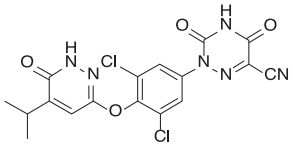
Resmirom™
(R e s m e t i r o m)

ریسمیروم

Film-coated Tablets 60mg, 80mg & 100mg

DESCRIPTION
Resmirom tablets contain Resmetirom, a thyroid hormone receptor-beta agonist. Its chemical name is 2-[3,5-Dichloro-4-((6-oxo-5-(propan-2-yl)-1,6-dihydropyridazin-3-yl)oxy)phenyl]-3,5-dioxo-2,3,4,5-tetrahydro-1,2,4-triazine-6-carbonitrile. Its molecular formula is $C_{17}H_{12}Cl_2N_6O_4$ and the structural formula is:



Resmetirom

QUALITATIVE AND QUANTITATIVE COMPOSITION
Resmirom (Resmetirom) Tablets are available for oral administration as:

Resmirom Tablets 60mg
Each film-coated tablet contains:
Resmetirom…60mg

Resmirom Tablets 80mg
Each film-coated tablet contains:
Resmetirom…80mg

Resmirom Tablets 100mg
Each film-coated tablet contains:
Resmetirom…100mg

CLINICAL PHARMACOLOGY
Mechanism of Action
Resmetirom is a partial agonist of the thyroid hormone receptor-beta (THR-β). Resmetirom 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. The same functional assay for thyroid hormone receptor-alpha (THR-α) agonism showed 48.6% efficacy for Resmetirom relative to T3, with an EC_{50} of 3.74 μM. 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.

Pharmacokinetics
Following once daily doses, steady state is typically reached within 3 to 6 days of dosing. Resmetirom steady state exposure increases in a dose proportional manner between doses of 40mg (0.5 times the lowest approved recommended dose) and 100mg. Resmetirom exposure increases in a greater than dose proportional manner between doses of 100mg and 200mg (2 times the highest approved recommended dose) by about 5.6-fold. Resmetirom exposure increased 1.5- to 3-fold following once daily dosing; however, the MGL-3623 metabolite does not accumulate. The estimated Resmetirom systemic exposure at steady state in NASH patients is summarized in table below. Resmetirom exposure is similar between NASH patients with F2 stage fibrosis and F3 stage fibrosis.

Parameter	Resmetirom 80 mg Once Daily Mean (CV%)	Resmetirom 100 mg Once Daily Mean (CV%)
$C_{max,ss}$ (ng/ml)[a]	778 (41.5)	971 (40.9)
$AUC_{tau,ss}$ (ng*h/ml)[a]	5850 (60.5)	7780 (65.5)

Absorption
The Resmetirom median time to maximum plasma concentration (T_{max}) is approximately 4 hours following multiple daily doses of Resmetirom 80mg or 100mg.

Effect of Food
No clinically significant differences in Resmetirom pharmacokinetics were observed following administration with a high-fat meal (approximately 150, 250, and 500-600 calories from protein, carbohydrate, and fat, respectively). Concomitant food administration resulted in a 33% decrease in C_{max}, an 11% decrease in AUC, and a delay in median T_{max} by about 2 hours compared to under fasted condition.

Distribution
Resmetirom apparent volume of distribution (Vd/F) at steady-state is 68L (227%). Resmetirom is greater than 99% protein-bound.

Metabolism
Resmetirom is metabolized by CYP2C8 and is not metabolized by other CYP enzymes in vitro. MGL-3623 is a major metabolite with a 28-times lower potency for THR-β than Resmetirom. MGL-3623 represents 33% to 51% of Resmetirom AUC at steady state following administration of 100mg once daily.

Elimination
Resmetirom median terminal plasma half-life (t½) is 4.5 hours and the steady state apparent clearance (CL/F) is 17.5 (56.3%) L/h. Following oral administration of a 100mg radio-labeled dose of Resmetirom, approximately 67% of the total radioactive dose was recovered in the feces, mostly as metabolites and 24% of the total radioactive dose was recovered in the urine. Unchanged labeled Resmetirom was not detected in feces and accounted for 1 % of the dose recovered in urine. A metabolite MGL-3623 accounted for 3.3% and 16% of the dose recovered in feces and urine, respectively. Oxalic acid metabolite was observed in plasma but not in urine.

Special Population
Body weight
A clinically significant difference in Resmetirom exposure was not observed with the recommended weight-based dosage. However, Resmetirom CL/F and Vd/F increase with increasing body weight, resulting in lower Resmetirom exposure in patients with higher body weight receiving the same dosage as lower weight patients.

Patients with Hepatic Impairment
Following repeated 80mg once daily dosing of Resmetirom for 6 days, Resmetirom AUC was 1.3-fold, 2.7-fold and 19-fold higher in patients with mild, moderate and severe hepatic impairment (Child-Pugh A, B and C), respectively compared to subjects with normal hepatic function. Resmetirom C_{max} was 1.2-fold, 1.7-fold and 8.1-fold higher in patients with mild, moderate and severe hepatic impairment, respectively, compared to subjects with normal hepatic function, which is summarized in the table below:

Table: Mean (CV%) Resmetirom systemic exposure in subjects with normal hepatic function and non-NASH patients with hepatic impairment following Resmetirom 80mg once daily for 6 days and exposure change relative to normal hepatic function

Parameter	Normal Hepatic Function (N = 7)	Child-Pugh Class A Mild (N = 10)	Child-Pugh Class B Moderate (N = 9)	Child-Pugh Class C Severe (N = 3)
Resmetirom				
$C_{max,ss}$ (ng/mL)[a]	1070 (51.0)	1390 (67.8)	1830 (47.5)	7730 (17.4)
$AUC_{tau,ss}$ (ng*h/mL)[a]	5100 (51.5)	5570 (66.4)	15100 (65.8)[b]	97600 (39.0)

a Exposure parameters presented as Mean (CV%)
b N=8

In the same study, MGL-3623 AUC_{tau} was 1.3-fold, 2-fold and 5.8-fold higher in patients with mild, moderate and severe hepatic impairment, respectively, compared to subjects with normal hepatic function.

NASH Patients with Mild Hepatic Impairment (Child-Pugh A)
Geometric mean AUC and C_{max} in NASH cirrhosis patients with mild hepatic impairment (Child-Pugh Class A; n = 20) were 6% higher and 10% lower, respectively, compared to non-cirrhotic NASH patients following repeated 100mg once daily dosing of Resmetirom for 6 days. The safety and effectiveness of Resmetirom have not been established in patients with NASH cirrhosis.

THERAPEUTIC INDICATIONS
Resmirom (Resmetirom) 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).

DOSAGE & ADMINISTRATION
The recommended dosage of RESMIROM (Resmetirom) is based on actual body weight. For patients weighing:
- <100kg, the recommended dosage is 80mg orally once daily.
- ≥100kg, the recommended dosage is 100mg orally once daily.

Administer Resmirom (Resmetirom) with or without food.

Dosage Modifications for CYP2C8 Inhibitors
Concomitant use of Resmirom (Resmetirom) with strong CYP2C8 inhibitors (e.g., gemfibrozil) is not recommended.
If Resmirom (Resmetirom) is used concomitantly with a moderate CYP2C8

inhibitor (e.g., clopidogrel), reduce the dosage of Resmirom (Resmetirom):

- <100kg, reduce the dosage of Resmirom (Resmetirom) to 60mg once daily.
- ≥100kg, reduce the dosage of Resmirom (Resmetirom) to 80mg once daily.

ADVERSE REACTIONS

Following adverse reactions have been reported with the use of Resmetirom: Hepatotoxicity, gallbladder-related adverse reactions , urticaria, rash, diarrhea, nausea, pruritus, vomiting, constipation, abdominal pain and dizziness.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS

Resmetirom is contraindicated in patients with a history of hypersensitivity to active substance or to any excipient of the product.

PRECAUTIONS

Hepatotoxicity

Hepatotoxicity has been observed with use of Resmetirom. Monitor patients during treatment with Resmetirom 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 Resmetirom and continue to monitor the patient. If laboratory values return to baseline, weigh the potential risks against the benefits of restarting Resmetirom. If laboratory values do not return to baseline, consider drug induced auto immune like hepatitis or autoimmune liver disease in the evaluation of elevations in liver tests.

Gallbladder-Related Adverse Reactions

In clinical trials, cholelithiasis, acute cholecystitis, and obstructive pancreatitis (gallstone) were observed more often in Resmetirom-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 Resmetirom treatment until the event is resolved.

Drug Interaction With Certain Statins

An increase in exposure of atorvastatin, pravastatin, rosuvastatin and simvastatin was observed when concomitantly administered with Resmetirom, 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.

Hepatic Impairment

Avoid use of Resmetirom 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.

Pregnancy

There are no or limited amount of data from the use of Resmetirom in pregnant women. Therefore, Resmetirom should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. However, there are risks to the mother and fetus related to underlying maternal NASH with liver fibrosis, such as increased risks of gestational diabetes, hypertensive complications, preterm birth, and postpartum hemorrhage.

Nursing Mothers

It is unknown whether Resmetirom metabolites are excreted in human breast milk or not. Resmetirom should be used during lactation only if the potential benefit justifies the potential risk to the newborns/infant.

DRUG INTERACTIONS

Effects of other drugs on Resmetirom

Strong or Moderate CYP2C8 Inhibitors

Resmetirom is a CYP2C8 substrate. Concomitant use with a strong or moderate CYP2C8 inhibitor can increase Resmetirom C_{max} and AUC, which may increase the risk of Resmetirom adverse reactions. Concomitant use of Resmetirom with strong CYP2C8 inhibitors (e.g., gemfibrozil) is not recommended. Reduce Resmetirom 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 and OATP1B3 inhibitors may increase Resmetirom C_{max} and AUC, which may increase the risk of Resmetirom adverse reactions. Concomitant use of Resmetirom with OATP1B1 or OATP1B3 inhibitors (e.g., cyclosporine) is not recommended.

Effects of Resmetirom on other drugs

Statins (Atorvastatin, Pravastatin, Rosuvastatin, or Simvastatin)

Resmetirom increased plasma concentrations of some statins (atorvastatin, pravastatin, rosuvastatin and simvastatin), which may increase the risk of adverse reactions related to these drugs.

Rosuvastatin and simvastatin: Limit daily statin dosage to 20mg.
Pravastatin and atorvastatin: Limit daily statin dosage to 40mg.

CYP2C8 Substrates

Resmetirom is a weak CYP2C8 inhibitor. Resmetirom increases exposure of CYP2C8 substrates, which may increase the risk of adverse reactions related to these substrates. Monitor patients more frequently for substrate-related adverse reactions if Resmetirom is co-administered with CYP2C8 substrates where minimal concentration changes may lead to serious adverse reactions.

OVERDOSAGE

In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

STORAGE

Do not store above 30°C.
Protect from sunlight and moisture.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

Resmirom (Resmetirom) Tablets 60mg are available in blister pack of 30's.
Resmirom (Resmetirom) Tablets 80mg are available in blister pack of 30's.
Resmirom (Resmetirom) Tablets 100mg are available in blister pack of 30's.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:

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Getz pharma (PVT) LIMITED
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