CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

217785Orig1s000

Trade Name:	Rezdiffra tablets
Generic or Proper Name:	resmetirom
Sponsor:	Madrigal Pharmaceuticals, Inc.
Approval Date:	March 14, 2024
Indication:	In conjunction with diet and exercise, for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis).

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217785Orig1s000

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APPLICATION NUMBER:

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APPROVAL LETTER

NDA 217785

ACCELERATED APPROVAL

Madrigal Pharmaceuticals, Inc.
200 Barr Harbor Drive
Suite 200
West Conshohocken, PA 19428

Attention: Rebecca Taub, MD
Chief Medical Officer, President, Research & Development

Dear Dr. Taub:

Please refer to your new drug application (NDA) dated and received July 14, 2023, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Rezdiffra (resmetirom) tablets.

This NDA provides for the use of Rezdiffra (resmetirom) tablets, in conjunction with diet and exercise, for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis).

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved under accelerated approval pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FDCA) and 21 CFR 314.510, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the accelerated approval statutory provisions and regulations.

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 the Patient Package Insert). Information on submitting SPL

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

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.

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on March 12, 2024, 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 titled *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (April 2018, Revision 5)*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved NDA 217785**." 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 Rezdiffra (resmetirom) shall be 36 months for 60 mg, 80 mg, and 100 mg tablets packaged in 30-count bottles, 24 months for 80 mg and 100 mg tablets packaged in 90-count bottles, and 18 months for 80 mg and 100 mg tablets packaged in 7-count bottles from the date of manufacture when stored at 20°C to 25°C (68 °F to 77 °F.5 to 86 °F) See USP controlled Room Temperature.

ADVISORY COMMITTEE

Your application for Rezdiffra was not referred to an FDA advisory committee because there were no issues that warranted an advisory committee discussion.

ACCELERATED APPROVAL REQUIREMENTS

Pursuant to section 506(c) of the FDCA and 21 CFR 314.510 you are required to conduct an adequate and well-controlled clinical trial intended to verify and describe clinical benefit. You are required to conduct this clinical trial with due diligence. If the required postmarketing clinical trial fails to verify clinical benefit or is not conducted with due diligence, including with respect to the conditions set forth below, we may withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated March 13, 2024. This requirement is listed below.

[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.

4577-1 Complete Trial MGL-3196-11, a randomized, double-blind, placebo-controlled 54-month trial in patients with non-alcoholic steatohepatitis (NASH) and liver fibrosis to demonstrate clinical benefit on the composite endpoint of progression to cirrhosis, hepatic decompensation events, liver transplant, and mortality.

The timetable you submitted on March 13, 2024, states that you will conduct this trial according to the following schedule:

Trial Completion:	08/2028
Final Report Submission:	03/2029

Submit clinical protocols to your IND 122865 for this product. FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.

You must submit status reports of the progress of the clinical trial required under section 506(c) (listed above) to the NDA 180 days after the date of approval of this NDA and approximately every 180 days thereafter (see section 506B(a)(2) of the FDCA) (hereinafter "180-day reports").

You are required to submit two 180-day reports per year for each open study or clinical trial required under section 506(c). The initial report will be a standalone submission and the subsequent report will be combined with your application's annual status report (ASR) required under section 506B(a)(1) of the FDCA and 21 CFR 314.81(b)(2). The standalone 180-day report will be due 180 days after the date of approval (with a 60-day grace period). Submit the subsequent 180-day report with your application's ASR. Submit both of these 180-day reports each year until the final report for the corresponding study or clinical trial is submitted[3].

Your 180-day reports must include the information listed in 21 CFR 314.81(b)(2)(vii)(a) . FDA recommends that you use FORM FDA 3989, *PMR/PMC Annual Status Report for Drugs and Biologics,* to submit your 180-day reports.[4]

180-day reports must be clearly designated "**NDA 217785 180-Day AA PMR Progress Report**."

[3] You are required to submit information related to your confirmatory trial as part of your annual reporting requirement under section 506B(a)(1) until the FDA notifies you, in writing, that the Agency concurs that the study requirement has been fulfilled or that the study either is no longer feasible or would no longer provide useful information.
[4] FORM FDA 3989, along with instructions for completing this form, is available on the FDA Forms web page at https://www.fda.gov/about-fda/reports-manuals-forms/forms.

FDA will consider the submission of your application's ASR under section 506B(a)(1) and 21 CFR 314.81(b)(2), in addition to the submission of reports 180 days after the date of approval each year (subject to a 60-day grace period), to satisfy the periodic reporting requirement under section 506B(a)(2).

Submit final reports to this NDA as a supplemental application. For administrative purposes, the cover page of all submissions relating to this postmarketing requirement must be clearly designated "**Subpart H Postmarketing Requirement(s)**."

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 ages less than 6 years because necessary studies are impossible or highly impracticable. This is because the estimated number of patients with non-alcoholic fatty liver disease (NAFLD)/ non-alcoholic steatohepatitis (NASH) less than 6 years of age is predicted to be quite low, and those with NASH with liver fibrosis is even lower. Accrual of an adequate number of patients to reliably inform efficacy and safety of a drug may be difficult, thus making conduct of trials in children less than 6 years highly impractical.

We are deferring submission of your pediatric studies for ages 6 to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(4)(C) of the FDCA. These required studies are listed below.

4577-2 Conduct a study of the safety, pharmacokinetics, and efficacy of REZDIFFRA in post-pubertal pediatric patients ages 12 to 17 years with non-alcoholic steatohepatitis (NASH) with stage F2 and F3 fibrosis.

Draft Protocol Submission:	04/2025
Final Protocol Submission:	10/2025
Trial Completion:	01/2028
Final Report Submission:	08/2028

4577-3 Conduct a study of the safety, pharmacokinetics, and efficacy of REZDIFFRA in pre-pubertal pediatric patients ages 6 to 12 years with non-alcoholic steatohepatitis (NASH) with stage F2 and F3 fibrosis.

Draft Protocol Submission:	04/2027
Final Protocol Submission:	10/2027
Trial Completion:	07/2030
Final Report Submission:	02/2031

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[5]

Submit the protocol(s) to your IND 122865, with a cross-reference letter to this NDA. Reports of these required pediatric postmarketing studies must be submitted as an NDA or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify the following unexpected serious risks:

- of adverse maternal and fetal outcomes in women and their offspring exposed to resmetirom during pregnancy.
- of infant exposure to resmetirom via breast milk
- of the potential for higher drug exposure and resultant serious drug risks in patients with renal impairment

[5] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these unexpected serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4577-4 Conduct a worldwide descriptive study that collects prospective and retrospective data from women exposed to resmetirom during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes should be assessed through the first year of life. The minimum number of patients should be specified in the protocol.

The timetable you submitted on March 13, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	09/2024
Final Protocol Submission:	03/2025
Interim Report Submission:	06/2027
Study Completion:	03/2030
Final Report Submission:	09/2030

4577-5 Perform a lactation study (milk only) in lactating women who have received resmetirom to measure concentrations of resmetirom in breast milk using a validated assay and to assess any reported adverse effects on the breastfed infant.

The timetable you submitted on March 13, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	09/2024
Final Protocol Submission:	03/2025
Study Completion:	03/2027
Final Report Submission:	09/2027

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

The timetable you submitted on March 13, 2024, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	11/2023 (already submitted)
Study Completion:	01/2025
Final Report Submission:	06/2025

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[6]

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

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.

The timetable you submitted on March 13, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	07/2024
Final Protocol Submission:	09/2024
Study/Trial Completion:	03/2025
Final Report Submission:	07/2025

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

The timetable you submitted on March 13, 2024, states that you will conduct this study according to the following schedule:

[6] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Draft Protocol Submission:	04/2024
Final Protocol Submission:	06/2024
Study/Trial Completion:	12/2024
Final Report Submission:	04/2025

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

4577-9 Complete the environmental fate and ecotoxicity studies for resmetirom and submit a final environmental analysis report.

The timetable you submitted on March 13, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2025

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit clinical protocols to your IND 122865 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," **or** "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

Under 21 CFR 314.550, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 314.550, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial

publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

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*.[7]

REPORTING REQUIREMENTS

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

REQUESTED PHARMACOVIGILANCE

Hepatotoxicity

We request that for REZDIFFRA, you submit all serious and non-serious cases of hepatotoxicity as 15-day "Alert reports" (described under 21 CFR 314.80(c)(1)) through the third year following initial U.S. approval date.

We also request that you provide a separate narrative summary and analysis of hepatotoxicity, apart from your required analysis of 15-day "Alert reports," as part of your required periodic safety reports [e.g., periodic adverse drug experience report (PADER) required under 21 CFR 314.80(c)(2)], quarterly during the first 3 years post-approval. Your analysis should include interval and cumulative data relative to the date of approval of REZDIFFRA.

Your narrative summaries should provide the following information:

- indication
- REZDIFFRA dosage
- duration of therapy
- temporal association
- dechallenge/rechallenge
- associated signs and symptoms
- hepatic enzymes and liver function tests
- concomitant drugs [list all, including prescription and over-the-counter medications (indication, dosage), herbal, and illicit substances]
- medical history

[7] https://www.fda.gov/media/128163/download.

- hospitalizations, testing (including imaging), and treatment given for the event
- outcome at the time of the report
- assessment of causality

To identify reports of hepatotoxicity, we request that you use the Standardised MedDRA Query (SMQ) *Drug related hepatic disorders – comprehensive search (SMQ) Broad search*.

Exposure during pregnancy/lactation

Through the second year following initial U.S. approval, we request that you provide a separate narrative summary and analysis of reports of confirmed or possible exposure to REZDIFFRA in pregnant patients, patients who are lactating, and infants exposed to REZDIFFRA *in utero* or through breastmilk, apart from your required analysis of 15-day "Alert reports," as part of your required periodic safety reports [e.g., periodic adverse drug experience report (PADER) required under 21 CFR 314.80(c)(2)], quarterly during the first 2 years post-approval. Your analysis should include interval and cumulative data relative to the date of approval of REZDIFFRA.

Your narrative summaries should provide the following information:

- manufacturer control number
- age of pregnant or lactating patient
- gestational age (weeks) and trimester(s) of exposure of fetus
- concurrent and past medical/surgical history, pregnancy history, and smoking status of pregnant or lactating patient
- concomitant drugs [list all, including prescription and over-the-counter medications (indication, dosage), herbal, and illicit substances
- REZDIFFRA indication and dosage; duration of exposure for the pregnant or lactating patient, fetus, or infant
- action taken with REZDIFFRA including dechallenge/rechallenge
- pregnancy outcome and outcomes for the pregnant or lactating patient
- infant outcomes through the first year of life

Furthermore, provide the total number of reports of confirmed or possible REZDIFFRA exposure during pregnancy or lactation that had no adverse pregnancy, fetal, or infant outcome; that had an unknown outcome; and that had an adverse pregnancy, fetal, or infant outcome.

POST APPROVAL FEEDBACK MEETING

New molecular entities qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to

learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

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[8].

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}

Nikolay Nikolov, MD
Director
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
- Carton and Container Labeling

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

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/

NIKOLAY P NIKOLOV
03/14/2024 02:55:25 PM