FIRST AND ONLY

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 MASH with moderate to advanced fibrosis

This indication is approved under accelerated approval based on improvement of MASH 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.[1]

MASH=metabolic dysfunction-associated steatohepatitis.

INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATION

Rezdiffra is indicated in conjunction with diet and exercise for the treatment of adults with noncirrhotic metabolic dysfunction-associated steatohepatitis (MASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis).

This indication is approved under accelerated approval based on improvement of MASH 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

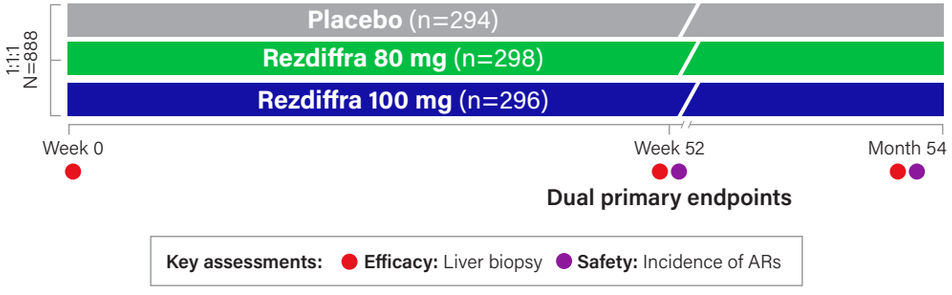
Hepatotoxicity

Hepatotoxicity has been observed with the use of Rezdiffra. One patient developed substantial elevations of liver biochemistries that resolved when treatment was interrupted. *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 at www.madrigalpharma.com/Rezdiffra-USPI.

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

MAESTRO-NASH is an ongoing Phase 3, randomized, double-blind, placebo-controlled trial. Efficacy and safety were evaluated in 888 adults with biopsy-confirmed MASH with liver fibrosis stages F2 and F3 (at eligibility).[1]



Week 52 dual primary endpoints[1]

- **Steatohepatitis resolution:** Resolution of steatohepatitis (score of 0-1 for inflammation, 0 for ballooning, and any value for steatosis) with no worsening of liver fibrosis
- **Fibrosis improvement:** ≥1-stage improvement in fibrosis with no 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.

Key inclusion criteria[1]:

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

Key exclusion criteria[1]:

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

Stratification[1]

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

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; MASH=metabolic dysfunction-associated steatohepatitis; NAFLD=nonalcoholic fatty liver disease; NASH=nonalcoholic steatohepatitis; Q=quartile; VCTE=vibration-controlled transient elastography.

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

Baseline patient characteristics in MAESTRO-NASH[1]

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[1]

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.[1]

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

Monitor for elevations in liver tests, liver-related adverse reactions, and symptoms/signs of hepatotoxicity (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash, and/or eosinophilia [>5%]). If hepatotoxicity is suspected, discontinue Rezdiffra and monitor. 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.

Rezdiffra™
resmetirom tablets
60 mg · 80 mg · 100 mg

Rezdiffra achieved statistically significant results for steatohepatitis resolution at Week 52[1]

Dual primary endpoint results

Steatohepatitis resolution with no worsening of fibrosis[1]

	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[1]
- 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)[1]

ALT=alanine transaminase; AST=aspartate transferase; CI=confidence interval.

IMPORTANT SAFETY INFORMATION (cont.)
WARNINGS AND PRECAUTIONS (cont.)
Gallbladder-Related Adverse Reactions

Cholelithiasis, acute cholecystitis, and obstructive pancreatitis (gallstone) were observed more often in Rezdiffra-treated patients than in placebo-treated patients. The exposure-adjusted incidence rates (EAIRs) for these events were less than 1 per 100 person-years (PY) for all treatment arms. If cholelithiasis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated. If an acute gallbladder event is suspected, interrupt treatment until the event is resolved.

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

Rezdiffra achieved statistically significant results for fibrosis improvement at Week 52[1]

Dual primary endpoint results

Fibrosis improvement with no worsening of steatohepatitis[1]

	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.[1]

IMPORTANT SAFETY INFORMATION (cont.)
WARNINGS AND PRECAUTIONS (cont.)
Drug Interaction with Certain Statins

An increase in exposure of atorvastatin, pravastatin, rosuvastatin and simvastatin was observed when concomitantly administered with Rezdiffra, which may increase the risk of adverse reactions related to these drugs.

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 Interactions *section of the Important Safety Information for more details.*

Rezdiffra™
resmetirom tablets
60 mg · 80 mg · 100 mg

Safety profile of Rezdiffra[1]

EAIR of common adverse reactions reported in ≥5% of patients in MAESTRO-NASH[1,*,†,‡]

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[1]

- 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[1]

- 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 MASH with liver fibrosis (stages F2 and F3 at eligibility).[1]

† 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.[1]

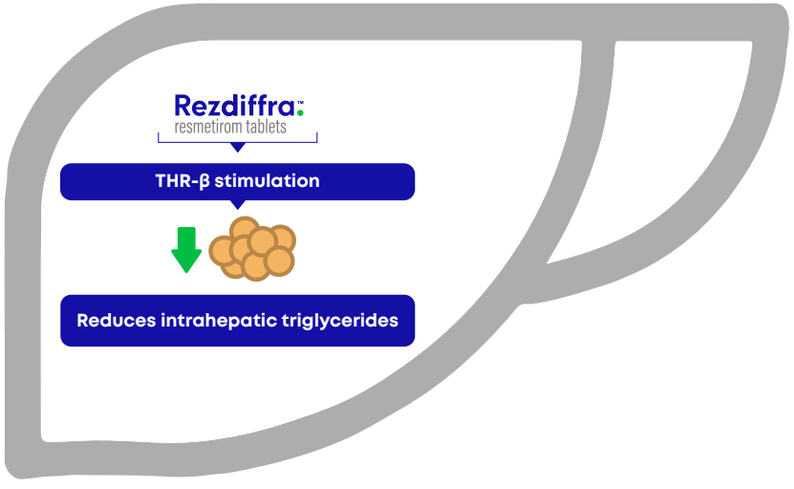
‡ EAIRs are per 100 PY where total PYs were 435, 435, and 407 for placebo, 80 mg once daily, and 100 mg once daily arms, respectively.[1]

§ 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.[1]

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

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

Rezdiffra is a first-in-class treatment that works directly in the liver by stimulating THR-β[1]



- Rezdiffra is a partial agonist of THR-β,[¶] which is the major form of THR in the liver[1]
- Stimulation of THR-β in the liver reduces intrahepatic triglycerides[1]
- Actions of thyroid hormone outside the liver (including the heart and bones) are largely mediated through THR-α[1]

[¶]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.[1]

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.

Rezdiffra™
resmetirom tablets
60mg · 80mg · 100mg

Rezdiffra is an oral, once-daily tablet that can be taken with or without food[1]

Tablet is not actual size.

Recommended dosage and administration[1]

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

IMPORTANT SAFETY INFORMATION (cont.)
DRUG INTERACTIONS
Clinically Significant Interactions Affecting Rezdiffra

- Concomitant use with strong CYP2C8 inhibitors (eg, gemfibrozil) is not recommended. Reduce dosage if used concomitantly with a moderate CYP2C8 inhibitor (eg, clopidogrel).
- Concomitant use with OATP1B1 or OATP1B3 inhibitors (eg, cyclosporine) is not recommended.

Clinically Significant Interactions Affecting Other Drugs

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

IMPORTANT SAFETY INFORMATION (cont.)
USE IN SPECIFIC POPULATIONS
Pregnancy

There are no available data on Rezdiffra use in pregnant women. 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.

Geriatric Use

Numerically higher incidence of adverse reactions have been observed in patients ≥65 years of age compared to younger adult patients.

Renal Impairment

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) may increase the risk of adverse reactions.

QD=once daily.

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

Rezdiffra™
resmetirom tablets
60mg · 80mg · 100mg

FIRST AND ONLY

Rezdiffra™
resmetirom tablets
60 mg · 80 mg · 100 mg

The first and only FDA-approved treatment for adults with noncirrhotic MASH with moderate to advanced fibrosis[1]

Rezdiffra achieved statistically significant results in both:

Steatohepatitis resolution[1] **Fibrosis improvement[1]**

The most common adverse reactions (≥5% of patients compared to placebo) were diarrhea, nausea, pruritus, vomiting, constipation, abdominal pain, and dizziness.[1]

Additional key points when considering Rezdiffra for your patients:

- First-in-class treatment that works directly in the liver by stimulating THR-β[1]
- Oral, once-daily dosing[1]
- Madrigal Patient Support is here for you and your patients at every step

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

MASH=metabolic dysfunction-associated steatohepatitis; THR-β=thyroid hormone receptor beta.

Reference: 1. Rezdiffra. Prescribing Information. Madrigal Pharmaceuticals, Inc.

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

The safety and effectiveness have not been established in patients with cirrhosis.

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

Madrigal