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Wolters Kluwer

Resmetirom

General

Pronunciation

(RES me TIR om)

Brand Names: U.S.

Rezdiffra

Indications

Use: Labeled Indications

Noncirrhotic metabolic dysfunction–associated steatotic liver disease: Treatment of noncirrhotic metabolic dysfunction–associated steatotic liver disease (formerly termed nonalcoholic steatohepatitis) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis), in conjunction with diet and exercise, in adults.

Limitations of use: Avoid use in patients with decompensated cirrhosis.

Contraindications

There are no contraindications listed in the manufacturer's labeling.

Dosing and Administration

Dosing: Adult

Noncirrhotic metabolic dysfunction–associated steatotic liver disease
Noncirrhotic metabolic dysfunction–associated steatotic liver disease:

<100 kg (actual body weight): **Oral:** 80 mg once daily.

Privacy - Terms

≥100 kg (actual body weight): **Oral:** 100 mg once daily.

Dosage adjustment for concomitant therapy: Significant drug interactions exist, requiring dose/frequency adjustment or avoidance. Consult drug interactions database for more information.

Dosing: Older Adult

Refer to adult dosing.

Administration

Oral: Administer with or without food.

Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Dosage Forms/Strengths

Dosage Forms

Excipient information presented when available (limited, particularly for generics); consult specific product labeling.

Tablet, Oral:

Rezdiffra: 60 mg, 80 mg, 100 mg

Drug Interactions

Alpelisib: BCRP/ABCG2 Inhibitors may increase the serum concentration of Alpelisib. Management: Avoid coadministration of BCRP/ABCG2 inhibitors and alpelisib due to the potential for increased alpelisib concentrations and toxicities. If coadministration cannot be avoided, closely monitor for increased alpelisib adverse reactions. *Consider therapy modification*

Asciminib: May increase the serum concentration of OATP1B1/1B3 (SLCO1B1/1B3) Substrates (Clinically Relevant with Inhibitors). *Monitor therapy*

Atogepant: OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors may increase the serum concentration of Atogepant. Management: For episodic migraine, the recommended atogepant dose is 10 mg or 30 mg once daily if given with OATP1B1/1B3 inhibitors. For chronic migraine, the recommended atogepant dose is 30 mg once daily with OATP1B1/1B3 inhibitors. *Consider therapy modification*

Atorvastatin: Resmetirom may increase the serum concentration of Atorvastatin. Management: Do not exceed atorvastatin doses of 40 mg daily during coadministration with resmetirom. Monitor for increased atorvastatin adverse effects (eg, myalgias) during coadministration. *Consider therapy modification*

Brincidofovir: OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors may increase the serum concentration of Brincidofovir. Management: Consider alternatives to OATP1B/1B3 inhibitors in patients treated with brincidofovir. If coadministration is required, administer OATP1B1/1B3 inhibitors at least 3 hours after brincidofovir and increase monitoring for brincidofovir adverse reactions. *Consider therapy modification*

Bulevirtide: May increase the serum concentration of OATP1B1/1B3 (SLCO1B1/1B3) Substrates (Clinically Relevant with Inhibitors). Management: Coadministration of bulevirtide with OATP1B1/1B3 (also known as SLCO1B1/1B3) substrates should be avoided when possible. If used together, close clinical monitoring is recommended. *Consider therapy modification*

Ceftobiprole Medocaril: May increase the serum concentration of OATP1B1/1B3 (SLCO1B1/1B3) Substrates (Clinically Relevant with Inhibitors). *Avoid combination*

Cladribine: BCRP/ABCG2 Inhibitors may increase the serum concentration of Cladribine. Management: Avoid concomitant use of BCRP inhibitors during the 4 to 5 day oral cladribine treatment cycles whenever possible. If combined, consider dose reduction of the BCRP inhibitor and separation in the timing of administration. *Consider therapy modification*

CYP2C8 Inhibitors (Moderate): May increase the serum concentration of Resmetirom. Management: During coadministration with moderate CYP2C8 inhibitors reduce the resmetirom dose to 80 mg daily for patients weighing 100 kg or more, or reduce the resmetirom dose to 60 mg daily for patients weighing less than 100 kg. *Consider therapy modification*

CYP2C8 Inhibitors (Strong): May increase the serum concentration of Resmetirom. *Avoid combination*

Daprodustat: CYP2C8 Inhibitors (Weak) may increase the serum concentration of Daprodustat. *Monitor therapy*

Elagolix: OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors may increase the serum concentration of Elagolix. *Avoid combination*

Elagolix, Estradiol, and Norethindrone: OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors may increase the serum concentration of Elagolix, Estradiol, and Norethindrone. Specifically, concentrations of elagolix may be increased. *Avoid combination*

Elbasvir and Grazoprevir: OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors may increase the serum concentration of Elbasvir and Grazoprevir. *Avoid combination*

Eluxadoline: May increase the serum concentration of Resmetirom. Resmetirom may increase the serum concentration of Eluxadoline. Management: Avoid use of eluxadoline and resmetirom whenever possible. If combined, decrease the eluxadoline dose to 75 mg twice daily and monitor patients for increased effects and toxicities of both eluxadoline and resmetirom. *Consider therapy modification*

Leniolisib: May increase the serum concentration of OATP1B1/1B3 (SLCO1B1/1B3) Substrates (Clinically Relevant with Inhibitors). *Avoid combination*

Lumacaftor and Ivacaftor: May decrease the serum concentration of CYP2C8 Substrates (High Risk with Inhibitors or Inducers). Lumacaftor and Ivacaftor may increase the serum concentration of CYP2C8 Substrates (High Risk with Inhibitors or Inducers). *Monitor therapy*

Momelotinib: OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors may increase the serum concentration of Momelotinib. *Monitor therapy*

OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors: May increase the serum concentration of Resmetirom. *Avoid combination*

PAZOPanib: BCRP/ABCG2 Inhibitors may increase the serum concentration of PAZOPanib. *Avoid combination*

Pravastatin: Resmetirom may increase the serum concentration of Pravastatin. Management: Limit the pravastatin dose to 40 mg daily during coadministration with resmetirom. Monitor for increased pravastatin adverse effects (eg, myalgias) during coadministration. *Consider therapy modification*

Pretomanid: May increase the serum concentration of OATP1B1/1B3 (SLCO1B1/1B3) Substrates (Clinically Relevant with Inhibitors). *Monitor therapy*

Repaglinide: CYP2C8 Inhibitors (Weak) may increase the serum concentration of Repaglinide. *Monitor therapy*

Revefenacin: OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors may increase serum concentrations of the active metabolite(s) of Revefenacin. *Avoid combination*

Rosuvastatin: Resmetirom may increase the serum concentration of Rosuvastatin. Management: Limit the rosuvastatin dose to 20 mg daily during coadministration with resmetirom. Monitor for increased rosuvastatin adverse effects (eg, myalgias) during coadministration. *Consider therapy modification*

Seladelpar: BCRP/ABCG2 Inhibitors may increase the serum concentration of Seladelpar. *Monitor therapy*

Simvastatin: Resmetirom may increase the serum concentration of Simvastatin. Management: Limit the simvastatin dose to 20 mg daily during coadministration with resmetirom. Monitor for increased simvastatin adverse effects (eg, myalgias) during coadministration. *Consider therapy modification*

Talazoparib: BCRP/ABCG2 Inhibitors may increase the serum concentration of Talazoparib. *Monitor therapy*

Taurursodiol: OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors may increase the serum concentration of Taurursodiol. *Avoid combination*

Topotecan: BCRP/ABCG2 Inhibitors may increase the serum concentration of Topotecan. *Avoid combination*

Trofinetide: May increase the serum concentration of OATP1B1/1B3 (SLCO1B1/1B3) Substrates (Clinically Relevant with Inhibitors). Management: Avoid concurrent use with OATP1B1/1B3 substrates for which small changes in exposure may be associated with serious toxicities. Monitor for evidence of an altered response to any OATP1B1/1B3 substrate if used together with trofinetide. *Consider therapy modification*

Ubrogepant: BCRP/ABCG2 Inhibitors may increase the serum concentration of Ubrogepant. Management: Use an initial ubrogepant dose of 50 mg and second dose (at least 2 hours later if needed) of 50 mg when used with a BCRP inhibitor. *Consider therapy modification*

Voclosporin: May increase the serum concentration of OATP1B1/1B3 (SLCO1B1/1B3) Substrates (Clinically Relevant with Inhibitors). *Monitor therapy*

Voxilaprevir: OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors may increase the serum concentration of Voxilaprevir. *Avoid combination*

Zavegepant: OATP1B1/1B3 (SLCO1B1/1B3) Inhibitors may increase the serum concentration of Zavegepant. *Avoid combination*

Monitoring Parameters

Evaluate liver biochemistries and signs or symptoms associated with liver (eg, fatigue, nausea, vomiting, right upper quadrant pain or tenderness, jaundice, fever, rash, eosinophilia) or gallbladder injury. Monitor for myopathy and rhabdomyolysis if concurrently used with HMG-CoA reductase inhibitors.

Adverse Reactions

The following adverse drug reactions and incidences are derived from product labeling unless otherwise specified. Adverse reactions reported in adults.
>10%:

Dermatologic: Pruritus (8% to 12%)

Gastrointestinal: Diarrhea (26% to 33%), nausea (17% to 22%)

Hepatic: Increased serum alanine aminotransferase (>3 × ULN: 11% to 13%), increased serum aspartate aminotransferase (>3 × ULN: 12%; >5 × ULN: 4%)

1% to 10%:

Cardiovascular: Cardiac arrhythmia (<5%), palpitations (<5%)

Dermatologic: Erythema of skin (<5%)

Endocrine & metabolic: Hypoglycemia (<5%)

Gastrointestinal: Abdominal pain (7% to 9%), abnormal stools (<5%), constipation (7% to 9%), decreased appetite (<5%), dysgeusia (<5%), flatulence (<5%), vomiting (9% to 10%)

Genitourinary: Abnormal uterine bleeding (<5%)

Hepatic: Increased serum bilirubin (>2 × ULN: 3%)

Nervous system: Depression (<5%), dizziness (6%), vertigo (<5%)

Neuromuscular & skeletal: Tendinopathy (<5%)

<1%: Hepatic: Hepatotoxicity

Frequency not defined:

Dermatologic: Skin rash, urticaria

Endocrine & metabolic: Decreased free T_4

Gastrointestinal: Cholecystitis (acute), cholelithiasis, pancreatitis (obstructive)

Warnings/Precautions

Concerns related to adverse effects:

- Gallbladder: Gallbladder related adverse effects, including cholelithiasis, acute cholecystitis, and obstructive pancreatitis secondary to gallstones, have been observed.
- Hepatotoxicity: Substantial elevations in liver biochemistries requiring therapy interruption have been observed. In one patient, upon reintroduction of resmetirom, liver biochemistries again increased along with immunologic markers (eg, immunoglobulin G), suggesting drug induced liver injury, which resolved following subsequent discontinuation.

Pregnancy Considerations

Adverse events in rat reproduction studies occurred with decreases in maternal T4, T3, and TSH following oral doses ~21 times the maximum recommended human dose, based on AUC.

Data collection to monitor pregnancy and infant outcomes following exposure to resmetirom is ongoing. Report pregnancies to Madrigal Pharmaceuticals (1-800-905-0324 or https://www.madrigalpharma.com/contact/).

Actions

Pharmacology

Resmetirom is a partial agonist of thyroid hormone receptor-beta (THR-β), the predominant thyroid hormone receptor in the liver. Stimulation of THR-β in the liver reduces intrahepatic triglycerides.

Distribution

V_{dss}: 68 L.

Metabolism

Hepatic via CYP2C8.

Excretion

Feces: ~67%; urine: 24%; primarily excreted as metabolites.

Clearance:17.5 L/hour.

Time to Peak

~4 hours; steady state achieved after 3 to 6 days of repeated dosing.

Half-Life Elimination

4.5 hours.

Protein Binding

>99%.

Patient and Family Education

Patient Education

What is this drug used for?

• It is used to treat a certain liver problem called nonalcoholic steatohepatitis (NASH).

All drugs may cause side effects. However, many people have no side effects or only have minor side effects. Call your doctor or get medical help if any of these side effects or any other side effects bother you or do not go away:

• Constipation, diarrhea, stomach pain, upset stomach, or throwing up

• Itching

• Dizziness

WARNING/CAUTION: Even though it may be rare, some people may have very bad and sometimes deadly side effects when taking a drug. Tell your doctor or get medical help right away if you have any of the following signs or symptoms that may be related to a very bad side effect:

• Liver problems like dark urine, tiredness, decreased appetite, upset stomach or stomach pain, light-colored stools, throwing up, or yellow skin or eyes

• Gallbladder problems like pain in the upper right belly area, right shoulder area, or between the shoulder blades; change in stools; dark urine or yellow skin or eyes; or fever with chills

• Signs of an allergic reaction, like rash; hives; itching; red, swollen, blistered, or peeling skin with or without fever; wheezing; tightness in the chest or throat; trouble breathing, swallowing, or talking; unusual hoarseness; or swelling of the mouth, face, lips, tongue, or throat.

Note: This is not a comprehensive list of all side effects. Talk to your doctor if you have questions.

Consumer Information Use and Disclaimer: This information should not be used to decide whether or not to take this medicine or any other medicine. Only the healthcare provider has the knowledge and training to decide which medicines are right for a specific patient. This information does not endorse any medicine as safe, effective, or approved for treating any patient or health condition. This is only a limited summary of general information about the medicine's uses from the patient education leaflet and is not intended to be comprehensive. This limited summary does NOT include all information available about the possible uses, directions, warnings, precautions, interactions, adverse effects, or risks that may apply to this medicine. This information is not intended to provide medical advice, diagnosis or treatment and does not replace information you receive from the healthcare provider. For a more detailed summary of information about the risks and benefits of using this medicine, please speak with your healthcare provider and review the entire patient education leaflet.