NDA 216482

NDA APPROVAL

Liqmeds Worldwide Limited
c/o MA Pharmaceutical Consulting, Inc.
Attention: Shehla Uraizee, PhD, RPh
President, MA Pharmaceutical Consulting, Inc.
384 Silver Sage Lane
St. Augustine, FL 32095

Dear Dr. Uraizee:

Please refer to your new drug application (NDA) dated and received March 8, 2022, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Myhibbin (mycophenolate mofetil oral suspension).

We acknowledge receipt of your amendment dated November 1, 2023, which constituted a complete response to our January 6, 2023, action letter.

This NDA provides for the use of Myhibbin (mycophenolate mofetil oral suspension) 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.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Medication Guide) as well as annual reportable changes

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

not included in the enclosed labeling. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As.*[2]

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the enclosed carton and container labeling, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *SPL Standard for Content of Labeling Technical Qs & As.* For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 216482**." Approval of this submission by FDA is not required before the labeling is used.

DATING PERIOD

Based on the stability data submitted to date, the expiry dating period for Myhibbin (mycophenolate mofetil oral suspension) shall be 18 months from the date of manufacture when stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for birth to less than 3 months of age for the heart, liver, and kidney transplant indications because necessary studies are impossible or highly impracticable.

This product is appropriately labeled for use in ages 3 months to less than 18 years for these indications. Therefore, no additional studies are needed in this pediatric group.

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks.

REMS requirements for Mycophenolate Mofetil were outlined in our Information Request dated June 22, 2022, to ensure the benefits of drug outweigh the risks of first trimester pregnancy loss and congenital malformations.

Your final proposed REMS, referenced in Drug Master File (DMF) 031030, is approved, and will be posted on the FDA REMS website: http://www.fda.gov/rems. Other products may be added in the future if additional NDAs or ANDAs are approved.

The Mycophenolate Shared System (SS) REMS consists of Elements to Assure Safe Use (ETASU).

Your REMS must be fully operational before you introduce your drug into interstate commerce.

Under section 505-1(g)(2)(C) of the FD&C Act, FDA can require the submission of a REMS assessment if FDA determines an assessment is needed to evaluate whether the REMS should be modified to ensure the benefits of the drug outweigh the risks or to minimize the burden on the healthcare delivery system of complying with the REMS.

FDA has determined that assessments are needed for the Mycophenolate SS REMS.

Additionally, the details for what should be included in your REMS assessments and the dates of the REMS assessments are listed in Appendix 1.

If the information provided in an assessment is insufficient to allow FDA to determine whether the REMS is meeting its goals or whether the REMS must be modified, FDA may require the submission of a new assessment plan that contains the metrics and/or methods necessary to make such a determination. Therefore, FDA strongly recommends obtaining FDA feedback on the details of your proposed assessment plan to ensure its success. To that end, we recommend that methodological approaches, other analysis plans and assessment approaches used to assess a REMS be submitted for FDA review.

Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

> **NDA 216482 REMS CORRESPONDENCE**
> **(**insert concise description of content in bold capital letters, e.g.,

ASSESSMENT METHODOLOGY, SURVEY METHODOLOGIES, CROSS REFERENCE TO THE REMS DMF)

We remind you that in addition to the REMS assessments submitted according to the timetable in the approved REMS, you must include an adequate rationale to support a proposed REMS modification for the addition, modification, or removal of any goal or element of the REMS, as described in section 505-1(g)(4) of the FDCA.

We also remind you that you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A). This assessment should include:

a) An evaluation of how the benefit-risk profile will or will not change with the new indication;

b) A determination of the implications of a change in the benefit-risk profile for the current REMS;

c) *If the new, proposed indication for use introduces unexpected risks*: A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS.

d) *If a REMS assessment was submitted in the 18 months prior to submission of the supplemental application for a new indication for use*: A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment.

e) *If a REMS assessment has not been submitted in the 18 months prior to submission of the supplemental application for a new indication for use:* Provision of as many of the currently listed assessment plan items as is feasible.

f) *If you propose a REMS modification based on a change in the benefit-risk profile or because of the new indication of use, submit an adequate rationale to support the modification, including*: Provision of the reason(s) why the proposed REMS modification is necessary, the potential effect on the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. Additionally, include any changes to the assessment plan necessary to assess the proposed modified REMS. *If you are not proposing a REMS modification*, provide a rationale for why the REMS does not need to be modified.

An authorized generic drug under this NDA must have an approved REMS prior to marketing. Should you decide to market, sell, or distribute an authorized generic drug under this NDA, contact us to discuss what will be required in the authorized generic drug REMS submission.

We remind you that section 505-1(f)(8) of FDCA prohibits holders of an approved covered application with elements to assure safe use from using any element to block or delay approval of an application under section 505(b)(2) or (j). A violation of this provision in 505-1(f) could result in enforcement action.

Prominently identify any submission containing the REMS assessments or proposed modifications of the REMS with the following wording in bold capital letters at the top of the first page of the submission as appropriate:

NDA 216482 REMS ASSESSMENT
CROSS REFERENCE TO THE REMS DMF

or

NEW SUPPLEMENT FOR NDA 216482/S-000
CHANGES BEING EFFECTED IN 30 DAYS
PROPOSED MINOR REMS MODIFICATION
CROSS REFERENCE TO THE REMS DMF

or

NEW SUPPLEMENT FOR NDA 216482/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED MAJOR REMS MODIFICATION
CROSS REFERENCE TO THE REMS DMF

or

NEW SUPPLEMENT FOR NDA 216482/S-000
PRIOR APPROVAL SUPPLEMENT
PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT XXX
CROSS REFERENCE TO THE REMS DMF

or

NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR NDA 216482/S-000
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)
CROSS REFERENCE TO THE REMS DMF

Should you choose to submit a REMS revision, prominently identify the submission containing the REMS revisions with the following wording in bold capital letters at the top of the first page of the submission:

REMS REVISION FOR NDA 216482
CROSS REFERENCE TO THE REMS DMF

The Mycophenolate SS REMS uses a Type V DMF for shared system REMS submissions. Please refer to the draft guidance for industry *Use of a Drug Master File for Shared System REMS Submissions*,[3] for instructions on how to submit and reference the shared system REMS DMF.

To facilitate review of your submission, we request that you submit your proposed modified REMS and other REMS-related materials in Microsoft Word format. If certain documents, such as enrollment forms, are only in PDF format, they may be submitted as such, but the preference is to include as many as possible in Word format.

SUBMISSION OF REMS DOCUMENT IN SPL FORMAT

As soon as possible, but no later than 14 days from the date of this letter, submit the REMS document in Structured Product Labeling (SPL) format as described in the Guidance for Industry, *Providing Regulatory Submission in Electronic Format – Content of the Risk Evaluation and Mitigation Strategies Document Using Structured Product Labeling*.

For more information on submitting REMS in SPL format, please email FDAREMSwebsite@fda.hhs.gov.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format—Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[4]

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the Prescribing Information, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at FDA.gov.[5] Information and Instructions for completing the form can be found at FDA.gov.[6]

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the FDA Drugs guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

COMPENDIAL STANDARDS

A drug with a name recognized in the official United States Pharmacopeia or official National Formulary (USP-NF) generally must comply with the compendial standards for strength, quality, and purity, unless the difference in strength, quality, or purity is plainly stated on its label (see FD&C Act § 501(b), 21 USC 351(b)). FDA typically cannot share application-specific information contained in submitted regulatory filings with third parties, which includes USP-NF. To help ensure that a drug continues to comply with compendial standards, application holders may work directly with USP-NF to revise official USP monographs. More information on the USP-NF is available on USP's website[7].

If you have any questions, contact Saharat Patanavanich, Regulatory Project Manager, at (240) 402-0139 or Saharat.patanavanich@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ozlem Belen, MD, MPH
Deputy Division Director
Division of Rheumatology and Transplant Medicine
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- REMS Assessment Plan
- Content of Labeling
  - Prescribing Information
  - Medication Guide
- Carton and Container Labeling

[7] https://www.uspnf.com/

Appendix 1: REMS Assessment Plan

The assessment plan must include, but is not limited to, the following:

PROGRAM OUTREACH AND COMMUNICATION

1) REMS Communication activities (provide for each reporting period and cumulatively)
   a) For both the Dear Healthcare Provider (DHCP) Letter (1&2) and the Dear Healthcare Provider (DHCP) Letter for Centers (1&2), provide the following:
      i) Sources for the distribution lists for healthcare providers
      ii) Number of healthcare providers targeted
      iii) The number of REMS materials packets sent by date and method of distribution
      iv) The number of emails successfully delivered, opened and unopened.
      v) The number of mailing successfully delivered, opened, and unopened
      vi) Date that the revised materials became available on the website
   b) For each professional society, or journal to be sent the banner provide the following:
      i) A summary of the extent to which the banner reached the intended stakeholders
      ii) The number of times the Mycophenolate REMS website was accessed via the banner

PROGRAM IMPLEMENTATION AND OPERATIONS

2) Status of Grants (provide for each reporting period and cumulatively)
   a) The status of the request for proposals for grants for REMS-compliant accredited CE including:
      i) Date Request for Application (RFA) issued
      ii) Date and number of applications submitted in response to each RFA
      iii) RFAs awarded: date, number, and name of grantee
      iv) Date/timeframe next RFA to be issued
3) Continuing Education (CE) Program (provide each reporting period and cumulatively)
   a) For CE programs awarded during the assessment period:
      i) Description of each grantee and projected number of participants and completers

ii) For the first assessment, the date the first REMS-compliant CE based upon the FDA Mycophenolate REMS Education Blueprint became available

b) Description of Continuing Education (CE) program:

i) CE format (live, webinar, etc.)

ii) Duration of activity for live or webinar activities

iii) Average duration to complete for internet/enduring activities

iv) Education methods and tools (case-based, multimedia, didactic, interactive, adaptive, etc.)

v) A summary of all reports submitted to the Mycophenolate REMS Applications by CE grantees during the assessment period

4) Audit: The aggregate results of independent audits of the CE. Audits must include/evaluate

a) A description of the organization(s) or independent auditors (accreditation bodies of CE Providers are considered independent and eligible to conduct the audits) conducting the audit(s);

b) Whether the content of the REMS-compliant accredited CE covers all elements of the FDA Blueprint approved as part of the REMS;

c) Whether the integrated or post-course knowledge assessment measures knowledge of all section of the FDA Blueprint;

d) Whether the REMS-compliant accredited CE was conducted in accordance with the Accreditation Council for Continuing Medication Education (ACCME) standards for CE or appropriate standards for accreditation bodies

5) Healthcare Provider Training (provide for each reporting period and cumulatively)

a) The number of healthcare providers who completed the *Prescriber Training Confirmation Form* in the Shared System REMS (during the reporting period and cumulatively), stratified by prescriber specialty.

b) A summary of the methods used to complete the *Prescriber Training Confirmation Form* (i.e., online, phone, fax).

c) The number of healthcare providers who have confirmed training through the Mycophenolate REMS website and were actively prescribing mycophenolate during the reporting period (i.e., have written at least one prescription in the time period) stratified by prescriber specialty.

d) The number of healthcare providers who have completed REMS-compliant accredited CE stratified by specialty, degree, and geographic region (defined by US Census) and those who report prescribing mycophenolate.

e) Provide an analysis comparing the number of healthcare providers who

completed the *Prescriber Training Confirmation Form* and/or a REMS-compliant accredited CE program to the total number of healthcare providers prescribing a mycophenolate-containing product stratified by specialty and degree.

f) A description of any activities undertaken during the assessment reporting period to increase training, not identified in other metrics.

6) Center training (provide for each reporting period and cumulatively)
   a) The total number of centers, stratified by type of center that confirmed training (during the reporting period and cumulative).
   b) A descriptive summary of how newly confirmed centers incorporated the REMS into their center's practice (as described on the *Center Training Confirmation Form*).
   c) Total prescribers confirmed by centers.
7) Mycophenolate Utilization Data (provide for each reporting period and cumulatively)
   a) Healthcare Provider Data
      i) The number and percentage of total prescriptions dispensed, by new and refill, stratified by specialty.
      ii) The number of unique prescribers stratified by specialty.
   b) Patient Utilization Data
      i) The number of unique patients receiving mycophenolate stratified by age, gender, and reasons for use/indication.

HEALTH OUTCOMES AND SURROGATES OF HEALTH OUTCOMES

8) Pregnancy Exposures (provide for each reporting period and cumulatively)
   a) An analysis of the post-marketing cases of pregnancy reported in association with mycophenolate (during the reporting period and cumulative) with attention to but not limited to:
      i) The number of pregnancy exposures* reported (during the reporting period and cumulative) and stratified by source (spontaneous report, reported via the Mycophenolate REMS Call Center, enrolled in the Mycophenolate Pregnancy Registry), age, and other demographics, and if the prescriber completed the REMS training and/or reports completing REMS-compliant accredited CE training.
      ii) The duration of mycophenolate exposure data.
      iii) The pregnancy outcome for each exposed pregnancy reported (during the reporting period and cumulative).

iv) The root cause analysis of each pregnancy reported to determine the cause of the pregnancy exposure (during the reporting period and cumulative).

v) Results of any follow up from previous years' exposures.

*All pregnancy exposures reported to the applicants from any source should be reported and analyzed as part of the SSS REMS assessment plan. The cases should be linked to allow matching of the cases reported in the Mycophenolate Pregnancy Registry to cases in the global safety database.

KNOWLEDGE

9) Healthcare Provider Knowledge (beginning with the 3-year assessment report and each reporting period thereafter) stratified by whether the HCP reports training through the REMS website, training through the REMS-compliant accredited CE program, neither, or both.

a) An evaluation of healthcare providers' understanding of:

i) First trimester pregnancy loss and congenital malformations associated with exposure to mycophenolate during pregnancy

ii) The need to counsel females of reproductive potential on the importance of pregnancy prevention and planning when taking mycophenolate

iii) The need to report pregnancies to the Mycophenolate Pregnancy Registry.

10) Patient Knowledge (beginning with the 3-year assessment report and each reporting period thereafter)

a) An evaluation of patients' understanding and awareness of the increased risks of miscarriage and birth defects when taking mycophenolate during pregnancy, and the importance of pregnancy prevention and planning when taking mycophenolate.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether one or more such goals or such elements should be modified.

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/

OZLEM A BELEN
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