active Ingredient (PAI): Remdesivir
MedDRA search terms (Version 23.0)	Preferred Terms (PTs): *Asymptomatic COVID-19, COVID-19, COVID-19 pneumonia, Suspected COVID-19, SARS-CoV-2 carrier, Exposure to SARS-CoV-2, Occupational exposure to SARS-CoV-2, SARS-CoV-2 test, SARS-CoV-2 test false negative, SARS-CoV-2 test positive, COVID-19 prophylaxis, COVID-19 treatment, Coronavirus test positive, Coronavirus infection*
Other criteria (text string searches)	Reported Reason for Use: Coronavirus infection, Corona virus infection, Coronavirus test positive Reporter Narrative: Coronavirus, Corona virus, Novel coronavirus, ncov, 2019-ncov, 2019 ncov, Hubei, Wuhan, COVID, SARS-COV-2, SARS COV 2, T705, T-705, Emergency use authorization, EUA Medical History Comments**:** SARS-COV-2, SARS COV2, ncov, 2019-ncov, Corona virus, Coronavirus, COVID
* See **Appendix B** for a description of the FAERS database † Searches recurring daily on Tuesday-Friday with a 1-day prior completion date and on Monday with a 3-day prior completion date	

2.3 LITERATURE CASE SEARCH STRATEGY

DPV II searched the medical literature with the search strategy described in **Table 2**.

Table 2. Literature Case Search Strategy	
Date of search	Recurring daily searches
Database	Embase
Search terms	Drug search for “remdesivir”
Time period of search	January 1, 2020 - June 3, 2020

In addition, weekly PubMed and EMBASE Early Alerts for COVID-19 and safety-related articles were reviewed (March 15, 2020 - May 28, 2020).

3 RESULTS

3.1 FAERS CASE SELECTION

From December 1, 2019 through June 3, 2020, 419 cases of adverse events with remdesivir use for the treatment of COVID-19 were identified in FAERS. Of those 419 cases, 402 reported remdesivir use under the EUA. A summary of the 17 excluded non-EUA cases is provided below. Of note, the findings from these non-EUA cases are consistent with those cases reported under the EUA.

- Fourteen cases were expedited reports and three cases were direct reports[b]
- Ten cases were from the U.S. and seven cases were foreign reports
- The most commonly reported adverse events were respiratory failure/acute respiratory distress syndrome (ARDS)/hypoxia (n=5), increased transaminases/liver disorder (n=4), and infections (n=3, all with concomitant sarilumab administration). Two cases described renal adverse events [acute kidney injury (AKI) and renal failure], both of which occurred in patients with multiorgan failure.
- Other notable adverse events include one case reporting a non-ST-elevation myocardial infarction (NSTEMI) with subsequent atrial fibrillation with rapid ventricular rate (RVR) on day 8 of treatment with remdesivir; remdesivir was not discontinued and the reporter noted that remdesivir was not felt to have caused this event (additionally, the patient had recent atrial fibrillation with RVR prior to this event). A second case reported an erythematous rash with elevated eosinophils one day after remdesivir was discontinued; this case noted the patient had an extensive medication list, including multiple antibiotics (ceftriaxone, azithromycin, clarithromycin).
- Eight cases were fatal. Reported causes of death included: multiorgan failure (n=2), respiratory failure/insufficiency (n=2), and coronavirus infection (n=1). Of the three cases that did not report a cause of death, one case described intraabdominal and retroperitoneal bleeds in the setting of disseminated intravascular coagulation (DIC) from septic shock due to COVID-19, one case involved a patient who was transitioned to comfort care, and one reported worsening condition before dying on an unknown date.

3.2 LITERATURE CASE SELECTION

From January 3, 2020 through June 3, 2020, 23 cases of adverse events with remdesivir use for the treatment of COVID-19 were identified in the medical literature. None of these cases reported remdesivir use under the EUA. A summary of these 23 cases is provided below:[c]

- Fourteen cases were from the U.S.
- The most commonly reported adverse events were increased transaminases (n=10) and AKI/increased blood creatinine (n=5). Cardiac adverse events reported included Torsades de Pointes (n=2, patient was also treated with hydroxychloroquine in both cases), atrial fibrillation (n=1), bradycardia (n=1), and hypotension (n=1).

[b] The three direct reports did not include language to specify that they were reported under the EUA. One of these three direct reports was submitted prior to the EUA approval for remdesivir.
[c] Nineteen of the cases reported compassionate use of remdesivir; three cases did not specify how remdesivir was obtained, but were published on or before the approval of the EUA; and the remaining case reported inclusion of the patient in a clinical trial (ClinicalTrials.gov number NCT04280705).

- Nine cases were fatal. Reported causes of death included (multiple causes may be reported in one case): multiorgan failure (n=4), respiratory failure/distress (n=3), coronavirus infection (n=1), and septic shock (n=1). One case did not report a cause of death but reported deteriorating condition before death.

3.3 FINAL CASE SERIES

Table 3 provides the total number of cases identified that met the case selection criteria (see **Section 2.1**) and describes the characteristics of these cases.

Table 3. <u>All</u> Remdesivir Cases Reporting Adverse Events in the Setting of COVID-19 under the EUA through June 3, 2020* (n=402)	
Sex	n=399
Male	223
Female	176
Age (years)	n=400
Range	2 months – 96
Median	64
Mean	62
Report Type	
Direct†	397
Expedited (Gilead)	5
Fatal Cases	100
* Of note, May 1, 2020 was the date of remdesivir EUA approval † Direct reports include reports sent from Gilead that were also received as direct reports to FAERS	

Table 4 describes the cases that reported adverse events (n ≥ 2) with the use of remdesivir in the setting of COVID-19 under the EUA.

Table 4. Remdesivir Cases Reporting Adverse Events (n ≥ 2) in the Setting of COVID-19 under the EUA through June 3, 2020* (n=365)	
<u>Renal and Urinary Disorders</u>	(n=137)†
AKI/renal impairment, renal failure	137
ATN	7
<u>Hepatobiliary Disorders</u>	(n=114)
Hepatitis/increased liver enzymes/hyperbilirubinemia	114
<u>Cardiac Disorders</u>‡	(n=54)†
Cardiac arrest§	28
Hypotension	19
Bradycardia	9
VF/VT/SVT	8
Atrial fibrillation	6
Tachycardia	2
<u>General Disorders and Administration Conditions</u>	(n=51)
Infusion-related reactions/Administration site reactions‖	43

Table 4. Remdesivir Cases Reporting Adverse Events (n ≥ 2) in the Setting of COVID-19 under the EUA through June 3, 2020* (n=365)	
Extravasation/Infiltration	8
Respiratory Disorders	(n=34)†
Respiratory failure/ARDS	19
Hypoxia/decreased oxygenation saturation	18
Pneumothorax	2
Blood and Lymphatic System Disorders	(n=17)†
Thrombocytopenia/anemia/leukopenia	10
Coagulopathy/Increased INR¶	8
Gastrointestinal	(n=12)†
Nausea/vomiting	10
Diarrhea	4
Abdominal pain	2
Immune System Disorders	(n=9)
Anaphylaxis	5
Angioedema	4
Neurologic Disorders	(n=6)
Seizure	2
Ischemic stroke	4
Skin and Subcutaneous Tissue Disorders	(n=5)
Erythematous rash/maculopapular rash	5
Investigations	(n=4)
Increased CPK	4
Metabolism and Nutrition Disorders	(n=3)†
Hyperkalemia	2
Hypernatremia	2
Psychiatric Disorders	(n=2)
Anxiety/agitation	2
Vascular Disorders	(n=2)
Pulmonary embolism	2

* Of note, May 1, 2020 was the date of remdesivir EUA approval
† A case may have more than one AE
‡ Cardiac AEs that were not reported in the context of an infusion-related reaction(s)
§ Cardiac arrest cases include those reporting cardiac arrest, cardio-respiratory arrest, no pulse/pulse absent (including reported PEA), asystole, a resuscitation attempt, or a code/code blue
|| Infusion-related reactions included symptoms of hypotension (n=14), chills (n=9), nausea/vomiting (n=9), VT/tachycardia (n=7), dyspnea/wheezing (n=5), hypertension (n=4), fever (n=3), diaphoresis (n=3), maculopapular rash/erythematous rash (n=3), bradycardia (n=3), abdominal pain (n=2), flushing (n=2), pruritis (n=2), burning sensation (n=2), atrial fibrillation (n=2), and/or diarrhea (n=1) occurring within 2 hours of infusion
¶ Three patients had increased liver function enzymes, including two patients who were also receiving warfarin, and one patient who was also receiving apixaban
Abbreviations: AE = adverse event, AKI = acute kidney injury, ARDS = acute respiratory distress syndrome, ATN = acute tubular necrosis, CPK= creatine phosphokinase, INR = international normalized ratio, PEA = pulseless electrical activity, SVT = supraventricular tachycardia, VF= ventricular fibrillation, VT = ventricular tachycardia

Key Findings:

- The majority of cases involved males. The median age of the patients in the cases was 64 years old.
- Of the 402 cases, the most commonly reported adverse events were AKI (34%) and transaminase elevations/increased liver function tests (28%). Transaminase elevations are listed under the WARNINGS AND PRECAUTIONS section and AKI is listed under the OVERALL SAFETY SUMMARY, *Clinical Trials Experience* section in the remdesivir Fact Sheet.[2]

- **Fatal outcomes**: a fatal outcome was reported in 100 of the 402 cases (25%). Of these 100 fatal cases:
    - Twenty-six cases occurred in patients for whom decisions were made to stop treatment or to switch to comfort care only.
    - Eight cases occurred in patients who were do not resuscitate (DNR) and/or do not intubate (DNI) [excluding those who were also comfort care].
    - Forty-four cases reported COVID-19 as a cause of death, described worsening COVID-19/clinical status at the time of death or described known COVID-19 complications (e.g., respiratory failure, sepsis, shock, multi-organ failure, pulmonary embolism) at the time of death.
    - Twelve cases did not report a cause of death.
    - Ten cases reported cardiac arrest (i.e., those reporting cardiac arrest, cardio-respiratory arrest, no pulse/pulse absent (including reported PEA), asystole, a resuscitation attempt, or a code/code blue) and were not otherwise classified in the above categories.[d] Of these ten, seven reported failed resuscitation attempts in the setting of cardiac arrest with ventricular fibrillation, ventricular tachycardia, or PEA and three did not report a rhythm or reported asystole.

Concomitant administration with hydroxychloroquine (n=16)

- Sixteen cases reported concomitant hydroxychloroquine administration.
- Adverse events[e] reported with concomitant hydroxychloroquine use included increased liver function tests (n=3), bradycardia (n=2), cardiac arrest (n=2), AKI (n=2), increased CPK level (n=2), increased INR level (n=1), hypertension (n=1), nausea/vomiting (n=1), septic shock (n=1), pneumothorax (n=1), ventricular tachycardia (n=1), and increased body temperature (n=1). None of the cases specifically reported ineffective treatment with remdesivir.
- Six cases were fatal.

Infusion-related reactions (n=43)

- Of the 43 infusion-related reaction cases, the most common adverse events[a] were hypotension (n=14), nausea/vomiting (n=9), chills/shivering (n=9), tachycardia (n=7; with 5 reporting ventricular tachycardia), and dyspnea/wheezing (n=5). Shivering,

[d] Sixteen additional death cases reported cardiac arrest, however, these cases are already separately accounted for in the other categories described: one was DNR/DNI (thus no resuscitation attempt was made), one was comfort care only, and 14 reported COVID-19 as a cause of death, described worsening COVID-19/clinical status at the time of death, or described other known COVID-19 complications at the time of death.
[e] A case may have reported more than one adverse event.

nausea, vomiting, and hypotension were listed in the original remdesivir Fact Sheet. On June 15, 2020, the Fact Sheet was updated to include tachycardia, bradycardia, dyspnea, wheezing, and rash under *Hypersensitivity including Infusion-Related and Anaphylactic Reactions* in the WARNINGS AND PRECAUTIONS section.

- The majority (86%; 36/43) of infusion-related reactions occurred with administration of the first dose.
- Therapeutic intervention[f] was reported in 21 (48%; 21/43) cases, which included holding or discontinuing the infusion (n=15), decreasing the infusion rate (n=6), adjusting or starting blood pressure medication (n=6), starting mechanical ventilation (n=3), administration of an antihistamine (n=3), a corticosteroid (n=3), an antipyretic (n=2), and/or an antiemetic (n=1).

Infusion-site extravasation/infiltration (n=8)

- Eight cases reported extravasation or infiltration during the remdesivir infusion.
  - Of the eight cases, one reported rash and pain at the injection site and one reported arm swelling at injection site. The remaining six cases did not report symptoms associated with the infusion-site extravasation/infiltration.

Anaphylaxis and angioedema (n=4)

- Four cases reported clinical manifestations of angioedema and five cases met the Sampson's criteria for anaphylaxis.[3] On June 15, 2020, the Fact Sheet was updated to include anaphylactic reactions and angioedema under *Hypersensitivity including Infusion-Related and Anaphylactic Reactions* in the WARNINGS AND PRECAUTIONS section.
  - Adverse events included angioedema, difficulty swallowing, rash, tachycardia, hypotension, diaphoresis, vomiting, dyspnea/wheezing, and hypertension.
  - Therapeutic intervention[f] was reported in eight cases, which included holding or discontinuing the infusion (n=6), administration of an antihistamine (n=4) or a corticosteroid (n=3), decreasing the rate of infusion (n=3), and/or intubating the patient (n=1).

Cardiac disorders (n=54)

- Many of the reported cardiac adverse events are also potential cardiac sequelae of COVID-19, including cardiac arrhythmias.[4]
- Cardiac arrest was the most commonly reported cardiac adverse event with remdesivir use.
  - The majority of these cases described cardiac arrest occurring in patients with a known cardiac history or cardiac risk factors (n=20), in patients with other COVID-19 complications or worsening clinical status (n=15), or in patients who had already completed their treatment course with remdesivir (n=7). It should be noted, however, 6 of the 28 cardiac arrest cases (21%) reported cardiac arrest within the first 24 hours after receiving remdesivir.
  - Of the 28 cardiac arrest cases, 7 reported asystole, 4 reported PEA, 3 reported ventricular fibrillation, 3 reported more than one rhythm (including ventricular

[f] A case may have reported more than one therapeutic intervention.

tachycardia, ventricular fibrillation, PEA and asystole), and 11 did not report a specific rhythm.

- Hypotension was the second most commonly reported cardiac adverse event with remdesivir use. The majority of these cases (n=14) described hypotension occurring in the setting of other symptoms suggestive of worsening clinical status (n=10) or with other potential causes of hypotension (e.g., cardiac arrhythmia, suspected pulmonary embolism) (n=4). Notably, hypotension was reported as one of the most common adverse events occurring in patients who received remdesivir under compassionate use.[5]
- The majority of cases reporting arrhythmias occurred in the setting of worsening clinical status or were associated with cardiac arrest (see above summary on cardiac arrest). Four cases reported bradycardia not associated with either of these conditions. Two of these cases reported onset of persistent bradycardia within hours of starting remdesivir. The third case reported later onset of bradycardia (day 4 of remdesivir) but reported resolution of bradycardia within 24 hours after the final dose of remdesivir. The fourth case reported intermittent bradycardia on day 2 of remdesivir use with no outcome reported.

Hepatobiliary disorders (n=114)

- Increased transaminases/liver function tests were one of the most commonly reported adverse events with remdesivir use. Transaminase elevations are a labeled adverse event for remdesivir. In clinical trials, transaminase elevations up to 20 times the upper limit of normal (ULN) were reported.[13]
- Of the 114 cases of increased transaminases/liver function tests, 55 (48%) reported an increase in alanine transaminase (ALT) or aspartate aminotransferase (AST) of $\geq$ 5 times the ULN, with 21 (19%) that reported an ALT or AST increase of $\geq$ 10 times the ULN. The majority of cases (57%) had both ALT and AST elevations.
- Of these 114 cases, two cases reported substantial ALT elevations (> than 3 times ULN) with bilirubin greater than 2 times ULN and normal alkaline phosphatase levels, three cases reported increased ALT and/or AST with increased alkaline phosphatase and total bilirubin, and three cases reported isolated hyperbilirubinemia. No cases reported signs and symptoms of liver inflammation or liver injury such as jaundice, ascites, weakness, nausea, and vomiting.
- Drug-induced liver injury (DILI) typically exhibits a variable latency to onset of days to weeks.[6] The time-to-onset of the hepatobiliary disorders (n=108) described in this section include:
    - Mean: 3.5 days
    - Median: 3 days
    - Range: 1 - 10 days
- Twenty-seven cases (24%) reported resolution of increased transaminases/liver function tests after discontinuation of remdesivir.
- Nine cases were fatal. Five of the fatal cases were likely due to worsening COVID-19 infection (e.g., septic shock, multi-organ failure, respiratory failure), three did not report the cause of death, and one was due to cardiac arrest. Of note, in one of the fatal cases, ALT levels were over 3300 (units unspecified) on the day the patient expired.

Acute kidney injury/renal failure (n=137)

- AKI is common in hospitalized COVID-19 patients not exposed to remdesivir, with incidence ranging from 10.2% - 42.9% depending on the publication, and with need for renal replacement therapy (e.g., dialysis) in up to 13.4% of cases.[7,8] Knowledge about the cause(s) of AKI in COVID-19 patients is very limited and mostly extracted from autopsy findings, including (1) high tropism of SARS-CoV-2 for the renal tissue suggesting direct invasion of the virus into the kidney;[9] (2) diffuse acute proximal tubular injury with cytoplasmic vacuolization possibly related to direct viral infection of the proximal tubular epithelium, along with evidence of virus particles in proximal tubular cells;[10] (3) collapsing focal glomerulopathy with inclusion of virus-like particles in the glomerular podocytes of one patient;[11] and (4) obstruction of glomerular and peritubular capillaries by erythrocyte aggregates without concomitant platelets or fibrin clots.[12]
- Most of the reviewed FAERS cases were complex, with severe AKI often requiring dialysis. The rapid rate of AKI progression from normal or near normal renal function to full blown renal failure is consistent with an acute severe tubulopathy. However, even assuming the main renal lesion is tubular, the differential diagnosis of AKI causality remains broad because of the concomitance of other possible causes of acute tubular injury, including direct proximal tubular injury from SARS-CoV-2, coagulopathy/disseminated intravascular coagulation , bacteremia or sepsis, hypotension requiring vasopressor support, high central venous pressure from mechanical ventilation, and polypharmacy. Most cases reported limited clinical information, and none reported renal histology or urine sediment results, which hinders efforts to narrow down the differential diagnosis of AKI causality.
- Concerns regarding possible nephrotoxicity of remdesivir in humans originate primarily from Investigational New Drug (IND) toxicology studies in rhesus monkeys and rats.[13] In rhesus monkeys, intravenous administration of remdesivir dosages ≥ 5-fold higher than in COVID-19 patients for 7 days caused a rise of blood creatinine concentration and renal tubular atrophy [not otherwise specified (NOS)], while in rats, intravenous administration of remdesivir dosages ≥ 3-fold higher than in COVID-19 patients for up to 28 days caused kidney injury and/or dysfunction (NOS). It is therefore possible that remdesivir is nephrotoxic in COVID-19 patients.
- Use of the remdesivir carrier sulfobutylether-b-cyclodextrin (SBECD) (b) (4) is another possible source of nephrotoxicity in humans. Animal studies that injected SBECD dosages ≥ 50-fold higher than in COVID-19 patients noted SBECD accumulation and renal tubule obstruction.[14] It is possible that SBECD is nephrotoxic in COVID-19 patients.

4 REVIEWER'S COMMENTS

- **Hypersensitivity Reactions, including Infusion-Related and Anaphylaxis Reactions:** On June 15, 2020, the Fact Sheet was updated to include the addition of anaphylaxis and infusion-related reactions, such as tachycardia, bradycardia, dyspnea, wheezing, angioedema and rash to the adverse events under *Hypersensitivity including Infusion-Related and Anaphylactic Reactions* in the WARNINGS AND PRECAUTIONS section.

- **Cardiac Adverse Events:** Cardiac arrest and hypotension were the two most commonly reported cardiac adverse events, however, many of these cases occurred in the setting of overall worsening clinical status or with other known COVID-19 complications. DPV II will continue to actively monitor for cardiac adverse events with remdesivir use.

- **Hepatobiliary Adverse Events:** Increased transaminases/liver function tests were one of the most commonly reported adverse events with remdesivir use. Transaminase elevations are listed under the WARNINGS AND PRECAUTIONS section of the remdesivir Fact Sheet. In clinical trials, transaminase elevations up to 20 times the ULN were reported. In addition, transaminase elevations have been reported as a complication of COVID-19 infection, making it difficult to determine the contribution of remdesivir to these event.[6] The incidence of transaminase elevations in hospitalized patients with COVID-19 ranges from 14% - 58% and occurs more commonly in severe COVID-19 infections than mild infections.[15] AST and ALT elevations are typically 1-2 times the ULN with mild fluctuations of total bilirubin levels early in the disease process. Liver injury in mild COVID-19 cases is usually transient and does not require specific treatment beyond supportive care. A severe cholestatic pattern is usually absent during COVID-19 infection.[15] Of the 114 increased transaminases/liver function tests cases, 55 (48%) reported an increase in ALT or aspartate aminotransferase AST of $\geq$ 5 times the ULN, with 21 (19%) that reported an ALT or AST increase of $\geq$ 10 times the ULN. The majority of cases (57%) had both ALT and AST elevations and only a few cases had increased total bilirubin and alkaline phosphatase levels. Because liver injury is common in patients with COVID-19, especially in severe infection, establishing a diagnosis of DILI with remdesivir is challenging. DPV II will continue to actively monitor for cases of hepatobiliary adverse events with remdesivir use.

- **Acute Kidney Injury:** AKI was the most frequently reported adverse event for remdesivir, and basic science studies in experimental animals raise concerns about possible nephrotoxicity of remdesivir in humans. However, the complexity of the cases and the limited clinical information, which in no case included renal histology or urine sediment, hinder the adjudication of AKI causality to remdesivir. On June 23, 2020, the Antiviral Products Drug Safety Team (DST) discussed in a meeting the reports of AKI with remdesivir, including the high incidence of this AE, the challenges in adjudicating causality due to complexity of the FAERS cases, the limited information (e.g., lack of renal histology data), and the lack of imbalance in AKI incidence in remdesivir and placebo-treated cases in the IND studies. DPV II and DAV agreed that continued surveillance is most appropriate at this time given the biological plausibility of remdesivir nephrotoxicity, and the immediate and long-term risk of morbidity and mortality linked to AKI.

- **Summary of Cases from June 4, 2020 through July 1, 2020:** Since the data lock point noted in **Tables 1 and 2**, an additional 589 remdesivir cases have been identified in FAERS and the literature. Of these cases, 552 were reported under the EUA. Reported adverse events are consistent with the key findings in this memorandum. No new safety signals were identified.

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6 APPENDICES

6.1 APPENDIX A. RELEVANT SECTIONS FROM THE REMDESIVIR FACT SHEET[2]

4 CONTRAINDICATIONS
Remdesivir is contraindicated in patients with known hypersensitivity to any ingredient of remdesivir

5 WARNINGS AND PRECAUTIONS
There are limited clinical data available for remdesivir. Serious and unexpected adverse events may occur that have not been previously reported with remdesivir 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 remdesivir. Signs and symptoms may include hypotension, tachycardia, bradycardia, dyspnea, wheezing, angioedema, rash, nausea, vomiting, 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. If signs and symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue administration of remdesivir and initiate appropriate treatment. The use of remdesivir is contraindicated in patients with known hypersensitivity to remdesivir [*see Contraindications (4)*].

5.2 Increased Risk of Transaminase Elevations
Transaminase elevations have been observed in healthy volunteers who received 200 mg of remdesivir followed by 100 mg doses for 5-10 days. Transaminase elevations have also been reported in patients with COVID-19 who received remdesivir in clinical trials. As transaminase elevations have been reported as a component of COVID-19, including in patients receiving placebo in clinical trials of remdesivir, discerning the contribution of remdesivir to transaminase elevations in this patient population is challenging.

Hepatic laboratory testing should be performed in all patients prior to starting remdesivir and daily while receiving remdesivir.

- Remdesivir should not be initiated in patients with ALT greater than or equal to 5 times the upper limit of normal at baseline.
- Remdesivir should be discontinued in patients who develop:
  - ALT greater than or equal to 5 times the upper limit of normal during treatment with remdesivir. Remdesivir may be restarted when ALT is less than 5 times the upper limit of normal.
    OR
  - ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR.

5.3 Risk of Reduced Antiviral Activity When Coadministered with Chloroquine or Hydroxychloroquine
Coadministration of remdesivir and chloroquine phosphate or hydroxychloroquine sulfate is not recommended based on in vitro data demonstrating an antagonistic effect of chloroquine on the intracellular metabolic activation and antiviral activity of remdesivir [*see Drug Interactions (10), Microbiology/Resistance Information (15)*].

6 OVERALL SAFETY SUMMARY

6.1 Clinical Trials Experience

Clinical Studies in Healthy Adults

Remdesivir was evaluated in four Phase 1 studies in 138 healthy adult volunteers (Studies GS-US-399-1812, GS-US-399-1954, GS-US-399-4231, and GS-US399-5505). In these studies, transient graded elevations in ALT and AST were observed at repeated once-daily doses of remdesivir.

NIAID ACTT-1 Trial

In a randomized, double-blind, placebo-controlled clinical trial (ACTT-1) of remdesivir in 1,063 hospitalized subjects with COVID-19 treated with remdesivir (n=541) or placebo (n=522) for 10 days, serious adverse events (SAEs) were reported in 21% and 27% of subjects, respectively, and Grade ≥ 3 non-serious adverse events were reported in 29% and 33% of subjects, respectively. The most common SAE was respiratory failure reported in 5% of subjects treated with remdesivir and 8% of subjects treated with placebo. The most common Grade ≥ 3 non-serious adverse events in the remdesivir treatment arm are shown in Table 7.

Table 7. Most Common Grade ≥ 3 Non-Serious Adverse Events in Subjects Receiving Remdesivir

n (%)	**Remdesivir n=538**	**Placebo n=521**
Anemia or decreased hemoglobin	43 (8%)	47 (9%)
Acute kidney injury, decreased eGFR or creatinine renal clearance, or increased blood creatinine	40 (7%)	38 (7%)
Pyrexia	27 (5%)	17 (3%)
Hyperglycemia or increased blood glucose	22 (4%)	17 (3%)
Increased transaminases, including ALT and/or AST	22 (4%)	31 (6%)

Study GS-US-540-5773

In a randomized, open-label clinical trial (Study GS-US-540-5773) of remdesivir in 397 hospitalized subjects with severe COVID-19 treated with remdesivir for 5 (n=200) or 10 days (n=197), adverse events were reported in 70% and 74% of subjects, respectively, SAEs were reported in 21% and 35% of subjects, respectively, and Grade ≥ 3 adverse events were reported in 30% and 43% of subjects, respectively. The most common adverse events were nausea (10% in the 5-day group vs 9% in the 10-day group), acute respiratory failure (6% vs 11%), ALT increased (6% vs 8%), and constipation (7% in both groups). Nine (4%) subjects in the 5-day group and 20 (10%) subjects in the 10-day group discontinued treatment due to an adverse event. All-cause mortality at Day 28 was 10% vs 13% in the 5- and 10-day treatment groups, respectively.

6.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

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