NDA 217785/S-002
NDA 217785/S-004
NDA 217785/S-005

SUPPLEMENT APPROVAL
FULFILLMENT OF POSTMARKETING
REQUIREMENT AND COMMITMENTS

Madrigal Pharmaceuticals, Inc.
Attention: Harris Rotman, PhD
Senior Vice President, Global Regulatory Affairs
200 Barr Harbor Drive
Suite 200
West Conshohocken, PA 19428

Dear Dr. Rotman:

Please refer to your supplemental new drug applications (sNDAs) dated and received April 30, June 30, and July 31, 2025, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Rezdiffra (resmetirom) tablets.

These Prior Approval sNDAs provide for the following:

- Supplement 002 – labeling revisions to the DRUG INTERACTIONS section of the prescribing information (PI) based on data generated from the completed study MGL-3196-22 titled, *A Phase 1, Single-center, Open-label, Drug Interaction Study of Resmetirom with Cyclosporine in Healthy Subjects*, to address postmarketing commitment (PMC) 4577-8 cited in the Accelerated Approval letter dated March 14, 2024

- Supplement 004 – labeling revisions to the USE IN SPECIFIC POPULATIONS, Renal Impairment subsection and CLINICAL PHARMACOLOGY, Pharmacokinetics subsection of the PI based on the results of study MGL-3196-21 titled, *A Phase 1, Multi-center, Open-label Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Multiple Oral Doses (6 days) of 100 mg Resmetirom in Subjects with Severe Renal Impairment and in Matched Healthy Control Subjects with Normal Renal Function*, to address postmarketing requirement (PMR) 4577-6 cited in the Accelerated Approval letter dated March 14, 2024

- Supplement 005 – labeling revisions to the CLINICAL PHARMACOLOGY, *Pharmacokinetics* subsection of the PI based on the results of study MGL-3196-21 titled, *A Phase 1, Single-center, Open-label, Drug Interaction Study of*

Resmetirom with Rosuvastatin in Healthy Subjects, to address PMC 4577-7 cited in the Accelerated Approval letter dated March 14, 2024

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.

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 (Prescribing Information and Patient Package Insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes 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 from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

FULFILLMENT OF POSTMARKETING REQUIREMENT AND COMMITMENTS

We have received your submissions dated April 30, June 30, and July 31, 2025, containing the final reports for the following postmarketing requirement and commitments listed in the March 14, 2024, Accelerated Approval letter.

4577-6 Conduct a clinical study to evaluate the effects of severe renal impairment on the pharmacokinetics of resmetirom and its major metabolite(s). Design and conduct the trial in accordance with the

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

draft guidance for industry, Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing.

4577-7 Conduct a clinical drug-drug interaction study to evaluate the effects of resmetirom on the pharmacokinetics of a sensitive substrate of Breast Cancer Resistance Protein (BCRP). Design and conduct the trial in accordance with the Guidance for Industry: Clinical Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions

4577-8 Conduct a clinical drug-drug interaction study to evaluate the effects of an inhibitor of organic anion transporting polypeptide (OATP) 1B1 and OATP1B3 on the pharmacokinetics of resmetirom. Design and conduct the trial in accordance with the Guidance for Industry: Clinical Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions

We have reviewed your submissions and conclude that the above requirement and commitments were fulfilled.

We remind you that there are postmarketing requirements and a postmarketing commitment listed in the March 14, 2024, Accelerated Approval letter that are still open.

We also remind you that accelerated approval PMR 4577-1 listed in the March 14, 2024, Accelerated Approval letter is still open. Pursuant to 21 CFR 314.510 (Subpart H) continued approval of the drug is contingent upon verification and description of clinical benefit and completion of the clinical trial for PMR 4577-1.

PATENT LISTING REQUIREMENTS

Pursuant to 21 CFR 314.53(d)(2) and 314.70(f), certain changes to an approved NDA submitted in a supplement require you to submit patent information for listing in the Orange Book upon approval of the supplement. You must submit the patent information required by 21 CFR 314.53(d)(2)(i)(A) through (C) and 314.53(d)(2)(ii)(A) and (C), as applicable, to FDA on Form FDA 3542 within 30 days after the date of approval of the supplement for the patent information to be timely filed (see 21 CFR 314.53(c)(2)(ii)). You also must ensure that any changes to your approved NDA that require the submission of a request to remove patent information from the Orange Book are submitted to FDA at the time of approval of the supplement pursuant to 21 CFR 314.53(d)(2)(ii)(B) and 314.53(f)(2)(iv).

REPORTING REQUIREMENTS

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

If you have any questions, contact Taiye Adedeji, PharmD, Senior Regulatory Health Project Manager, at Taiye.Adedeji@fda.hhs.gov or at (240) 402-8561.

Sincerely,

{See appended electronic signature page}

Katherine S. Won PharmD, MBA, BCSCP, RAC
CDR, U.S. Public Health Service
Acting, Deputy Director for Safety
Division of Hepatology and Nutrition
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Patient Package Insert

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/

KATHERINE S WON
12/19/2025 11:46:34 AM