DIVISION OF RHEUMATOLOGY AND TRANSPLANT MEDICINE

NDA Complete Response Resubmission Clinical Review

Drug	**Mycophenolate mofetil oral suspension (Myhibbin)**
NDA/ Supporting document number	**NDA 216482 / 23**
Sponsor	**Liqmeds Worldwide Ltd.**
Submission Date	**November 01, 2023**
Date of Review	**April 25, 2024**
Clinical Reviewer	**Nadia Chaudhri, MD**
Clinical Team Leader	**Ergun Velidedeoglu, MD**
Deputy Director	**Ozlem Belen, MD, MPH**

1) Background / Summary

Liqmeds (applicant) received a complete response (CR) for their NDA 216482 for MMF Oral suspension on January 6, 2023. The proposed formulation is a ready-to-use oral suspension. The approved reference listed drug (RLD) (CellCept® for oral suspension, NDA 050759) formulation requires reconstitution of a powder for use as an oral suspension. The applicant was seeking approval through the 505(b)2 pathway for the same indications as the RLD including, 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. Labeling was finalized and agreed upon as of December 20, 2022. See Unireview finalized in DARRTS on January 5, 2023 for summary of the application and review of the safety issues that were resolved during the initial review cycle. The application ultimately received a complete response (CR) decision because the applicant failed to join the single shared REMS that has been established for mycophenolate products to manage the risk of embryo-fetal toxicity associated with their use. In response to the CR decision, the applicant submitted a Class 2 resubmission for NDA 216482 on November 1, 2023. The following review summarizes the Clinical team's review of the applicant's resubmission.

2) Sponsor's Response to CR Decision:

Deficiencies are in bold Arial font size 12, applicant's response is in italicized Arial font 12, and reviewer's comments are in gray boxes in normal Arial font size 12.

1. **RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS: As described in our correspondences dated June 22 and October 17, 2022, in accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for mycophenolate mofetil to ensure that the benefits of the drug outweigh the risks of first trimester pregnancy loss and congenital malformations. Your application cannot be approved without a REMS. Therefore, you must include your**

proposed REMS to address this deficiency. Our communications dated June 22 and October 17, 2022 provide information about the elements your proposed REMS must include.

Applicant response: *As recommended by the Agency in the correspondence dated June 22, 2022 and September 14, 2022 to join the Mycophenolate SS REMS program, Liqmeds has joined the established Shared System REMS (SS REMS) for Mycophenolate managed by* (b) (4) *and is now part of the Mycophenolate REMS group. The letter of authorization (LOA) for Type V DMF # 031030 for Mycophenolate SS REMS issued by DMF Holder: ICON Clinical Research LLC to the NDA 214682 sponsor Liqmeds is provided in section 1.4.2. We also received notification that on Oct 27, 2022, ICON Clinical Research submitted an amendment to the DMF 031030 with the issuance of LOA to Liqmeds and to incorporate the contents of the Mycophenolate Shared System REMS (MREMS) into NDA # 216482 for Mycophenolate mofetil oral suspension, 200 mg/mL, filed by Liqmeds on March 07, 2022.*

Reviewer's comment: The Division of Risk Management (DRM) completed their review of the applicant's proposal to join the ss-REMS on January 18, 2024 (see entry in DARRTS dated January 18, 2024) and concluded, "DRM recommends approval of the REMS for mycophenolate NDA 216482 as the REMS is acceptable." This reviewer concurs with their decision.

2. **PROPRIETARY NAME: Refer to the correspondence dated November 17, 2022, which addresses the proposed proprietary name,** (b) (4) **. This name was found acceptable pending approval of application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.**

Applicant response: (b) (4) *Liqmeds is withdrawing the conditionally approved proprietary name and is submitting a new request for proprietary name review in this resubmission. Preferential Name: MYHIBBIN.*

Reviewer's comment: The Division of Medication Error Prevention and Analysis 1 (DMEPA 1) reviewed the applicant's proposal for a new proprietary name. See DARRTS entry January 22, 2024 for details of the review. DMEPA 1 determined the name, Myhibbin, is conditionally acceptable. This reviewer concurs with their decision.

3. **PRESCRIBING INFORMATION: We reserve any additional comments on the proposed labeling until the application is otherwise adequate. If you revise labeling, use the Selected Requirements for Prescribing Information (SRPI) checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response**

must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.

Applicant response: *Liqmeds Worldwide Limited confirms that there is no update to the proposed prescribing information which aligns with the most recent RLD labeling (CellCept, NDA # 050759, S-055 and S-056).*

Reviewer's comment: The proposed labeling did not include any major amendments such as, adding a new indication or condition of use, adding a new strength, minor changes in product formulation, or change to the physical form or crystalline structure of the active ingredient.

DMEPA 1 reviewed the labeling submitted by the applicant on November 1, 2023 and requested the applicant make the following updates (see Labeling review finalized in DARRTS January 30, 2024):

1. Replace the proprietary name with the conditionally acceptable name, "Myhibbin" throughout the labels and labeling and resubmit for review.
2. Per the Drug Supply Chain Security Act (DSCSA), the "smallest saleable unit" must include the NDC in both human-readable and machine-readable forms. See Guidance for Industry, Product Identifiers under the Drug Supply Chain Security Act – Questions and Answers (June 2021). Include the machine-readable forms of the NDC.

These comments were relayed to the applicant on March 15, 2024. The applicant complied with this request and submitted their response on March 20, 2024 (SDN 25, eCTD sequence number 0025). Additional comments were relayed on March 27, 2024 (See "Labeling Comments" finalized in DARRTS on March 27, 2024.) for the applicant to:

3. Revise the Medication Guide to have storage conditions consistent with that on the Prescribing Information, container (bottle) and carton labels.

The applicant complied with this request and submitted an acceptable response with updated labeling on April 1, 2024 (SDN 27, eCTD sequence number 0027). An additional request to update labeling to comply with PLR formatting was relayed to the applicant on April 12, 2024. The applicant complied with this request and submitted their updated labeling on April 15, 2024 (SDN 28, eCTD sequence number 0028). This labeling is considered the final agreed upon labeling.

4. **SAFETY UPDATE: When you respond to the above deficiency(ies), include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.**

Applicant response: *Liqmeds Worldwide Limited confirms that no new clinical or non-clinical studies have been conducted since the submission of the original NDA and, therefore, there are no significant changes or findings in the safety profile of mycophenolate mofetil.*

Reviewer's comment: This reviewer confirms the applicant did not submit any new clinical studies conducted by them or published with this resubmission.

5. PEDIATRIC RESEARCH EQUITY ACT (PREA) WAIVER:

Applicant response*: Reference is made to the Liqmeds Worldwide Limited's Agreed Initial Pediatric Study Plan-Agreement, Reference#4764578, received from the Agency on 03/22/2021. According to the agreed initial pediatric study plan-agreement letter, the sponsor was granted with:*

1. *A partial waiver of pediatric studies for pediatric allogeneic kidney transplant patients of less than 3 months old, and*
2. *A deferral of pediatric studies for allogeneic liver and heart transplant patients for a 10-year timeline.*

*A review of the CELLCEPT labeling indicated that the RLD holder has recently completed additional clinical studies and established the safety and effectiveness of CELLCEPT (mycophenolate mofetil) in pediatric patients 3 months and older for the prophylaxis of organ rejection of allogenic heart or liver transplants***.**

The IND sponsorship was transferred from Alkem Laboratories Limited to Liqmeds Worldwide Limited on December 30, 2021. Therefore, Liqmeds (as per FDA's recommendation provided in email on September 22, 2023) is submitting this amendment to agreed initial pediatric study plan (iPSP) requesting to change from the planned deferral of pediatric studies to a request for a partial waiver for conducting studies in pediatric heart and liver transplant patients.

Reviewer's comment: This application was presented to the PeRC after complete response resubmission on March 19, 2024. This was the third PeRC discussion for this product. First pediatric plan for this product was discussed at PeRC in 2019 when the product was at the pIND stage and the RLD had only been approved for pediatric patients down to 3 months of age who had undergone renal transplantation. Initial agreed upon iPSP is noted above in the applicant's response and was finalized on March 22, 2021. During the initial review cycle, this product was discussed at PeRC in February 2022, and PeRC recommended that the product be approved for all three indications in patients down to 3 months of age to be consistent with most recently updated RLD labeling (CellCept® for oral suspension had received approval for use in pediatric heart and liver transplant recipients down to 3 months of age in June 2022). PeRC recommendations from the March 19, 2024 meeting include:

1. The PeRC agreed with granting a partial waiver in pediatric patients from birth to less than 3 months of age for the heart, liver, and kidney transplant indications on the basis that necessary studies are impossible or highly impracticable.
2. The PeRC also agreed the product has been full assessed in pediatric patient 3 months to less than 18 years of age for all three indications based on bioequivalence of MMF RTU Suspension to CellCept for oral suspension.

The PeRC stated the applicant did not need to submit a revised iPSP reflecting these changes and their proposed amended iPSP can serve as the agreed iPSP for this application.

3) Reviewer's Conclusions

This reviewer concludes the applicant has sufficiently replied to the listed deficiencies in the CR letter dated January 5, 2023. The major deficiency pertained to the applicant not submitting an adequate REMS or joining the ss-REMS. The applicant joined the ss-REMS and submitted adequate documentation of their compliance with this requirement, according to DRM review. The remaining deficiencies have also been resolved.

This reviewer recommends approval of this NDA 216482, MMF (b) (4) 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.

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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