CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215596Orig1s000

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	215596
PDUFA Goal Date	November 23, 2021
OSE RCM #	2021-596
Reviewer Name(s)	Naomi Boston, Pharm.D.[a]
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	November 4, 2021
Subject	Evaluation of Need for a REMS
Established Name	Maribavir
Trade Name	Livtencity
Name of Applicant	Takeda Pharmaceuticals
Therapeutic Class	Benzimidazole riboside CMV pUL97 protein kinase inhibitor
Formulation(s)	200 mg tablets
Dosing Regimen	400 mg twice daily

[a] Dr. Joyce Weaver, Pharm.D., contributed to this review but is no longer with the FDA.

Table of Contents

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) maribavir is necessary to ensure the benefits outweigh its risks. Takeda Pharmaceuticals submitted a New Drug Application (NDA) 215596 for maribavir with the proposed indication for the treatment of patients with post-transplant cytomegalovirus (CMV) infection including infections resistant to ganciclovir, valganciclovir, cidofovir, and foscarnet.

Maribavir has risks of treatment failure, reduced antiviral activity when co-administered with ganciclovir and valganciclovir, and other drug-drug interactions.

The applicant did not propose a REMS or a risk management program for maribavir. DRM agrees that a REMS is not needed to mitigate the risks of maribavir. The risk of virologic failure during treatment and relapse post-treatment and drug interactions will be described in the Warnings and Precautions section of the labeling. A boxed warning will not be required for any risk. Healthcare providers who will prescribe and administer maribavir are expected to be able to manage maribavir-emergent adverse events without additional risk mitigation measures beyond labeling.

1 Introduction

This review by the DRM evaluates whether a REMS for the NME maribavir is needed to ensure its benefits outweigh its risks. Takeda submitted NDA 215596 for maribavir with the proposed indication for the treatment of patients with post-transplant cytomegalovirus (CMV) infection including infections resistant to ganciclovir, valganciclovir, cidofovir, and foscarnet. This application is under review by the Division of Antiviral Products (DAV).

2 Background

2.1 PRODUCT INFORMATION

Maribavir, a new molecular entity[b], is to be supplied as 200 mg tablets. The proposed dose is 400 mg twice daily. In clinical testing, treatment continued for 8 weeks.[c] Maribavir is not approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 215596 relevant to this review:

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

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

- 6/7/2011: Received orphan designation for the treatment of clinically significant cytomegalovirus viremia and disease in at-risk patients.
- 12/15/2017: Breakthrough Therapy Designation granted for the treatment of CMV infection and disease in transplant patients resistant or refractory to prior therapy.
- 1/28/2021: Pre-NDA meeting; FDA stated there was insufficient information to determine whether a REMS will be needed but the FDA agreed that the Sponsor did not need to submit a REMS as part of the NDA submission.
- 03/23/2021: NDA submitted.
- 7/7/2021: Mid-cycle meeting held with applicant; FDA stated no safety signals requiring a REMS had emerged.
- 10/7/2021: Antimicrobial Drugs Advisory Committee Meeting held. The questions posed to the committee were: 1) Does the committee agree that the overall benefit/risk assessment is adequate to support use of maribavir for the treatment of refractory CMV infection and disease due to resistance. If not, what additional information is required to support the indication for this population. 2) Does the committee agree that the overall benefit/risk assessment is adequate to support use of maribavir for the treatment of refractory CMV infection and disease not due to resistance? If not, what additional information is required to support the indication for this population. The committee voted unanimously (13-0) for the approval of maribavir to treat refractory CMV infection in post-transplant patients with or without genotypic resistance to ganciclovir, valganciclovir, foscarnet or cidofovir.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

The risk of CMV disease in patients who have undergone transplantation varies with the type of transplantation and the serological match between donor and recipient. In the absence of prophylaxis, the incidence is 50−75% in patients undergoing lung or heart-lung transplantation and about 50% in patients undergoing pancreas or kidney-pancreas transplantation. The incidence of CMV is between 9 and 23% after heart transplantation, between 22 and 29% after liver transplantation and between 8 and 32% after kidney transplantation. Thirty percent of patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) and

approximately 5% of patients undergoing autologous HSCT develop CMV disease.[d,1] In solid organ transplantation, the greatest risk factor for CMV disease is a serological mismatch between the donor (seropositive) and the recipient (seronegative).[2]

3.2 Description of Current Treatment Options

Treatment options for patients include with oral valganciclovir, intravenous ganciclovir or foscarnet.[3]

4 Benefit Assessment

The efficacy of maribavir was evaluated in a multicenter, randomized, open-label, active-controlled superiority trial (NCT02931539) to assess the efficacy and safety of maribavir compared to Investigator-Assigned Treatment (IAT) (ganciclovir, valganciclovir, foscarnet, or cidofovir) in 352 HSCT or SOT recipients with CMV infections that were refractory to treatment with ganciclovir, valganciclovir, foscarnet, or cidofovir, including CMV infections with or without confirmed resistance to 1 or more of other agents.[4] Patients with CMV disease involving the central nervous system were excluded. Subjects were stratified by transplant type (HSCT or SOT) and screening CMV DNA levels and then randomized in a 2:1 allocation ratio to receive either maribavir 400 mg twice daily or IAT as dosed by the investigator for up to 8 weeks.

The mean age of trial subjects was 53 years, and most subjects were male (61%), white (76%) and not Hispanic or Latino (83%). The most common treatment used in the IAT arm was foscarnet (administered in 47 [41%] subjects), and ganciclovir or valganciclovir (each administered in 28 [24%] subjects). Cidofovir was administered in 6 subjects, foscarnet + valganciclovir in 4 subjects and foscarnet + ganciclovir in 3 subjects.

The primary efficacy endpoint was CMV viremia clearance at the end of Week 8. The key secondary endpoint was CMV viremia clearance and CMV infection symptom control at the end of Study Week 8 with maintenance of this treatment effect through Study Week 16. For the primary endpoint, maribavir was superior to IAT (56% vs. 24%, respectively). For the key secondary endpoint, 19% vs. 10% in the maribavir and IAT group, respectively, achieved both CMV viremia clearance and control of symptoms associated with CMV infection.

5 Risk Assessment & Safe-Use Conditions

The safety database for maribavir comprises data from 234 patients who received maribavir in the clinical study.

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

Serious adverse events occurred in patients treated with maribavir and IAT (38% and 37%, respectively). The most common serious adverse event in both treatment arms was CMV infection or disease, 23% in the maribavir arm and 15%, with IAT.[5] A higher proportion of subjects in the IAT group discontinued study medication due to an adverse event compared to the maribavir group (32% and 13%, respectively). The most commonly reported causes that led to study drug discontinuation were leukopenia (10%) and acute kidney injury (6%) in the IAT arm and dysgeusia, diarrhea, nausea, and malignancy each reported at 1% in the maribavir arm.

The safety issues in the draft Warnings and Precautions section of the labeling include treatment failure, reduced antiviral activity when co-administered with ganciclovir and valganciclovir, and other drug-drug interactions. A boxed warning has not been proposed for any risk.[e]

5.1 TREATMENT FAILURE

Virologic failure can occur during and after treatment with maribavir. Failure occurs more frequently during treatment than during the post-treatment period. Relapse following treatment usually occurs within 4-8 weeks after treatment discontinuation. The draft labeling advises healthcare providers to monitor CMV DNA levels and check for resistance if the patient does not respond to treatment.

5.2 REDUCED ANTIVIRAL ACTIVITY WHEN CO-ADMINISTERED WITH GANCICLOVIR AND VALGANCICLOVIR

Maribavir may antagonize the antiviral activity of ganciclovir and valganciclovir by inhibiting a kinase required for activation/phosphorylation of ganciclovir and valganciclovir. The draft labeling advises healthcare providers that coadministration of maribavir with ganciclovir or valganciclovir is not recommended.

5.3 DRUG-DRUG INTERACTIONS

The concomitant use of maribavir and certain drugs may result in potentially significant drug interactions, some of which may lead to reduced therapeutic effect of maribavir or adverse reactions of concomitant drugs. The draft labeling advises healthcare providers to consider the potential for drug interactions prior to and during treatment with maribavir and provides dosing guidance to minimize this possibility.

Maribavir has the potential to increase the drug concentrations of immunosuppressant drugs that are CYP3A and/or P-gp substrate. Draft labeling advises healthcare providers to frequently

[e] 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.*

monitor immunosuppressant drug levels throughout treatment with maribavir, and adjust the immunosuppressant dose, as needed.

6 Expected Postmarket Use

As an orally administered product, maribavir would likely be used by all healthcare settings, including outpatient care (e.g., within the patients' homes).

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose a REMS or other risk mitigation measures.

8 Discussion of Need for a REMS

CMV is a common opportunistic infection that may occur after transplant and can invade multiple organs and cause extensive tissue damage. CMV is treated with antivirals, primarily valganciclovir, ganciclovir, and foscarnet; however, infections that are clinically and virologically refractory to antiviral drug therapies have emerged.[6] There are currently no FDA approved treatment options for patients with post-transplant CMV disease that have antiviral resistance to the treatment options currently available.

Maribavir was discussed at an Antimicrobial Advisory Committee on October 7, 2021 primarily because of emergence of resistance virus in the clinical trial program, and whether the data submitted support approval for the indication. Although the Advisory Committee voted unanimously to approve maribavir, the open-label nature of the clinical trial design, and lack of diversity were noted as potential drawbacks. Overall, the committee expressed that the potential benefit of having this product available outweighed the risk of breakthrough viremia or resistance with maribavir treatment. If approved, maribavir will be the first treatment for post-transplant patients with CMV disease, with or without resistance.

The clinical team have proposed the following postmarketing requirements (PMRs) to obtain additional data regarding the resistance of maribavir. At the time of this writing, these PMRs were in negotiation with Takeda and are as follows:

- Conduct phenotypic analysis of maribavir against human cytomegalovirus carrying the following substitutions: High priority: pUL97 M460I/T, C592G, A594E/G/P/T, L595F/T/W, C603R/S/W/Y and Medium priority: pUL97 K359Q, L405P, A440V, V466M, C518Y, A591D/V, E596D/G/Y, K599E/M, C607F/S/Y, I610T, A613V. Low priority: pUL97 N68D, L126Q, P132L, I244V, pUL27 P10L. L11P, H97R, L133I, N289D, H297Y, D298G, N300G, P307L, V310A, D351N, I367V, H557Q, A565T. The rationale is based on known valganciclovir/ganciclovir resistance-associated substitutions for which maribavir susceptibility has not been evaluated. These substitutions have previously been

characterized and the strains should be available. Evaluation of cross-resistance to ganciclovir should be included in the analysis if not previously known.[7]

- Determine the human cytomegalovirus gB subtype for each of the subjects in study SHP620-303 "A Phase 3, Multicenter, Randomized, Open-label, Active-controlled Study to Assess the Efficacy and Safety of Maribavir Treatment Compared to Investigator-assigned Treatment in Transplant Recipients with Cytomegalovirus (CMV) Infections that are Refractory or Resistant to Treatment with Ganciclovir, Valganciclovir, Foscarnet, or Cidofovir."

The safety issues in the draft Warnings and Precautions section of the labeling include treatment failure, reduced antiviral activity when co-administered with ganciclovir and valganciclovir, and other drug-drug interactions. There is no boxed warning proposed for any of these risks or any adverse events of maribavir.[5]

This reviewer recommends that, should maribavir be approved, a REMS is not needed to ensure its benefits outweigh its risks. The risks will be described in the labeling. Healthcare providers who will prescribe and administer maribavir are expected to be able to manage the maribavir-emergent adverse events without additional risk mitigation measures beyond labeling.

9 Conclusion & Recommendations

Based on the available data, DAV and DRM agree that a REMS is not necessary to mitigate the risks of maribavir. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that sheds light on the risk profile; this recommendation can be reevaluated.

10 Appendices

10.1 References

[1] Azevedo LS, Pierrotti LC, et al. Cytomegalovirus infection in transplant recipients. Clinics (Sao Paulo). 2015;70(7):515-523. doi:10.6061/clinics/2015(07)09.

[2] Styczynski J. Who Is the Patient at Risk of CMV Recurrence: A Review of the Current Scientific Evidence with a Focus on Hematopoietic Cell Transplantation. *Infect Dis Ther*. 2018;7(1):1-16. doi:10.1007/s40121-017-0180-z.

[3] Tan BH. Cytomegalovirus Treatment. *Curr Treat Options Infect Dis*. 2014;6(3):256-270. doi:10.1007/s40506-014-0021-5.

[4] https://Clinicaltrials.gov. NCT02931539 Accessed August 20 2021.

[5] Maribavir draft prescribing Information, October 2021

[6] Razonable R. Drug-resistant cytomegalovirus: clinical implications of specific mutations. *Current Opinion in Organ Transplantation.* August 2018 volume 23 (4) pgs 388-394

[7] Clinical Virology PMRs, Information Request sent to Takeda via email correspondence October 21, 2021

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/

NAOMI S BOSTON
11/04/2021 02:56:51 PM

CYNTHIA L LACIVITA
11/05/2021 08:11:19 AM
Concur