CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214787Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	214787
Action Goal Date	October 2, 2020
OSE RCM #	2020-1163, 1164
Reviewer Name(s)	Joyce Weaver, Pharm.D.
Team Leader	Naomi Boston, Pharm.D.
Acting Deputy Division Director	Doris Auth, Pharm.D.
Review Completion Date	September 14, 2020
Subject	Evaluation of Need for a REMS
Established Name	Remdesivir
Trade Name	Veklury
Name of Applicant	Gilead Sciences, Inc.
Therapeutic Class	Nucleotide analog SARS-CoV-2 ribonucleic acid (RNA) polymerase inhibitor
Formulation(s)	Injection, lyophilized powder and concentrated solution
Dosing Regimen	200 mg infusion loading dose, then 100 mg daily

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) remdesivir is necessary to ensure the benefits outweigh its risks. Gilead submitted a New Drug Application (NDA) 214787 for remdesivir with the proposed indication (b) (4)

Remdesivir has risks of hypersensitivity infusion reactions, hepatotoxicity, loss of virologic response with concomitant use with chloroquine phosphate or hydroxychloroquine sulfate, nausea, and increased prothrombin time. A boxed warning has not been proposed.

The Applicant did not propose a REMS for remdesivir. The Applicant submitted a risk management plan that proposes labeling and routine pharmacovigilance to manage the risks of remdesivir. DRM agrees that a REMS is not needed to ensure the benefits of remdesivir exceeds its risks for the proposed indication.

1 Introduction

This review by the DRM evaluates whether a REMS for the NME remdesivir is needed to ensure its benefits outweigh its risks. Novartis submitted a New Drug Application (NDA) 214787 for remdesivir with the proposed indication (b) (4)

2 Background

2.1 PRODUCT INFORMATION

Remdesivir, a new molecular entity[a], is a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor supplied as lyophilized powder and concentrated solution for infusion. The proposed dose is 200 mg loading dose on day 1, followed by 100 mg daily. Treatment continues for 5 days (for patients not requiring invasive mechanical ventilation or extracorporeal membrane oxygenation [ECMO]) to 10 days (for patients requiring invasive mechanical ventilation or ECMO).[b]

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 214787 relevant to this review:

- 3/26/2020: Fast Track designation granted
- 4/6/2020: Rolling Review Submission Plan approved
- 8/7/2020: Final review module submitted

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

In December 2019, an outbreak of COVID-19 was detected in China. By February 2020, cases were identified in numerous other countries. On March 11, 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a global pandemic, as cases rapidly increased worldwide.[1] By September 2020, there were over 26 million confirmed cases worldwide, with over 800,000 deaths. In the United States, 3 million confirmed cases have occurred by September 2020, with over 186,000 patients succumbing to the disease.[2]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Treatment options include supportive care. No antiviral drug has been approved for use in COVID-19 illness.[3]

4 Benefit Assessment

The efficacy of remdesivir was examined in the following studies submitted to support the application.

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

This study was a randomized, double-blind, placebo-controlled clinical trial of hospitalized adult subjects with mild, moderate, or severe COVID-19. It compared treatment with remdesivir for 10 days (n=541) with placebo (n=521).[4] Mild/moderate disease was defined as oxygen saturation greater than 94% and respiratory rate less than 24 breaths/minute without supplemental oxygen; severe disease was defined as oxygen saturation less than or equal to 94% on room air, a respiratory rate at or greater than 24 breaths/minute, an oxygen requirement, or a requirement for mechanical ventilation. Patients treated with remdesivir received 200 mg loading dose followed by 100 mg once daily, for up to a total of 10 days of treatment via intravenous infusion. Treatment with remdesivir was stopped in subjects who were discharged from the hospital prior to the completion of 10 days of treatment.

The mean age of patients was 59 years, 64% of subjects were male, 53% were White, 21% were Black, 13% were Asian and 24% were Hispanic or Latino. One hundred five patients had mild or moderate disease (10% in each treatment group). Nine hundred and fifty-seven patients had severe disease (90% in each treatment group). A total of 285 patients (27%) (n=131 received remdesivir) were receiving invasive mechanical ventilation or ECMO. Most patients had comorbidities, including hypertension (51%), obesity (45%), and type 2 diabetes mellitus (31%); the distribution of comorbidities was similar between the two treatment groups.

The primary endpoint was time to recovery. Recovery was defined as discharged from the hospital without limitations on activities, discharged from the hospital with limitations on activities and/or requiring home oxygen, or hospitalized but not requiring supplemental oxygen and no longer requiring ongoing medical care. The median time to recovery was 10 days in the remdesivir group compared to 15 days in the placebo group (recovery rate ratio 1.30 [95% CI 1.13 to 1.50], p<0.001). Among subjects with mild/moderate disease at enrollment (n=105), the median time to recovery was 5 days in both the groups (recovery rate ratio 1.22 [95% CI 0.82 to 1.81]). Among subjects with severe disease at enrollment (n=957), the median time to recovery was 11 days in the remdesivir group compared to 18 days in the placebo group (recovery rate ratio 1.31 [95% CI 1.12 to 1.52]).

Overall, 29-day mortality was 11% for the remdesivir group vs 15% for the placebo group (hazard ratio 0.73 [95% CI 0.52 to 1.02], p=0.066).

Study 2 in Subjects with Severe COVID-19

This study was a randomized, open-label multi-center clinical trial in adult subjects with COVID-19, oxygen saturation of ≤94% on room air, and radiological evidence of pneumonia.[5] The study compared 200 patients who received remdesivir for up to a total of 5 days with 197 patients who received remdesivir for up to a total of 10 days. Treatment with remdesivir was stopped in patients who were discharged from the hospital prior to completion of their protocol-defined duration of treatment. All patients received 200 mg of remdesivir on Day 1 and 100 mg once daily on subsequent days via intravenous infusion, plus standard of care.

Median age of patients was 61 years (range, 20 to 98 years); 64% were male, 75% were White, 12% were Black, and 12% were Asian; 22% were Hispanic or Latino. Median duration of symptoms and hospitalization prior to first dose of remdesivir were similar across treatment groups.

The primary endpoint was clinical status on Day 14 assessed on an ordinal scale consisting of the following categories:

1. death

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

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

Study 3 in Subjects with Moderate COVID-19

This study was a randomized, open-label multi-center clinical trial of hospitalized adult subjects with Covid-19 and radiological evidence of pneumonia without reduced oxygen levels.[6] The study compared treatment with remdesivir for up to a total of 5 days (n=191) and treatment with remdesivir for up to a total of 10 days (n=193) with standard of care (n=200). Treatment with remdesivir was stopped in subjects who were discharged from the hospital prior to completion of their protocol-defined duration of treatment. Subjects treated with remdesivir received 200 mg on Day 1 and 100 mg once daily on subsequent days via intravenous infusion.

The median age of subjects was 57 years (range, 12 to 95 years), 61% were male, 61% were White, 19% were Black, 19% were Asian, 18% were Hispanic or Latino. Baseline clinical status, oxygen support status, and median duration of symptoms and hospitalization prior to first dose of remdesivir were similar across treatment groups.

The primary endpoint was clinical status on Day 11 assessed on an ordinal scale consisting of the following categories:

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

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

5 Risk Assessment & Safe-Use Conditions

The safety database comprises 1322 patients. The safety issues included in the draft *Warnings and Precautions* section of the labeling include hypersensitivity, including infusion-related reactions and anaphylaxis, increased risk of transaminase elevations, and risk of reduced antiviral activity when administered with chloroquine or hydroxychloroquine.[c] The most commonly occurring adverse reaction was nausea, which occurred in up to 7% of patients receiving remdesivir.

5.1 Hypersensitivity including Infusion-related Reactions and Anaphylaxis

Hypersensitivity reactions including infusion-related and anaphylactic reactions have been observed following administration of remdesivir. Signs and symptoms include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, diaphoresis, and shivering.

The draft labeling advises that slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms.[d] If signs and symptoms of a clinically significant hypersensitivity reaction occur, the draft labeling advises that remdesivir should be discontinued and supportive treatment initiated.

5.2 Increased Risk of Transaminase Elevation

Transaminase elevations have been observed in healthy volunteers who received remdesivir. Mild (Grade 1) or moderate (Grade 2) elevations in ALT were observed in 9 of 20 healthy participants receiving 10 days of remdesivir; the elevations in ALT resolved upon discontinuation of remdesivir.

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[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

[d] Clinical study protocol allowed for slowing of infusion rates for Grade I infusion reactions but required discontinuation for Grade II and higher reactions.

Transaminase elevations have also been reported in patients with COVID-19 who received remdesivir. Attribution to remdesivir for transaminase elevations in patients with COVID-19 can be challenging because COVID-19 can also cause transaminase elevations.

The draft labeling[7] states to perform hepatic laboratory testing performed in all patients prior to starting remdesivir and while receiving remdesivir. The draft labeling also advises prescribers to consider discontinuing remdesivir if ALT levels increase to greater than 10 times the upper limit of normal, and to discontinue remdesivir if ALT elevation is accompanied by signs or symptoms of liver inflammation.

5.3 Risk of Reduced Antiviral Activity if Administered with Chloroquine or Hydroxychloroquine

The draft labeling states that 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.

5.4 Nausea

Nausea occurred in up to 7% of patients. Patients were able to continue treatment with remdesivir despite experiencing nausea.

5.5 Increased Prothrombin Time

In the randomized controlled trial, 9% of patients receiving remdesivir had increased prothrombin time (PT), compared with 4% in the placebo group. No patient had to discontinue remdesivir because of this adverse event. The draft labeling states PT should be measured before instituting therapy, and as clinically indicated thereafter.

6 Expected Postmarket Use

Remdesivir would likely be used by patients at least 12 years of age for the treatment of COVID-19 (the proposed indication). As a medication administered by intravenous infusion, remdesivir likely would be used in hospitals. Other healthcare settings (e.g., outpatient infusion centers) that administer intravenous medications could be used to complete the course of therapy for patients who can be discharged before the course of therapy is completed.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose a REMS. The Applicant submitted a non-REMS risk management plan that proposes routine labeling and pharmacovigilance to manage the risks of remdesivir.

8 Discussion of Need for a REMS

The clinical reviewers concluded the data support a favorable benefit:risk assessment for remdesivir for the treatment of patients 12 years and older with COVID-19. The clinical trial showed a clinically meaningful treatment effect, with a significantly shorter time to recovery in patients receiving remdesivir, and a significant improvement in an ordinal scale of severity in some groups. Trends to improvement in the ordinal scale of severity were observed in other groups.

The review team believes that the application is appropriate for approval and the risks of hypersensitivity, transaminase increases, and the risk of loss of antiviral activity if administered with chloroquine or hydroxychloroquine will be included in *Warnings and Precautions* (not boxed).[e] The clinical reviewers believe the adverse events are manageable with slowing the infusion or discontinuing remdesivir, as was done in clinical testing, and the events can be appropriately handled with labeling alone.

This reviewer recommends that, should remdesivir be approved, a REMS is not needed to ensure its benefits outweigh its risks. Hypersensitivity, increased risk of transaminase elevations, and a possible loss of antiviral activity if co-administered with chloroquine or hydroxychloroquine can be adequately described and communicated in the labeling. None of the risks of remdesivir warrants a boxed warning. DRM agrees with this analysis; healthcare providers who will prescribe and administer remdesivir are expected to be able to manage the remdesivir-emergent adverse events without additional risk mitigation measures beyond labeling.

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits of remdesivir outweigh its risks. At the time of this review, evaluation of safety information and labeling was ongoing. Post-marketing requirements are being negotiated to study remdesivir in pediatric patients, in patients with renal function impairment, in patients with hepatic function impairment, as well as resistance, and drug-drug interactions. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

10 Appendices

[e] The clinical review was ongoing at the time of this review.

10.1 REFERENCES

[1] World Health Organization (WHO). Available at: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarksat-the-media-briefing-on-covid-19. Accessed September 3. 2020

[2] New York Times online. Data accessed September 3, 2020.

[3] Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-nCoV. Accessed September 3, 2020.

[4] Clinical Trials Register NCT04280705

[5] Clinical Trials Register NCT04292899

[6] Clinical Trials Register NCT04292730

[7] Draft Veklury labeling as of September 11, 2020.

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