CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216482Orig1s000

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	216482
PDUFA Goal Date	May 1, 2024
OSE TTT #	2022-1533
Reviewer Name	Brian Caruth, Pharm.D., BCPS
Team Leader	Yasmeen Abou-Sayed, Pharm.D.
Deputy Director	Laura Zendel, Pharm.D.
Review Completion Date	January 18, 2024
Subject	Review of proposed REMS
Established Name	Mycophenolate
Trade Name	Myhibbin
Name of Applicant	Liqmeds Worldwide Limited (Liqmeds)
Therapeutic Class	Antimetabolite immunosuppressant
Formulation	Oral Suspension

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1 Introduction

This review by the Division of Risk Management (DRM) evaluates the proposed risk evaluation and mitigation strategy (REMS) for Myhibbin[a] (mycophenolate oral suspension). The Division of Rheumatology and Transplant Medicine (DRTM) issued a Complete Response Letter (CRL) on January 6, 2023, citing a REMS deficiency.[1] Liqmeds Worldwide Limited utilized the 505(b)2 pathway and resubmitted the New Drug Application[2] (NDA) 216482 for mycophenolate oral suspension with the proposed indication for the prophylaxis of organ rejection in adult and pediatric recipients 3 months of age and older of allogeneic kidney, heart or liver transplants, in combination with other immunosuppressants. The reference listed drug (RLD) is CellCept, NDA 050759. The established Mycophenolate Shared System (SS) REMS uses a Type-V Drug Master File (DMF) 031030 for the REMS. The Applicant submitted a Letter of Authorization (LOA) referencing the shared system REMS DMF to the application and a cross referenced LOA was submitted to the DMF.[3] This application is under review in DRTM.

2 Background

2.1 Product Information

Mycophenolate is an antimetabolite immunosuppressant indicated for the prophylaxis of organ rejection in adult and pediatric recipients 3 months of age and older of allogeneic kidney, heart or liver transplants, in combination with other immunosuppressants. If approved, NDA 216482 will have the same indication.

The RLD, CellCept (NDA 050759), for mycophenolate oral suspension was initially approved on October 1, 1998. Post-marketing data including spontaneous reports, data from the National Transplantation Pregnancy Registry, information from Roche Pharmaceuticals, and a review by the Division of Pharmacovigilance (DPV) at the FDA all supported a causal role for mycophenolate contributing to pregnancy loss and malformations when taken by females of reproductive potential. The findings resulted in the Agency requiring a REMS for all mycophenolate products. The Mycophenolate SS REMS was originally approved on September 25, 2012 and last modified on August 11, 2021, and a separate Parallel System (PS) Mycophenolate SS REMS was approved on June 1, 2023.

The goal of the REMS is to mitigate the risk of embryofetal toxicity associated with use of mycophenolate during pregnancy by:

1. Educating healthcare providers on the following:
    - The increased risks of first trimester pregnancy loss and congenital malformations associated with exposure to mycophenolate during pregnancy
    - The need to counsel females of reproductive potential on the importance of pregnancy prevention and planning when taking mycophenolate
    - The need to report pregnancies to the Mycophenolate Pregnancy Registry

[a] The proposed proprietary name submitted during the previous review cycle was withdrawn and the Applicant resubmitted a *Request for a Proprietary Name Review* of the new proposed name Myhibbin.

2. Informing females of reproductive potential who are prescribed mycophenolate about:

    - The increased risks of pregnancy loss (miscarriage) and birth defects
    - The importance of pregnancy prevention and planning when taking mycophenolate

The established Mycophenolate Shared System (SS) REMS uses a Type-V Drug Master File (DMF) 031030 for the REMS. At the time of this review, the REMS includes 26 Applicants marketing 45 ANDA products and five NDA products. The PS Mycophenolate SS REMS also uses a Type-V DMF 038542 and includes two Applicants marketing two ANDA products. The REMS consists of ETASU A (prescribers are trained), ETASU F (patients using the drug are enrolled in a registry), and a timetable for submission of assessments of the REMS. While Mycophenolate Applicants must provide training to healthcare providers who prescribe mycophenolate, training is elective for healthcare providers and not a requirement linked to dispensing.

The Applicant previously submitted two relative bioavailability studies comparing the proposed product to the RLD. The RLD is a powder for reconstitution to a 200 mg/mL oral suspension. Myhibbin is proposed to be available as 200 mg/mL ready-to-use oral suspension.

2.2 Regulatory History

The following is a summary of the regulatory history for NDA 216482 relevant to this review:

- 01/06/2023: FDA issued a CRL to the Applicant citing a REMS deficiency
- 11/01/2023: The Applicant submitted a Class 2 Resubmission for NDA 216482 including a LOA referencing the Mycophenolate SS REMS DMF 031030 and a cross referenced LOA was submitted to the DMF

3 Benefit Assessment

The efficacy of mycophenolate has been demonstrated, with the approval of NDA 050759 (CellCept, Roche Pharmaceuticals), on October 1, 1998, for the prophylaxis of organ rejection in recipients of allogeneic kidney, heart or liver transplants, and should be used in combination with other immunosuppressants. An expanded indication for the RLD was approved on June 6, 2022 and will be applied to this application.

Bioequivalency of mycophenolate oral suspension was evaluated in two relative bioavailability studies submitted during the previous review cycle.[4] At that time, the clinical pharmacology reviewer verified the pharmacokinetic data and concluded the results supported evidence of bioequivalency for mycophenolate oral suspension.

4 Risk Assessment & Safe-Use Conditions

Use of mycophenolate during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations. The Applicant did not conduct non-clinical studies to evaluate the embryofetal toxicity risk and this product is expected to have the same embryofetal toxicity risk as other mycophenolate products. Mycophenolate products are approved for marketing only with a REMS known as the Mycophenolate SS REMS or PS Mycophenolate SS REMS.

5 Risk Management Activities Proposed by the Applicant

5.1 Review of Applicant's Proposed REMS

The Applicant submitted an LOA referencing the Mycophenolate SS REMS DMF 031030 with this resubmission and a cross referenced LOA was submitted to the DMF.

6 Conclusion & Recommendations

The Applicant submitted an LOA referencing the Mycophenolate SS REMS DMF 031030 to the application and a cross referenced LOA was submitted to the DMF. Therefore, DRM recommends approval of the REMS for mycophenolate NDA 216482 as the REMS is acceptable. Should DRTM have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

7 Appendices

7.1 References

[1] Mycophenolate (NDA 216482) Complete Response Letter. DARRTS Reference ID: 5105621. January 6, 2023.

[2] Liqmeds Worldwide Limited. Mycophenolate (NDA 216482). Class 2 Resubmission. Submitted November 1, 2023.

[3] ICON Clinical Research LLC. Mycophenolate SS REMS (DMF 031030). Letter of Authorization. Submitted October 27, 2023.

[4] Mycophenolate (NDA 216482) Unireview. DARRTS Reference ID: 5105174. January 5, 2023.

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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	216482
PDUFA Goal Date	January 8, 2023
OSE RCM #	2022-538
Reviewer Name	Brian Caruth, Pharm.D., BCPS
Team Leader	Yasmeen Abou-Sayed, Pharm.D.
Associate Director for REMS Design and Evaluation	Laura Zendel, Pharm.D., BCPS
Review Completion Date	January 4, 2022
Subject	Review of proposed REMS
Established Name	Mycophenolate
Trade Name	(b) (4)
Name of Applicant	Liqmeds Worldwide Limited (Liqmeds)
Therapeutic Class	Antimetabolite immunosuppressant
Formulation	Oral Suspension

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1 Introduction

This review by the Division of Risk Management (DRM) evaluates the proposed risk evaluation and mitigation strategy (REMS) for (b) (4) (mycophenolate oral suspension). Liqmeds Worldwide Limited utilized the 505(b)2 pathway and submitted a New Drug Application (NDA) 216482 for mycophenolate oral suspension with the proposed indication for the prophylaxis of organ rejection in adult and pediatric recipients 3 months of age and older of allogeneic kidney, heart or liver transplants, in combination with other immunosuppressants. The reference listed drug (RLD) is CellCept, NDA 050759. The established Mycophenolate Shared System (SS) REMS uses a Type-V Drug Master File (DMF) 31030 for the REMS. The Applicant did not submit a proposed REMS with this application. This application is under review in the Division of Rheumatology and Transplant Medicine (DRTM).

2 Background

2.1 Product Information

Mycophenolate is an antimetabolite immunosuppressant indicated for the prophylaxis of organ rejection in adult and pediatric recipients 3 months of age and older of allogeneic kidney, heart or liver transplants, in combination with other immunosuppressants. If approved, NDA 216482 will have the same indication.

The RLD (CellCept [NDA 050759]) for mycophenolate oral suspension was initially approved on October 1, 1998. Post-marketing data including spontaneous reports, data from the National Transplantation Pregnancy Registry, information from Roche Pharmaceuticals, and a review by the Division of Pharmacovigilance (DPV) at the FDA all supported a causal role for mycophenolate contributing to pregnancy loss and malformations when taken by females of reproductive potential. The findings resulted in the Agency requiring a REMS for all mycophenolate products. The Mycophenolate SS REMS was originally approved on September 25, 2012 and last modified on August 11, 2021.

The goal of the REMS is to mitigate the risk of embryofetal toxicity associated with use of mycophenolate during pregnancy by:

1. Educating healthcare providers on the following:
    - The increased risks of first trimester pregnancy loss and congenital malformations associated with exposure to mycophenolate during pregnancy
    - The need to counsel females of reproductive potential on the importance of pregnancy prevention and planning when taking mycophenolate
    - The need to report pregnancies to the Mycophenolate Pregnancy Registry
2. Informing females of reproductive potential who are prescribed mycophenolate about:
    - The increased risks of pregnancy loss (miscarriage) and birth defects
    - The importance of pregnancy prevention and planning when taking mycophenolate

The established Mycophenolate Shared System (SS) REMS uses a Type-V Drug Master File (DMF) 31030 for the REMS. At the time of this review, the REMS includes 24 Applicants marketing 42 generic products and five NDA products. The REMS consists of ETASU A (prescribers are trained), ETASU F (patients using the drug are enrolled in a registry), and a timetable for submission of assessments of the REMS. While Mycophenolate Applicants must provide training to healthcare providers who prescribe mycophenolate, training is elective for healthcare providers and not a requirement linked to dispensing.

The Applicant submitted two relative bioavailability studies comparing the proposed product to the RLD. The RLD is a powder for reconstitution to a 200 mg/mL oral suspension. (b) (4) is proposed to be available as 200 mg/mL ready-to-use oral suspension.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 216482 relevant to this review:

- 03/08/2022: NDA 216482 received for mycophenolate oral suspension
- 06/22/2022: FDA issues an Information Request (IR) informing the Applicant about the requirement to include a proposed REMS for their NDA and provided a point of contact for the established Mycophenolate SS REMS
- (b) (4)
- 09/14/2022: FDA issued an IR to the Applicant requesting a response to the 07/21/2022 IR and reiterated the recommendation to join the established Mycophenolate SS REMS
- 10/07/2022: The Applicant submitted email correspondence with additional questions about timelines and process for submitting a REMS as a requirement of the application
- 10/17/2022: FDA responded to 10/07/2022 questions regarding timelines and process for submitting a REMS as a requirement of the application

3 Benefit Assessment

The efficacy of mycophenolate has been demonstrated, with the approval of NDA 050759 (CellCept [Roche Pharmaceuticals]), on October 1, 1998, for the prophylaxis of organ rejection in recipients of allogeneic kidney, heart or liver transplants, and should be used in combination with other immunosuppressants.

Bioequivalency of mycophenolate oral suspension was evaluated in two relative bioavailability studies in the fasting state (CL-155-18) and fed state (CL-156-18). The two studies represented a total of 96 subjects, of whom 82 completed all dosing periods (40/48 [fasting state]) and (42/48 [fed state]). All subjects were healthy males 18 to 45 years of age with a body mass index (BMI) between 18.5 and 29.9 kg/m^2. Both studies compared a 1000 mg oral dose of mycophenolate oral suspension to the RLD. The studies were open-label, laboratory-blind, randomized, four-period, two-treatment, two-sequence, single-dose crossover studies. Bioequivalency was evaluated using a 90% confidence interval (CI) for the geometric least square means ratios for C_{max}, AUC_{0-t}, and AUC_{0-inf} of the active metabolite, mycophenolic acid (MPA). The geometric mean ratios and associated 90% CI for all three pharmacokinetic parameters of MPA relative to the RLD were completely contained within the 80% to 125% equivalence margin. The Applicant concluded the pharmacokinetic data from the two studies demonstrated bioequivalency between mycophenolate oral suspension and the RLD. The clinical pharmacology reviewer verified the pharmacokinetic data and concluded the results supported evidence of bioequivalency for mycophenolate oral suspension.

An expanded indication for the RLD was approved on June 6, 2022 and will be applied to this application.

4 Risk Assessment & Safe-Use Conditions

Use of mycophenolate during pregnancy is associated with an increased risk of first trimester pregnancy loss and an increased risk of congenital malformations. The applicant did not conduct non-clinical studies to evaluate the embryofetal toxicity risk and this product is expected to have the same embryofetal toxicity risk as other mycophenolate products. Mycophenolate products are approved for marketing only with a REMS known as the Mycophenolate SS REMS.

5 Risk Management Activities Proposed by the Applicant

5.1 Review of Applicant's Proposed REMS

The Applicant did not submit a proposed REMS with this application.

6 Conclusion & Recommendations

As of January 4, 2023, the Applicant has not submitted a proposed REMS to the Application. Therefore, DRM does not recommend approval of the REMS for mycophenolate NDA 216482 as the REMS is deficient. Should DRTM have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

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/s/

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