NOW APPROVED

Rezdiffra™

resmetirom tablets

60 mg · 80 mg · 100 mg

In conjunction with diet and exercise

The first and only FDA-approved treatment for adults with noncirrhotic NASH with moderate to advanced 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.

NASH=nonalcoholic steatohepatitis.

INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATION

Rezdiffra is 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.

Limitation of Use: Avoid use in patients with decompensated cirrhosis.

WARNINGS AND PRECAUTIONS

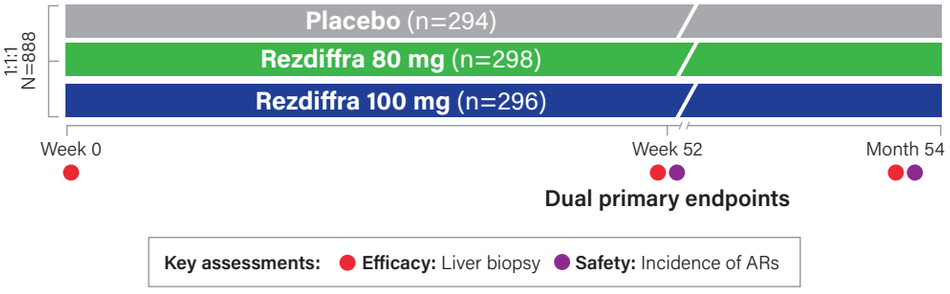
Hepatotoxicity

Hepatotoxicity has been observed in one patient. *Please see full Prescribing Information for more details on this specific case of Hepatotoxicity [see Warnings and Precautions (5.1)].*

Please see additional Important Safety Information throughout and accompanying full Prescribing Information for Rezdiffra or visit www.madrigalpharma.com/Rezdiffra-USPI.

The efficacy and safety of Rezdiffra were evaluated in Trial 1 (MAESTRO-NASH; N=888)

MAESTRO-NASH is an ongoing Phase 3, randomized, double-blind, placebo-controlled trial. Efficacy and safety were evaluated in 888 adults with biopsy-confirmed NASH with liver fibrosis stages F2 and F3 (at eligibility).



Week 52 dual primary endpoints

- **NASH Resolution:** resolution of steatohepatitis (score of 0-1 for inflammation, 0 for ballooning, and any value for steatosis) and no worsening of liver fibrosis.
- **Fibrosis Improvement:** ≥1-stage improvement in fibrosis without worsening of steatohepatitis (defined as no increase in score for ballooning, inflammation, or steatosis). Liver fibrosis was evaluated on the NASH Clinical Research Network (CRN) fibrosis score as 0 to 4.

Safety

- Incidence of adverse reactions

Key inclusion criteria:

- Presence of metabolic risk factors
- NAFLD Activity Score (NAS) ≥4
- Fibrosis stage: F2 or F3

Stratification

- Patients were stratified based on baseline type 2 diabetes status (present/absent) and fibrosis stage (F2 or F3)

Key exclusion criteria:

- Moderate to severe hepatic impairment (Child-Pugh B or C)
- Cirrhosis
- Liver decompensation

AR=adverse reaction; BMI=body mass index; CAP=controlled attenuation parameter; dB/m=decibels per meter; ELF=enhanced liver fibrosis; FIB-4=Fibrosis-4; kPa=kilopascal; NAFLD=nonalcoholic fatty liver disease; NASH=nonalcoholic steatohepatitis; Q=quartile; VCTE=vibration-controlled transient elastography.

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Baseline patient characteristics in MAESTRO-NASH

Demographics and comorbidities	Overall (N=888)
Age, years, median (Q1, Q3)	58 (51, 65)
Female, %	56
Hispanic, %	21
White, %	89
Asian, %	3
Black or African American, %	2
BMI, kg/m^2, median (Q1, Q3)	35 (31, 40)
Body weight, kg, median (Q1, Q3)	99 (85, 114)
Type 2 diabetes, n (%)	608 (68)
Hypertension, n (%)	700 (79)
Dyslipidemia, n (%)	633 (71)
Statin use, n (%)	434 (49)
Thyroxine use, n (%)	124 (14)

- Patients were on stable doses of medications for diabetes, dyslipidemia, and hypertension

Assessment of baseline disease severity			Overall (N=888)
Liver Biopsy	Fibrosis stage, n (%)	F2	328 (37)
		F3	560 (63)
Other Assessments	VCTE, kPa, median (Q1, Q3)*		12 (10, 15)
	CAP, dB/m, median (Q1, Q3)*		349 (320, 378)
	FIB-4, median (Q1, Q3)*		1.3 (1.0, 1.8)
	ELF, median (Q1, Q3)*		9.7 (9.2, 10.4)

*Less than 5% missingness in these variables is omitted.

IMPORTANT SAFETY INFORMATION (cont.)
WARNINGS AND PRECAUTIONS (cont.)
Hepatotoxicity (cont.)

Monitor patients during treatment for elevations in liver tests and for the development of liver-related adverse reactions. Monitor for symptoms and signs of hepatotoxicity (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash, and/or eosinophilia [>5%]). 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 DI-ALH or autoimmune liver disease in the evaluation of elevations in liver tests.

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Rezdiffra achieved statistically significant results for NASH resolution at Week 52

Dual primary endpoint results

Resolution of steatohepatitis and no worsening of liver fibrosis

	Placebo (n=294)	Rezdiffra 80 mg (n=298)	Rezdiffra 100 mg (n=296)
Response rate, Pathologist A (%)	**13**	**27**	**36**
Difference in response rate vs placebo (95% CI)		14 (8, 20)	23 (16, 30)
Response rate, Pathologist B (%)	**9**	**26**	**24**
Difference in response rate vs placebo (95% CI)		17 (11, 23)	15 (9, 21)

- Rezdiffra achieved statistical significance on both histopathology endpoints for both doses in a statistical analysis incorporating both pathologists' independent readings
- There were no differences in response to Rezdiffra based on age, gender, type 2 diabetes status (yes or no), or fibrosis stage (F2 or F3)

ALT=alanine transaminase; AST=aspartate transferase; NASH=nonalcoholic steatohepatitis.

IMPORTANT SAFETY INFORMATION (cont.)
WARNINGS AND PRECAUTIONS (cont.)

Gallbladder-Related Adverse Reactions

In clinical trials, cholelithiasis, acute cholecystitis, and obstructive pancreatitis (gallstone) 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 treatment until the event is resolved.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information for Rezdiffra or visit www.madrigalpharma.com/Rezdiffra-USPI.

Rezdiffra achieved statistically significant results for fibrosis improvement at Week 52

Dual primary endpoint results

Improvement in liver fibrosis and no worsening of steatohepatitis

	Placebo (n=294)	Rezdiffra 80 mg (n=298)	Rezdiffra 100 mg (n=296)
Response rate, Pathologist A (%)	**15**	**23**	**28**
Difference in response rate vs placebo (95% CI)		8 (2, 14)	13 (7, 20)
Response rate, Pathologist B (%)	**13**	**23**	**24**
Difference in response rate vs placebo (95% CI)		11 (5, 17)	11 (5, 17)

Liver enzymes: 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 the placebo group.

IMPORTANT SAFETY INFORMATION (cont.)
WARNINGS AND PRECAUTIONS (cont.)

Drug Interaction with Certain Statins

Dosage adjustment for certain statins is recommended. Monitor for statin-related adverse reactions including but not limited to elevation of liver tests, myopathy, and rhabdomyolysis. *Please see the upcoming* Drug Interaction *section of the Important Safety Information for more details.*

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Safety profile of Rezdiffra

EAIR of Common Adverse Reactions Reported in ≥5% of Patients in MAESTRO-NASH[*,†,‡]

Adverse Reaction	Placebo (n=294) n (EAIR[§])	Rezdiffra 80 mg (n=298) n (EAIR[§])	Rezdiffra 100 mg (n=296) n (EAIR[§])
Diarrhea	52 (14)	78 (23)	98 (33)
Nausea	36 (9)	65 (18)	51 (15)
Pruritus	18 (4)	24 (6)	36 (10)
Vomiting	15 (4)	27 (7)	30 (8)
Constipation	18 (4)	20 (5)	28 (8)
Abdominal pain	18 (4)	22 (5)	27 (7)
Dizziness	6 (1)	17 (4)	17 (4)

Adverse reactions leading to discontinuation

- Placebo: 4 per 100 PY vs Rezdiffra: 80 mg, 5 per 100 PY, and 100 mg, 8 per 100 PY
  - Diarrhea and nausea were the most common causes of treatment discontinuation

Gastrointestinal adverse reactions

- Diarrhea and nausea typically began early in treatment initiation and were mild to moderate in severity
  - Median time (Q1, Q3) to a diarrheal event: placebo: 39 (2, 195) days; Rezdiffra 80 mg: 17 (3, 70) days; and Rezdiffra 100 mg: 6 (2, 54) days
  - Median duration of diarrhea: 9 days in the placebo arm, and 20 days in both the Rezdiffra 80 mg and 100 mg arms
  - Median time (Q1, Q3) to a nausea event: placebo: 85 (24, 347) days; Rezdiffra 80 mg: 28 (2, 162) days; and Rezdiffra 100 mg: 5 (2, 40) days
  - Median duration of nausea: 17 days in the placebo arm, 26 days in the Rezdiffra 80 mg arm, and 28 days in the Rezdiffra 100 mg arm
- Vomiting and abdominal pain were mild to moderate in severity

*Population includes adult patients with noncirrhotic NASH with liver fibrosis (stages F2 and F3 at eligibility).

† Median exposure duration was 68 weeks for placebo, 74 weeks for Rezdiffra 80 mg once daily, and 66 weeks for Rezdiffra 100 mg once daily.

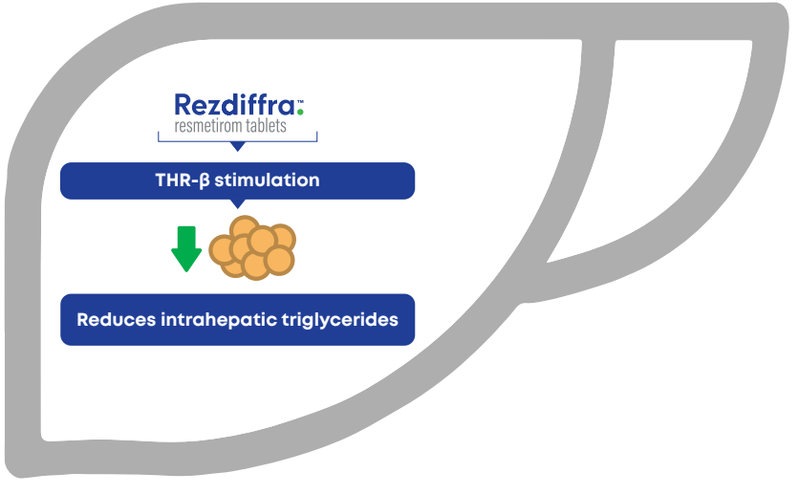
‡ EAIRs are per 100 PY where total PYs were 435, 435, and 407 for placebo, 80 mg once daily, and 100 mg once daily arms, respectively.

§ The EAIR per 100 PY can be interpreted as an estimated number of first occurrences of the adverse reaction of interest if 100 patients are treated for 1 year.

EAIR=exposure-adjusted incidence rate; EC_{50}=half maximal effective concentration; NASH=nonalcoholic steatohepatitis; PY=person-years; THR-α=thyroid hormone receptor alpha; Q=quartile.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information for Rezdiffra or visit www.madrigalpharma.com/Rezdiffra-USPI.

Rezdiffra is a first-in-class thyroid hormone receptor beta (THR-β) agonist that works directly in the liver



- Rezdiffra is a partial agonist of THR-β,¶ which is the major form of THR in the liver
- Stimulation of THR-β in the liver reduces intrahepatic triglycerides
- Actions of thyroid hormone outside the liver (including the heart and bones) are largely mediated through THR-α

¶Rezdiffra produced 83.8% of the maximum response compared to triiodothyronine (T3), with an EC_{50} of 0.21 µM in an in vitro functional assay for THR-β activation.

IMPORTANT SAFETY INFORMATION (cont.)

ADVERSE REACTIONS

The most common adverse reactions with Rezdiffra (reported in ≥ 5% of patients and higher compared to placebo) are: diarrhea, nausea, pruritus, vomiting, constipation, abdominal pain, and dizziness. Diarrhea and nausea were the most common causes of treatment discontinuation.

Hypersensitivity Reactions

Reactions such as urticaria and rash, which may reflect drug hypersensitivity, were observed in patients receiving Rezdiffra.

Laboratory Abnormalities

Increases in mean ALT and AST levels were observed in the first 4 weeks after initiating treatment with Rezdiffra. The mean elevation in ALT and AST values was less than 1.5 times baseline at 4 weeks after treatment initiation. These values returned to baseline around 8 weeks after initiating treatment.

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Rezdiffra is an oral, once-daily tablet that can be taken with or without food

Tablet is not actual size.

Recommended dosage and administration

Dosage	Rezdiffra 80 mg	Rezdiffra 100 mg
	One tablet QD	One tablet QD
Weight	<100 kg (220 lbs)	≥100 kg (220 lbs)

Drug Interactions

- Concomitant use of Rezdiffra with strong CYP2C8 inhibitors (eg, gemfibrozil) is not recommended
- For concomitant use with moderate CYP2C8 inhibitors (eg, clopidogrel), reduce the dose of Rezdiffra:
  - 60 mg if <100 kg (220 lbs) and 80 mg if ≥100 kg (220 lbs)
- Concomitant use of Rezdiffra with OATP1B1 or OATP1B3 inhibitors (eg, cyclosporin) is not recommended
- Rezdiffra increased plasma concentration of some statins. Limit the daily dosage of: rosuvastatin and simvastatin to 20 mg; pravastatin and atorvastatin to 40 mg
- 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

CYP2C8=cytochrome P450 2C8; EC_{50}=half maximal effective concentration; OATP1B1=organic anion transporting polypeptide 1B1; OATP1B3=organic anion transporting polypeptide 1B3; QD=once daily.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information for Rezdiffra or visit www.madrigalpharma.com/Rezdiffra-USPI.

IMPORTANT SAFETY INFORMATION (cont.)

DRUG INTERACTIONS

Clinically Significant Interactions Affecting Rezdiffra

- **Strong or Moderate CYP2C8 Inhibitors:** Resmetirom is a CYP2C8 substrate. Concomitant use with strong CYP2C8 inhibitors (e.g., gemfibrozil) is not recommended. Reduce dosage if used concomitantly with a moderate CYP2C8 inhibitor (e.g., clopidogrel).
- **Organic Anion-Transporting Polypeptides (OATP) 1B1 and OATP1B3 Inhibitors:** Resmetirom is an OATP1B1 and OATP1B3 substrate. Concomitant use with OATP1B1 or OATP1B3 inhibitors (e.g., cyclosporine) is not recommended.

Clinically Significant Interactions Affecting Other Drugs

- **Statins**
  - Limit daily rosuvastatin and simvastatin dosage to 20 mg
  - Limit daily pravastatin and atorvastatin dosage to 40 mg
- **CYP2C8 Substrates:** 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.

USE IN SPECIFIC POPULATIONS

Pregnancy

There are no available data on Rezdiffra use in pregnant women to evaluate 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, such as increased risks of gestational diabetes, hypertensive complications, preterm birth, and postpartum hemorrhage. Report pregnancies to Madrigal Pharmaceuticals, Inc.'s Adverse Event reporting line at 1-800-905-0324 and https://www.madrigalpharma.com/contact/.

Lactation

There is no information regarding the presence of Rezdiffra in human or animal milk, the effects on the breast-fed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Rezdiffra and any potential adverse effects on the breastfed infant from Rezdiffra or from the underlying maternal condition.

Pediatric Use

The safety and effectiveness have not been established in pediatric patients.

Geriatric Use

No overall differences in effectiveness but numerically higher incidence of adverse reactions have been observed in patients ≥65 years of age compared to younger adult patients.

Renal Impairment

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.

Hepatic Impairment

Avoid use 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 C_{max} and AUC, which may increase the risk of adverse reactions.

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The first and only FDA-approved treatment for adults with noncirrhotic NASH with moderate to advanced fibrosis

Rezdiffra achieved statistically significant results in both:

✓ **NASH resolution** ✓ **Fibrosis improvement**

Most common adverse reactions (≥5% of patients compared to placebo) were diarrhea, nausea, pruritus, vomiting, constipation, abdominal pain, and dizziness.

Additional key points when considering Rezdiffra for your patients:

- First-in-class THR-β agonist that works directly in the liver
- Oral, once-daily dosing
- Madrigal Patient Support is here to help you and your patients start on Rezdiffra

Visit **RezdiffraHCP.com** to learn more and get patients started

NASH=nonalcoholic steatohepatitis; THR-β=thyroid hormone receptor beta.

IMPORTANT SAFETY INFORMATION (cont.)
USE IN SPECIFIC POPULATIONS (cont.)
Hepatic Impairment (cont.)

No dosage adjustment is recommended for patients with mild hepatic impairment (Child-Pugh Class A). The safety and effectiveness have not been established in patients with NASH cirrhosis.

Please see accompanying full Prescribing Information for Rezdiffra or visit www.madrigalpharma.com/Rezdiffra-USPI.

Madrigal Pharmaceuticals