# PDL DRUG REVIEW

## Proprietary Name: Rezdiffra®
## Common Name: resmetirom
## PDL Category: Endocrine Metabolic Agents

**Pharmacology/Usage:** Resmetirom, the active ingredient of Rezdiffra®, is a thyroid hormone receptor-beta agonist. It is a partial agonist of the thyroid hormone receptor-beta (THR-β). Resmetirom produced 83.8% of the maximum response compared to triiodothyronine (T3). THR-β is the major form of THR in the liver, and stimulation of THR-β in the liver reduces intrahepatic triglycerides, whereas actions of thyroid hormone outside the liver, including in heart and bone, are largely mediated through THR-α.

**Indication:** In conjunction with diet and exercise for the treatment of adults with non-cirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis). This indication is approved under accelerated approval based on improvement of NASH and fibrosis. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. Limitations of use include to avoid use of Rezdiffra® in patients with decompensated cirrhosis.

There is no pregnancy category for this medication; however, the risk summary indicates that there are no available data on use in pregnant women to assess for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. There are risks to the mother and fetus related to underlying NASH with liver fibrosis. Report pregnancies to Madrigal Pharmaceuticals Adverse Event reporting line at 1-800-905-0324 and online at https://www.madrigalpharma.com/contact. The safety and efficacy of use in the pediatric population have not been established.

**Dosage Form:** Film-Coated Tablets: 60mg, 80mg, 100mg.

**Recommended Dosage:** The recommended dosage is based on actual body weight. For patients weighing:

- <100kg, the recommended dosage is 80mg PO QD.
- ≥100kg, the recommended dosage is 100mg PO QD.

Administer Rezdiffra® with or without food.

The recommended dosage in patients with mild or moderate renal impairment is the same as in patients with normal kidney function. Rezdiffra® has not been studied in patients with severe renal impairment. Dosage adjustments are not recommended for patients with mild hepatic impairment. Avoid use of Rezdiffra® in patients with decompensated cirrhosis (consistent with moderate to severe hepatic impairment). Moderate or severe hepatic impairment (Child-Pugh Class B or C) increases resmetirom Cmax and AUC, which may increase the risk of adverse reactions. The safety and efficacy of Rezdiffra® have not been established in patients with NASH cirrhosis.

**Drug Interactions:** Resmetirom is a CYP2C8 substrate. Concomitant use of Rezdiffra® with strong CYP2C8 inhibitors (e.g., gemfibrozil) is not recommended. Reduce Rezdiffra® dosage if used concomitantly with a moderate CYP2C8 inhibitor (e.g., clopidogrel). If Rezdiffra® is used concomitantly with a moderate CYP2C8 inhibitor (e.g., clopidogrel), reduce the dosage of Rezdiffra®:

- <100kg, reduce the dosage of Rezdiffra® to 60mg QD.
- ≥100kg, reduce the dosage of Rezdiffra® to 80mg QD.

Resmetirom is an OATP1B1 and OATP1B3 substrate. Concomitant use of Rezdiffra® with OATP1B1 or OATP1B3 inhibitors (e.g., cyclosporine) is not recommended.

Rezdiffra® increased plasma concentrations of some statins (atorvastatin, pravastatin, rosuvastatin, and simvastatin). Limit the daily statin dosage to 20mg for rosuvastatin and simvastatin if use concomitantly with Rezdiffra®. Limit the daily statin dosage to 40mg for pravastatin and atorvastatin if use concomitantly with Rezdiffra®.

Resmetirom is a weak CYP2C8 inhibitor. Monitor patients more frequently for substrate-related adverse reactions if Rezdiffra® is co-administered with CYP2C8 substrates where minimal concentration changes may lead to serious adverse reactions.

**Box Warning:** There is no box warning listed with this product.

**Common Adverse Drug Reactions:** *Listed % incidence for adverse drug reactions= reported % incidence for drug (Rezdiffra® 80mg) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included diarrhea (9%), nausea (9%), pruritus (2%), vomiting (3%), constipation (1%), abdominal pain (1%), and dizziness (3%).

*Listed % incidence for adverse drug reactions= reported % incidence for drug (Rezdiffra® 100mg) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included diarrhea (19%), nausea (6%), pruritus (6%), vomiting (4%), constipation (4%), abdominal pain (3%), and dizziness (3%).

Hepatotoxicity has been observed with Rezdiffra® use. Monitor patients during treatment for elevations in liver tests and for the development of liver-related adverse reactions. Monitor for symptoms and sings of hepatotoxicity. If hepatotoxicity is suspected, discontinue Rezdiffra® and continue to monitor the patient. If laboratory values return to baseline, weigh the potential risks against the benefits of restarting Rezdiffra®. If laboratory values do not return to baseline, consider drug-induced autoimmune-like hepatitis (DI-ALH) or autoimmune liver disease in the evaluation of elevations in liver tests.

In clinical studies, cholelithiasis, acute cholecystitis, and obstructive pancreatitis (gallstones) were observed more often in Rezdiffra®-treated patients than in placebo-treated patients. If cholelithiasis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated. If an acute gallbladder event is suspected, interrupt Rezdiffra® until the event is resolved.

**Contraindications:** There are no contraindications listed with this product.

**Manufacturer:** Madrigal Pharmaceuticals, Inc.

**Analysis:** The efficacy of Rezdiffra® was assessed based on an efficacy analysis at month 12 in Trial 1, a 54- month, randomized, double-blind, placebo-controlled trial. Enrolled patients had metabolic risk factors and a baseline or recent liver biopsy showing NASH with fibrosis stage 2 or 3 and a NAFLD Activity Score (NAS) of at least 4. Efficacy was based on the effect of Rezdiffra® on resolution of steatohepatitis without worsening of fibrosis and one stage improvement in fibrosis without worsening of steatohepatitis, on post-baseline liver biopsies collected at 12 months.

The month 12 analysis included F2 and F3 (at eligibility) patients (N=888) randomized to receive placebo (N=294), Rezdiffra® 80mg QD (N=298), or Rezdiffra® 100mg (N=296), in addition to lifestyle counseling on nutrition and exercise. Patients were on stable doses of medications for diabetes, dyslipidemia, and hypertension.

Baseline characteristics were balanced between treatment and placebo groups. Overall, the median age of patients at baseline was 58 years (51 to 65), while 56% were female, 89% were white, the median body mass index (BMI) was 35kg/$m^2$, and the median body weight was 99kg. Furthermore, 68% had type 2 DM, 79% had hypertension, 71% had dyslipidemia, 49% were on statins, and 14% were thyroxine users.

The table below, adapted from the prescribing information, presents the month 12 histopathology results comparing Rezdiffra® with placebo on:

- The percentage of patients with resolution of steatohepatitis and no worsening of liver fibrosis.
- The percentage of patients with at least one stage improvement in liver fibrosis and no worsening of steatohepatitis.

Two pathologists, Pathologist A and Pathologist B, independently read the liver biopsies for each patient. Both the 80mg QD and the 100mg QD dosages of Rezdiffra® demonstrated improvement on these histopathology endpoints at month 12 compared to placebo. In a statistical analysis incorporating both pathologists' independent readings, Rezdiffra® achieved statistical significance on both histopathology endpoints for both doses. Note that examination of age, gender, diabetes status, and fibrosis stage (F2 or F3) subgroups did not identify differences in response to Rezdiffra® among these subgroups. Most patients in the trial were white (89%); there were too few patients of other races to adequately assess differences in response by race.

| | Placebo (N=294) | Rezdiffra® 80mg (N=298) | Rezdiffra® 100mg (N=296) |
|---|---|---|---|
| Resolution of steatohepatitis and no worsening of liver fibrosis | | | |
| Response rate, Pathologist A (%) | 13 | 27 | 36 |
| Difference in response rate vs placebo | | 14 | 23 |
| Response rate, Pathologist B (%) | 9 | 26 | 24 |
| Difference in response rate vs placebo | | 17 | 15 |
| Improvement in liver fibrosis and no worsening of steatohepatitis | | | |
| Response rate, Pathologist A (%) | 15 | 23 | 28 |
| Difference in response rate vs placebo | | 8 | 13 |
| Response rate, Pathologist B (%) | 13 | 23 | 24 |
| Difference in response rate vs placebo | | 11 | 11 |

Starting at month 3 and through month 12, there was a trend of greater reductions from baseline in average ALT and AST in the Rezdiffra® groups as compared to placebo group.

**Place in Therapy:** Rezdiffra® is a thyroid hormone receptor-beta (THR-beta) agonist indicated 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). This indication is approved under accelerated approval based on improvement of NASH and fibrosis. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. A limitation of use includes to avoid use of Rezdiffra® in patients with decompensated cirrhosis. Its efficacy was assessed based on an efficacy analysis at month 12 in a 54-month, randomized, double-blind, placebo-controlled trial.

The month 12 histopathology results comparing Rezdiffra® with placebo included the percentage of patients with resolution of steatohepatitis and no worsening of liver fibrosis, as well as the percentage of patients with at least one stage improvement in liver fibrosis and no worsening of steatohepatitis. Two pathologists, Pathologist A and Pathologist B, independently read the liver biopsies for each patient. Results suggested that both the 80mg and 100mg dosages of Rezdiffra® demonstrated improvement on

these histopathology endpoints at month 12 compared to placebo. Furthermore, in a statistical analysis incorporating both pathologists' independent readings, Rezdiffra® achieved statistical significance on both histopathology endpoints for both doses. Rezdiffra® is the first FDA approved, once-daily treatment for adults with NASH with liver fibrosis.

## Summary

It is recommended that Rezdiffra® should be non-preferred in order to confirm the appropriate diagnosis and clinical parameters for use.

**PDL Placement:** ☐ **Preferred**
☒ **Non-Preferred**

## References

[1] Rezdiffra [package insert]. West Conshohocken, PA: Madrigal Pharmaceuticals; 2024.