For the use of a Specialist only

Resmetirom Tablets 60 mg, 80 mg and 100 mg

ReMASH

Name of the Medicinal Product
ReMASH (Resmetirom Tablets 60 mg, 80 mg and 100 mg)

Qualitative and Quantitative Composition

ReMASH 60

Each film coated tablet contains:

Resmetirom …… 60 mg

Excipients…… qs

Colour: Titanium dioxide USP-NF

ReMASH 80

Each film coated tablet contains:

Resmetirom …… 80 mg

Excipients…… qs

Colour: Iron oxide Yellow USP-NF & Titanium dioxide USP-NF

ReMASH 100

Each film coated tablet contains:

Resmetirom ……..… 100 mg

Excipients…… qs

Colour: Iron oxide Red USP-NF, Iron oxide Yellow USP-NF & Titanium dioxide USP-NF

Pharmaceutical Form
Film coated tablet

Description:

Resmetirom Tablets 60 mg
White colour, oval shaped, biconvex, plain on both sides film coated tablets

Resmetirom Tablets 80 mg
Yellow colour, oval shaped, biconvex, plain on both sides film coated tablets.

Resmetirom Tablets 100 mg
Beige colour, capsule shaped, biconvex, plain on both sides film coated tablets.

Clinical Particulars

Therapeutic Indications

ReMASH is indicated in conjunction with diet and exercise for the treatment of adults with noncirrhotic non-alcoholic 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
Avoid use of ReMASH in patients with decompensated cirrhosis.

Posology and Method of Administration

Recommended Dosage and Administration
The recommended dosage of ReMASH is based on actual body weight. For patients weighing:

- <100 kg, the recommended dosage is 80 mg orally once daily.
- ≥100 kg, the recommended dosage is 100 mg orally once daily.

Administer ReMASH with or without food.

Dosage Modifications for CYP2C8 Inhibitors
Concomitant use of ReMASH with strong CYP2C8 inhibitors (e.g., gemfibrozil) is not recommended.

If ReMASH is used concomitantly with a moderate CYP2C8 inhibitor (e.g., clopidogrel), reduce the dosage of ReMASH:

- <100 kg, reduce the dosage of ReMASH to 60 mg once daily.
- ≥100 kg, reduce the dosage of ReMASH to 80 mg once daily.

Contraindications
None.

Special Warnings and Precautions for use

Hepatotoxicity
Hepatotoxicity has been observed with use of resmetirom. One patient had normal alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin (TB) levels at baseline, who received resmetirom 80 mg daily, developed substantial elevations of liver biochemistries that resolved when treatment was interrupted. After reinitiating resmetirom, the patient had elevations of ALT, AST, and TB. Peak values observed were 58 x upper limit of normal (ULN) for ALT, 66 x ULN for AST, 15 x ULN for TB, with no elevation of alkaline phosphatase (ALP). Elevations in liver enzymes were accompanied by elevations in immunoglobulin G levels, suggesting drug-induced autoimmune-like hepatitis (DI-ALH). The liver tests returned to baseline following hospitalization and discontinuation of resmetirom without any therapeutic intervention.

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 DI-ALH 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.

Interaction with Other Medicinal Products and Other Forms of Interactions

Effects of Other Drugs on Resmetirom

Table 1: Clinically Significant Interactions Affecting Resmetirom

Strong or Moderate CYP2C8 Inhibitors	
Clinical Impact	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.
Intervention	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	
Clinical Impact	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.
Intervention	Concomitant use of resmetirom with OATP1B1 or OATP1B3 inhibitors (e.g., cyclosporine) is not recommended.

Effects of Resmetirom on Other Drugs

Table 2: Clinically Significant Interactions Affecting Other Drugs

Statins (Atorvastatin, Pravastatin, Rosuvastatin, or Simvastatin)	
Clinical Impact	Resmetirom increased plasma concentrations of some statins (atorvastatin, pravastatin, rosuvastatin and simvastatin), which may increase the risk of adverse reactions related to these drugs.
Intervention	Rosuvastatin and simvastatin: Limit daily statin dosage to 20 mg. Pravastatin and atorvastatin: Limit daily statin dosage to 40 mg.
CYP2C8 Substrates	
Clinical Impact	Resmetirom is a weak CYP2C8 inhibitor. Resmetirom increases exposure of CYP2C8 substrates, which may increase the risk of adverse reactions related to these substrates.
Intervention	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.

Undesirable Effects

Clinical Trials Experience

The safety of resmetirom was evaluated in two randomized, double-blind, placebo-controlled trials that enrolled a total of 2019 patients.

Trial 1 included patients who had noncirrhotic NASH with stages F2 and F3 fibrosis at eligibility (n=888).

Adverse Reactions Leading to Discontinuations

The exposure-adjusted incidence rates (EAIRs) per 100 person-years (PY) for treatment discontinuation due to any adverse reaction were higher in the resmetirom dosage arms: 4 per 100 PY, 5 per 100 PY, and 8 per 100 PY in placebo, resmetirom 80 mg once daily, and resmetirom 100 mg once daily arms, respectively. Diarrhoea and nausea were the most common causes of treatment discontinuation.

Table 3: Exposure-Adjusted Incidence Rates (EAIR) of Common Adverse Reactions (Occurred in at least 5% of Patients) Reported with Resmetirom in Adult Patients with Noncirrhotic NASH (Trial 1)[a,b,c]

Adverse Reaction	Placebo N=294 n (EAIR[d])	Resmetirom 80 mg Once Daily N=296 n (EAIR[d])	Resmetirom 100 mg Once Daily N=296 n (EAIR[d])
Diarrhoea	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)

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

[b] Median exposure duration was 68 weeks for placebo, 74 weeks for resmetirom 80 mg once daily, and 66 weeks for resmetirom 100 mg once daily.

[c] EAIRs are per 100 person-years (PY) where total PYs were 435, 435, and 407 for placebo, 80 mg once daily, and 100 mg once daily arms, respectively.

[d] 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 one year.

Abbreviations: EAIR, exposure-adjusted incidence rate; PY, person-years; NASH, nonalcoholic steatohepatitis

Gastrointestinal Adverse Reactions

The incidence of gastrointestinal adverse reactions was higher for the resmetirom drug arms compared to placebo. The EAIRs for gastrointestinal adverse reactions were 57 per 100 PY, 73 per 100 PY, and 89 per 100 PY in the placebo, resmetirom 80 mg once daily, resmetirom 100 mg once daily arms, respectively. Diarrhoea typically began early in treatment initiation and was mild to moderate in severity. The median time (Q1 to Q3) to a diarrhoeal event was 39 (2 to 195) days, 17 (3 to 70) days, and 6 (2 to 54) days in the placebo, resmetirom 80 mg once daily, and resmetirom 100 mg once daily arms, respectively.

Median duration of diarrhoea was 9 days for placebo compared to 20 days for both resmetirom 80 mg once daily and resmetirom 100 mg once daily dosage arms.

Nausea also began early in treatment and was mild to moderate in severity. Among patients with nausea, the median time (Q1 to Q3) to a nausea event was 85 (24 to 347) days, 28 (2 to 162) days, and 5 (2 to 40) days in the placebo, resmetirom 80 mg once daily, and resmetirom 100 mg once daily arms, respectively. Median duration of nausea was 17 days, 26 days, and 28 days for patients in the placebo, resmetirom 80 mg once daily, and resmetirom 100 mg once daily arms, respectively. Vomiting and abdominal pain adverse reactions were mild to moderate in severity.

Hypersensitivity Reactions

Reactions such as urticaria and rash, which may reflect drug hypersensitivity, were observed in patients receiving resmetirom. The EAIRs for urticaria were 0.2 per 100 PY, 0.7 per 100 PY, and 1.5 per 100 PY in the placebo, resmetirom 80 mg once daily, and resmetirom 100 mg once daily arms, respectively. The EAIRs for rash were 3 per 100 PY in the placebo and resmetirom 80 mg once daily arms compared to 5 per 100 PY in the resmetirom 100 mg once daily arm.

Gallbladder-Related Adverse Reactions

A higher incidence of cholelithiasis, acute cholecystitis, and obstructive pancreatitis (gallstone) was observed in the treatment arms compared to placebo. However, the EAIRs for these events were less than 1 per 100 PY for all treatment arms.

Less Common Adverse Reactions

Additional adverse reactions that occurred more frequently in the resmetirom arms compared to placebo, in less 5% of patients, included decreased appetite, flatulence, abnormal feces, dysgeusia, vertigo, arrythmia, palpitations, depression, erythema, hypoglycemia, tendinopathy, abnormal uterine bleeding.

Laboratory Abnormalities

Liver Tests

Increases in mean alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were observed in the first 4 weeks after initiating treatment with resmetirom. In both resmetirom dosage arms, 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.

Table 4: Frequency of Liver Test Elevations in Trial 1

	Placebo (%)	Resmetirom 80 mg Once Daily (%)	Resmetirom 100 mg Once Daily (%)
ALT > 3x ULN	10	11	13
ALT > 5x ULN	2	2	2
AST > 3x ULN	10	9	12
AST > 5x ULN	2	1	4
TB[a] > 2x ULN	2	1	3

[a] TB elevations include patients with Gilbert syndrome.

Thyroid Function Tests

A decrease in levels of prohormone free T4 (FT4) of mean 2%, 13%, and 17% was seen at 12 months in patients treated with placebo, resmetirom 80 mg once daily, and resmetirom 100 mg once daily, respectively, with minimal changes in active hormone T3 or in TSH. There were no clinical findings associated with FT4 decreases.

Additional Safety Data

The safety evaluation of resmetirom also included an analysis of an additional randomized placebo-controlled safety trial which included 969 patients from a relevant patient population (placebo [n=318], resmetirom 80 mg once daily [n=327], and resmetirom 100 mg once daily [n=324]).

Data from the safety trial was combined with data from NASH patients with F2 and F3 fibrosis at eligibility (n=888) and data from an additional 162 patients from a relevant patient population enrolled in Trial 1. In the combined safety population (n=2019), the median (Q1 to Q3) age of patients at baseline was 58 (50 to 65) years; 55% were female, 28% were Hispanic, 89% were White, 2% were Asian, and 4% were Black or African American.

The safety profile from this combined analysis was similar to that in Trial 1, other than the one case of hepatotoxicity in the safety trial.

Use in Specific Populations

Pregnancy

Risk Summary

There are no available data on resmetirom 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 foetus related to underlying NASH with liver fibrosis (see Clinical Considerations). In animal reproduction studies, adverse effects on embryo-fetal development occurred in pregnant rabbits treated with Resmetirom at 3.5 times the maximum recommended dose during organogenesis. These effects were associated with maternal toxicity, whereas no embryo-fetal effects were observed at lower dose levels with better tolerance in pregnant rabbits. No embryo-fetal developmental effects occurred in pregnant rats treated with Resmetirom or the metabolite MGL-3623. A pre-and postnatal development study in rats with maternal dosing of Resmetirom during organogenesis through lactation showed a decrease in birthweight and increased incidence of stillbirths and mortality (postnatal days 1-4) at 37 times the maximum recommended dose. These effects were associated with marked suppression of maternal T4, T3, and TSH levels.

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, and other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

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 haemorrhage.

Data

Animal Data

No effects on embryo-fetal development were observed in pregnant rats treated orally with up to 100 mg/kg/day (21 times the maximum recommended dose based on AUC [area under the plasma concentration-time curve]) or in pregnant rabbits treated orally with up to 30 mg/kg/day (2.8 times the maximum recommended dose based on AUC) during the period of organogenesis. Oral administration of 75 mg/kg/day in pregnant rabbits (3.5 times the maximum recommended dose based on AUC) produced an increase in post-implantation loss and decreases in viable fetuses and fetal weight. These effects were likely due to maternal toxicity (i.e., marked reductions in weight gain and food consumption).

A pre-and postnatal development study was performed using oral administration of 3, 30, or 100 mg/kg/day in female rats during organogenesis through lactation. Treatment with 100 mg/kg/day (37 times the maximum recommended dose based on AUC) produced increases in number of stillborn, pup deaths during postnatal days 1-4, and pups with absence of milk in stomach. Birthweight was decreased by 10% in this dose group, with recovery to normal body weight thereafter. The effects in offspring were associated with marked reductions in maternal plasma levels of T4 (88% decrease), T3 (79% decrease), and TSH (44% decrease). No effects on postnatal development were observed at doses up to 30 mg/kg/day (7.2 times the maximum recommended dose based on AUC). This study lacked a complete evaluation of physical and neurobehavioral development in offspring; however, no effects of Resmetirom were noted in tests of learning and memory.

The metabolite MGL-3623 was tested for its effects on embryo-fetal development. No effects were observed in pregnant rats treated orally with up to 100 mg/kg/day MGL-3623 (4.7 times the maximum recommended dose based on AUC for MGL-3623) during the period of organogenesis.

Lactation

Risk Summary

There is no information regarding the presence of resmetirom 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 resmetirom and any potential adverse effects on the breastfed infant from resmetirom or from the underlying maternal condition.

Pediatric Use

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

Geriatric Use

In Trial 1, of the 594 patients with NASH who received at least one dose of resmetirom, 149 (25%) were 65 years of age and older and 13 (2%) were 75 years of age and older No overall differences in effectiveness but numerically higher incidence of adverse reactions have been observed in patients 65 years of age and older 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. Resmetirom has not been studied in patients with severe renal impairment.

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.

No dosage adjustment is recommended for patients with mild hepatic impairment (Child-Pugh Class A).

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

Pharmacological Properties

Pharmacotherapeutic group: selective thyroid hormone receptor-beta (THR-β) agonists, ATC code: H03AA06.

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.

Pharmacodynamics

Liver Fat Content

Resmetirom decreases liver fat content as measured by magnetic resonance imaging-protein density fat fraction (MRI-PDFF) or FibroScan controlled attenuation parameter (CAP).

Reductions in liver fat content by MRI-PDFF were observed at 16 (the first assessment) and 52 weeks of treatment. Reductions in liver fat content by CAP were observed at 52 weeks of treatment.

Prohormone FT4

Resmetirom decreased concentrations of prohormone FT4 were observed at the first assessment at 4 weeks of treatment. Similar decreases in FT4 were observed during the treatment.

Sex Hormone Binding Globulin (SHBG)

Resmetirom increased concentrations of sex hormone binding globulin (SHBG) were observed at the first assessment at 4 weeks of treatment, and at longer durations of treatment. The clinical significance of this change is unknown.

Cardiac Electrophysiology

At a dose two times the maximum recommended dose, resmetirom does not prolong the QT interval to any clinically relevant extent.

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 40 mg (0.5 times the lowest approved recommended dose) and 100 mg. Resmetirom exposure increases in a greater than dose proportional manner between doses of 100 mg and 200 mg (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 3. Resmetirom exposure is similar between NASH patients with F2 stage fibrosis and F3 stage fibrosis.

Table 5: Resmetirom Estimated Systemic Exposure at Steady State in Patients with NASH with Fibrosis (F2 and F3)

Parameters	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)

Abbreviations: $AUC_{tau,ss}$ = area under the concentration-versus-time curve over one dosing interval at steady state; $C_{max,ss}$ = maximum concentration at steady state; CV = arithmetic coefficient of variation

Absorption

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

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 68 (227%) L. Resmetirom is greater than 99% protein bound.

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.

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 100 mg once daily.

Excretion

Following oral administration of a 100 mg radio-labelled 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 labelled 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.

Specific Populations

No clinically significant differences in the pharmacokinetics of resmetirom were observed based on age (18 to 83 years), sex, race (White, Black, or Asian), or ABCG2 genotype (BCRP p.Gln141Lys, p.Val12Met).

Population PK analyses indicated no clinically significant difference in the pharmacokinetics of resmetirom by mild to moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m^2, Modification of Diet in Renal Disease (MDRD)). The effect of severe renal impairment (eGFR < 30 mL/min/1.73 m^2, MDRD) on resmetirom pharmacokinetics is unknown.

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.

Patient with Hepatic Impairment

Following repeated 80 mg 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 (Table 4).

In the same study, MGL-3623 AUCtau 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.

Table 6: Mean (CV%) Resmetirom Systemic Exposure in Subjects with Normal Hepatic Function and Non-NASH Patients with Hepatic Impairment Following Resmetirom 80 mg Once Daily for 6 Days and Exposure Change Relative to Normal Hepatic Function

Parameters	Normal Hepatic Function (N = 7)	Child-Pugh Class		
		A Mild (N = 10)	B Moderate (N = 9)	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

Abbreviations: $AUC_{tau,ss}$ = area under the concentration-versus-time curve over one dosing interval at steady state; $C_{max,ss}$ = maximum concentration at steady state; CV = arithmetic coefficient of variation

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 100 mg once daily dosing of resmetirom for 6 days. The safety and effectiveness of resmetirom have not been established in patients with NASH cirrhosis.

Drug Interaction Studies

Moderate CYP2C8 Inhibitors: Resmetirom C_{max} increased 1.3-fold and AUC 1.7-fold following concomitant use of multiple doses of resmetirom 100 mg/day with clopidogrel (a moderate CYP2C8 inhibitor) at steady-state in healthy subjects.

CYP2C8 Substrates: Pioglitazone (a CYP2C8 substrate) C_{max} was unchanged and AUC increased 1.5-fold following concomitant use of a single oral dose of pioglitazone (15 mg) with resmetirom at steady state (100 mg/day) in healthy subjects.

Simvastatin: Simvastatin (OATP1B1 and OATP1B3 substrate) C_{max} increased 1.4-fold and AUC 1.7-fold following concomitant use of a single oral dose of simvastatin (20 mg) with resmetirom at steady state (100 mg/day) in healthy subjects

Rosuvastatin: Rosuvastatin (BCRP, OATP1B1, and OATP1B3 substrate) C_{max} increased 2.9-fold and AUC 1.8-fold following concomitant use of a single oral dose of rosuvastatin (10 mg) with resmetirom at steady state (at two times the highest recommended dosage) in healthy subjects.

Pravastatin: Pravastatin (OATP1B1 and OATP1B3 substrate) C_{max} increased 1.3-fold and AUC 1.4-fold following concomitant use of a single oral dose of pravastatin (40 mg) with resmetirom at steady state (100 mg/day) in healthy subjects.

Atorvastatin: Atorvastatin (BCRP, OATP1B1, and OATP1B3 substrate) C_{max} was unchanged and AUC increased 1.4-fold following concomitant use of a single oral dose of atorvastatin (20 mg) with resmetirom at steady state (100 mg/day) in healthy subjects. Atorvastatin lactone C_{max} increased 2.0-fold and AUC increased 1.8-fold.

Other Drugs: No clinically significant differences in the pharmacokinetics of R-warfarin or S-warfarin were observed when used concomitantly with resmetirom.

***In Vitro* Studies**

CYP450 Enzymes: Resmetirom is an inhibitor of CYP2C8.

Glucuronidation Enzymes: Resmetirom is an inhibitor of UDP-glucuronosyltransferases (UGTs) 1A4 and 1A9. The clinical relevance of UGT1A4 and UGT1A9 inhibition is unknown.

Transporters: Resmetirom is a substrate for organic anion-transporting polypeptides (OATP) 1B1 and 1B3 and breast cancer resistance protein (BCRP). Resmetirom inhibits OATP1B1, OATP1B3, BCRP, OAT3, and bile salt export pump (BSEP). The clinical significance of OAT3 and BSEP inhibition is unknown.

Nonclinical Toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a 2-year study in CD-1 mice, resmetirom produced leiomyoma or leiomyosarcoma in the uterus at a dose of 100 mg/kg/day (51 times the maximum recommended dose based on AUC). No tumorigenic effects were observed in female mice at doses of up to 30 mg/kg/day (14 times the maximum recommended dose based on AUC) or in male mice at doses of up to 100 mg/kg/day (35 times the maximum recommended dose based on AUC).

In a 2-year study in Sprague-Dawley rats, resmetirom produced benign fibroadenoma in the mammary gland of males at a dose of 30 mg/kg/day (6.5 times the maximum recommended dose based on AUC). No tumorigenic effects were observed in male rats at doses of up to 6 mg/kg/day (3.7 times the maximum recommended dose based on AUC) or in female rats at doses of up to 30 mg/kg/day (3.4 times the maximum recommended dose based on AUC).

In a 26-week study in transgenic [CByB6F1-Tg (HRAS)2Jic] mice, the major metabolite of resmetirom, MGL-3623, was not tumorigenic at doses of up to 1500 mg/kg/day.

Mutagenesis

Resmetirom was negative in the *in vitro* bacterial reverse mutation (Ames) assay, the chromosomal aberration assay in human peripheral blood lymphocytes, the in vitro micronucleus assay in L5178Y tk+/-mouse lymphoma cells, and the in vivo rat micronucleus assay.

The metabolite MGL-3623 was negative in the in vitro bacterial reverse mutation (Ames) assay and the in vivo rat micronucleus assay. MGL-3623 tested positive in the presence of metabolic activation in the in vitro micronucleus assay with TK6 human lymphoblast cells, with the increase in micronuclei limited to a single concentration that produced 59% growth inhibition.

Impairment of Fertility

Resmetirom had no effects on fertility or reproductive function in male and female rats at oral doses of up to 30 mg/kg/day (6.9 times and 2.6 times the maximum recommended dose in male and female rats, respectively, based on AUC).

Pharmaceutical Particulars

Incompatibilities

Not applicable.

Shelf life

Refer the outer carton for the date of expiry. The date of expiry is the last day of the month.

Special Precautions for Storage

Store Protected from light and moisture at a temperature not exceeding 30°C.

Packaging Information

HDPE Bottle of 30 Tablets

TAM No.: DRA-TAM-20-04

Manufactured by:

Azista Bhutan Healthcare Limited
Motanga Industrial Park, Plot No. M-22 & M-25,
Samdrup Jongkhar, Bhutan - 41001.

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May 2025.

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