Obeticholic Acid Tablets 5 mg and 10 mg
Ocatab 5 / 10 mg ओकाटब ५/१०

To be sold by retail on the prescription of a Registered Medical Practitioner only

PRESCRIBING INFORMATION

WARNING
HEPATIC DECOMPENSATION AND FAILURE IN INCORRECTLY DOSED PBC PATIENTS WITH CHILD-PUGH CLASS B OR C OR DECOMPENSATED CIRRHOSIS

- In postmarketing reports, hepatic decompensation and failure, in some cases fatal, have been reported in patients with primary biliary cholangitis (PBC) with decompensated cirrhosis or Child-Pugh Class B or C hepatic impairment when Obeticholic acid was dosed more frequently than recommended.
- The recommended starting dosage of Obeticholic acid is 5 mg once weekly for patients with Child-Pugh Class B or C hepatic impairment or a prior decompensation event.

1. GENERIC NAME
Obeticholic Acid tablets 5 mg and 10 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Obeticholic Acid Tablets 5 Mg
Each film coated tablet contains
Obeticholic Acid …..……5 mg

Obeticholic Acid Tablets 10 Mg
Each film coated tablet contains
Obeticholic Acid …..……10 mg

3. DOSAGE FORM AND STRENGTH
Obeticholic acid tablets are available as 5mg and 10mg film coated tablets.

4. CLINICAL PARTICULARS

4.1 Indications
Obeticholic acid is indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA.

This indication is approved under accelerated approval based on a reduction in alkaline phosphatase (ALP). An improvement in survival or disease-related symptoms has not been established.

4.2 Posology and Method of Administration

Important Dosage and Administration Instructions
Prior to the initiation of Obeticholic acid in patients with suspected cirrhosis, use the nomogram to calculate the patient's score to determine their Child-Pugh classification (A, B, or C) and determine the appropriate starting dosage.

Table 1: Child-Pugh Nomogram

Parameter	Points Scored for Observed Filings		
	1 Point	**2 Points**	**3 Points**
Encephalopathy grade	None	1 or 2	3 or 4
Ascites	Absent	Slight	Moderate
Serum bilirubin (mg/dL)	<2	2 to 3	>3
Serum albumin (mg/dL)	>3.5	2.8 to 3.5	<2.8
International Normalized Ratio (INR)	<1.7	1.7 to 2.2	>2.2
Child-Pugh Class is obtained by adding the points from all 5 parameters to derive a total score, which can range from 5 to 15 points. Child-Pugh Class A: 5 to 6 points Child-Pugh Class B: 7 to 9 points Child-Pugh Class C: 10 to 15 points			

- Routinely monitor patients during obeticholic acid treatment for biochemical response, tolerability, progression of PBC disease, and re-evaluate Child-Pugh classification to determine if dosage adjustment is needed.
- Reduce the dosing frequency from once daily to once weekly as appropriate for patients who progress to advanced disease (i.e., from Child-Pugh Class A to Child-Pugh Class B or C).

Recommended Dosage Regimen
The recommended starting dose and titration dosage regimen of Obeticholic acid for patients who have not achieved an adequate biochemical response to an appropriate dosage of UDCA for at least 1 year or are intolerant to UDCA is dependent upon disease stage.

- Non-cirrhotic patients or compensated cirrhotic patients with no or mild hepatic impairment (Child-Pugh Class A) are dosed once daily.
- Cirrhotic patients with moderate or severe hepatic impairment (Child-Pugh Class B or C) or patients who have previously experienced a decompensation event are dosed initially once weekly and not more than twice weekly.

Table 2: Dosage Regimen by Disease Stage

Staging / Classification	Non-Cirrhotic or Compensated Child-Pugh Class A	Child-Pugh Class B or C or Patients with a Prior Decompensation Event[a]
Starting Obeticholic acid Dosage for first 3 months	5 mg once daily	5 mg once weekly
Obeticholic acid Dosage Titration after first 3 months, for patients who have not achieved an adequate reduction in ALP and/or total bilirubin and who are tolerating Obeticholic acid	10 mg once daily	5 mg twice weekly (at least 3 days apart) Titrate to 10 mg twice weekly (at least 3 days apart) based on response and tolerability
Maximum Obeticholic acid Dosage	10 mg once daily	10 mg twice weekly (at least 3 days apart)
[a] Gastroesophageal variceal bleeding, new or worsening jaundice, spontaneous bacterial peritonitis, etc. [b] Prior to dosage adjustment, re-calculate the Child-Pugh classification		

No dose adjustment of concomitant UDCA is required in patients receiving obeticholic acid.

Monitoring to Assess Safety, Treatment Interruption or Discontinuation
Routinely monitor patients during Obeticholic acid treatment for progression of PBC disease with laboratory and clinical assessments to determine whether dosage adjustment is needed. Reduce the dosing frequency for patients who progress from Child-Pugh Class A to Child-Pugh Class B or C. Close monitoring is recommended for patients at an increased risk of hepatic decompensation, including those with laboratory evidence of worsening liver function (i.e., total bilirubin, INR, albumin) and/or progression to cirrhosis.

Interrupt treatment with Obeticholic acid in patients with laboratory or clinical evidence of worsening liver function indicating risk of decompensation, and monitor the patient's liver function.

If the patient's condition returns to baseline, weigh the potential risks and benefits of restarting Obeticholic acid treatment. If Obeticholic acid is re-initiated, use the recommended starting dosage with adjustment for Child-Pugh classification.

Consider discontinuing Obeticholic acid in patients who have experienced clinically significant liver-related adverse reactions.

Management of Patients with Intolerable Pruritus on Obeticholic acid
For patients with intolerable pruritus on Obeticholic acid, consider one or more of the following management strategies:

<u>For Non-Cirrhotic or Compensated Cirrhotic Child-Pugh Class A Patients:</u>

- Add an antihistamine or bile acid binding resin
- Reduce the dosage of Obeticholic acid to:
  - 5 mg every other day, for patients intolerant to 5 mg once daily
  - 5 mg once daily, for patients intolerant to 10 mg once daily.
- Temporarily interrupt Obeticholic acid dosing for up to 2 weeks. Restart at a reduced dosage.

For patients whose dosage is reduced or interrupted, titrate the dosage based on biochemical response, tolerability and adjust according to Child-Pugh classification.

<u>For Child-Pugh Class B or C or Patients with a Prior Decompensation Event:</u>

- Add an antihistamine or bile acid binding resin
- Reducing the dosage of obeticholic acid to:
  - 5 mg once weekly, for patients intolerant to 5 mg twice weekly
  - 10 mg once weekly, for patients intolerant to 10 mg twice weekly
- Temporarily interrupt Obeticholic acid dosing for up to 2 weeks. Restart at a reduced dosage if applicable. Titrate the dosage based on biochemical response, tolerability and adjust according to Child-Pugh classification.

<u>Treatment Discontinuation</u>
Consider discontinuing Obeticholic acid treatment in patients who continue to experience persistent, intolerable pruritus despite management strategies.

Administration Instructions

- Take Obeticholic acid orally with or without food.
- For patients taking a bile acid binding resin, take Obeticholic acid at least 4-6 hours before or 4-6 hours after taking the bile acid binding resin, or at as great an interval as possible.

4.3 Contraindications
Obeticholic acid is contraindicated in patients with complete biliary obstruction.

4.4 Special Warnings and Precautions for Use
Hepatic Decompensation and Failure in Incorrectly Dosed PBC Patients with Child-Pugh Class B or C or Decompensated Cirrhosis.
In postmarketing reports, hepatic decompensation and failure, in some cases fatal, have been reported in PBC patients with decompensated cirrhosis or Child-Pugh Class B or C hepatic impairment when Obeticholic acid was dosed more frequently than the recommended starting dosage of 5 mg once weekly. Reported cases typically occurred within 2 to 5 weeks after starting Obeticholic acid and were characterized by an acute increase in total bilirubin and/or ALP concentrations in association with clinical signs and symptoms of hepatic decompensation (e.g., ascites, jaundice, gastrointestinal bleeding, worsening of hepatic encephalopathy). A few cases reported improvement after Obeticholic acid discontinuation; however, some cases reported ongoing symptoms. Because postmarketing cases often contain limited clinical information, there was insufficient information to rule out confounding factors (e.g., concomitant medications) or the role of the patient's underlying advanced disease in the events.

Patients who died due to liver-related complications generally had decompensated cirrhosis prior to treatment and were started on Obeticholic acid mg once daily, which is 7-fold greater than the once weekly starting regimen in this population.

<u>Patient Management</u>
Routinely monitor patients for progression of PBC disease, including liver-related complications, with laboratory and clinical assessments. Dosage adjustment, interruption or discontinuation may be required.

Close monitoring is recommended for patients at an increased risk of hepatic decompensation. Severe intercurrent illnesses that may worsen renal function or cause dehydration (e.g., gastroenteritis), may exacerbate the risk of hepatic decompensation.

Interrupt treatment with obeticholic acid in patients with laboratory or clinical evidence of worsening liver function indicating risk of decompensation, and monitor the patient's liver function. Consider discontinuing obeticholic acid in patients who have experienced clinically significant liver-related adverse reactions.

Discontinue obeticholic acid in patients who develop complete biliary obstruction.

Liver-Related Adverse Reactions
Monitor patients during treatment with obeticholic acid for elevations in liver biochemical tests and for the development of liver-related adverse reactions. Close monitoring is recommended for patients at an increased risk of hepatic decompensation. Interrupt treatment with obeticholic acid in patients with laboratory or clinical evidence of worsening liver function indicating risk of decompensation, and monitor the patient's liver function.

Severe Pruritus
The chances of developing severe pruritus was more in patients taking obeticholic acid 10 mg. Consider clinical evaluation of patients with new onset or worsening severe pruritus. Management strategies include the addition of bile acid resins or antihistamines, obeticholic acid dosage reduction, and/or temporary interruption of obeticholic acid dosing.

Reduction in HDL-C
Patients with PBC generally exhibit hyperlipidemia characterized by a significant elevation in total cholesterol primarily due to increased levels of high density lipoprotein-cholesterol (HDL-C). Monitor patients for changes in serum lipid levels during treatment. For patients who do not respond to obeticholic acid after 1 year at the highest recommended dosage that can be tolerated (maximum of 10 mg once daily), and who experience a reduction in HDL-C, weigh the potential risks against the benefits of continuing treatment.

4.5 Drug Interactions

Bile Acid Binding Resins
Bile acid binding resins such as cholestyramine, colestipol, or colesevelam adsorb and reduce bile acid absorption and may reduce the absorption, systemic exposure, and efficacy of obeticholic acid. If taking a bile acid binding resin, take obeticholic acid at least 4 hours before or 4 hours after taking the bile acid binding resin, or at as great an interval as possible.

Warfarin
The International Normalized Ratio (INR) decreased following coadministration of warfarin and obeticholic acid. Monitor INR and adjust the dosage of warfarin, as needed, to maintain the target INR range when co-administering obeticholic acid and warfarin.

CYP1A2 Substrates with Narrow Therapeutic Index
Obeticholic acid may increase the exposure to concomitant drugs that are CYP1A2 substrates. Therapeutic monitoring of CYP1A2 substrates with a narrow therapeutic index (e.g. theophylline and tizanidine) is recommended when co-administered with obeticholic acid.

Inhibitors of Bile Salt Efflux Pump
Avoid concomitant use of inhibitors of the bile salt efflux pump (BSEP) such as cyclosporine. Concomitant medications that inhibit canalicular membrane bile acid transporters such as the BSEP may exacerbate accumulation of conjugated bile salts including taurine conjugate of obeticholic acid in the liver and result in clinical symptoms. If concomitant use is deemed necessary, monitor serum transaminases and bilirubin.

4.6 Use in Special Populations (such as pregnant women, **lactating women, paediatric patients, geriatric patients etc.)**

Pregnancy

<u>Risk Summary</u>
The limited available human data on the use of obeticholic acid during pregnancy are not sufficient to inform a drug-associated risk. In animal reproduction studies, no developmental abnormalities or fetal harm was observed when pregnant rats or rabbits were administered obeticholic acid during the period of organogenesis at exposures approximately 13 times and 6 times human exposures, respectively, at the maximum recommended human dose (MRHD) of 10 mg.

The estimated background risks of major birth defects and miscarriage for the indicated population are unknown.

Lactation

<u>Risk Summary</u>
There is no information on the presence of obeticholic acid in human 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 obeticholic acid and any potential adverse effects on the breastfed infant from obeticholic acid or from the underlying maternal condition.

Pediatric Use
The safety and effectiveness of obeticholic acid in pediatric patients have not been established.

Geriatric Use
There are no differences in safety or effectiveness in subjects less than 65 years of age, but greater sensitivity of some older individuals cannot be ruled out. No dose adjustment is required for elderly patients.

Hepatic Impairment
Hepatic decompensation and failure, in some cases fatal, have been reported postmarketing in primary biliary cholangitis (PBC) patients with decompensated cirrhosis or Child-Pugh B or C hepatic impairment when of obeticholic acid was dosed more frequently than recommended.

Plasma exposure to obeticholic acid and its active conjugates increases significantly in patients with moderate to severe hepatic impairment (Child-Pugh Classes B and C).

Prior to the initiation of obeticholic acid determine the patient's Child-Pugh classification to determine the starting dosage. Re-evaluate the dosing regimen periodically during treatment.

Dosage adjustment is required in patients with Child-Pugh Class B and C. Routinely monitor patients for progression of PBC disease with laboratory and clinical assessments. Dosage adjustment, interruption or discontinuation may be required.

Renal impairment
Limited data exists in patients with mild and moderate renal impairment and no data exists in severe renal impairment. No dose adjustment is required for patients with renal impairment.

4.7 Effects on Ability to Drive and Use Machines
Obeticholic acid has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable Effects
The following clinically significant adverse reactions of Obeticholic acid:

- Hepatic Decompensation and Failure in Incorrectly Dosed PBC Patients with Child-Pugh Class B or C or Decompensated Cirrhosis
- Liver-Related Adverse Reactions
- Severe Pruritus [Reduction in HDL-C

The most commonly reported adverse reactions were pruritus and fatigue. The most common adverse reaction leading to discontinuation was pruritus. The majority of pruritus occurred within the first month of treatment and tended to resolve over time with continued dosing.

Tabulated list of adverse reactions
The adverse reactions frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

System Organ Class	Very common	Common
Endocrine disorders		Thyroid function abnormality
Nervous system disorders		Dizziness
Cardiac disorders		Palpitations
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain		
Gastrointestinal disorders	Abdominal pain and discomfort	Constipation
Skin and subcutaneous tissue disorders	Pruritus	Eczema, Rash
Musculoskeletal and connective tissue disorders		Arthralgia
General disorders and administration site conditions	Fatigue	Oedema peripheral, Pyrexia

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. To report Suspected Adverse Reactions, contact MSN Laboratories Private Limited at pharmacovigilance@msnlabs.com or through company website www.msnlabs.com->Contact us->Medical Enquiry/ to report a side effect.

4.9 Overdose
The highest single dose exposure of obeticholic acid was 500 mg. In PBC patients who received obeticholic acid 25 mg once daily (2.5 times the highest recommended dosage) or 50 mg once daily (5 times the highest recommended dosage), a dose-dependent increase in the incidence of liver-related adverse reactions (e.g., ascites, primary biliary cholangitis flare, new onset jaundice), and transaminase and bilirubin elevations (up to greater than 3-times upper limit of normal [ULN]) were reported. In the case of overdose, patients should be carefully observed and supportive care administered, as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of action
Obeticholic acid is an agonist for FXR, a nuclear receptor expressed in the liver and intestine. FXR is a key regulator of bile acid, inflammatory, fibrotic, and metabolic pathways. FXR activation decreases the intracellular hepatocyte concentrations of bile acids by suppressing de novo synthesis from cholesterol as well as by increased transport of bile acids out of the hepatocytes. These mechanisms limit the overall size of the circulating bile acid pool while promoting choleresis, thus reducing hepatic exposure to bile acids.

Cardiac Electrophysiology
At a dose of 10-times the maximum recommended dose, Obeticholic acid does not prolong the QT interval to any clinically relevant extent.

5.2 Pharmacokinetic Properties

Absorption
Following multiple oral doses of Obeticholic acid 10 mg once daily, peak plasma concentrations (C_{max}) of obeticholic acid occurred at a median time (T_{max}) of approximately 1.5 hours. The median T_{max} for both the glyco-and tauro-conjugates of obeticholic acid was 10 hours.

Following multiple-dose administration of Obeticholic acid 5, 10, and 25 mg once daily (2.5 times the highest recommend dosage) for 14 days, systemic exposures of obeticholic acid increased dose proportionally. Exposures to glyco-obeticholic acid and tauro-obeticholic acid and total obeticholic acid (the sum of obeticholic acid and its two active conjugates) increased more than proportionally with dose. The steady-state systemic exposure (AUC0-24h) achieved on Day14 of total obeticholic acid was 4.2-, 6.6-, and 7.8-fold the systemic exposure (AUC0-24h) achieved on Day 1 after 5, 10, and 25 mg once daily dosing, respectively.

Food Effect
Coadministration with food did not alter the extent of absorption of obeticholic acid.

Distribution
Human plasma protein binding of obeticholic acid and its conjugates is greater than 99%. The volume of distribution of obeticholic acid is 618 L. The volumes of distribution of glyco-and tauro-obeticholic acid have not been determined.

Elimination

Metabolism
Obeticholic acid is conjugated with glycine or taurine in the liver and secreted into bile. These glycine and taurine conjugates of obeticholic acid are absorbed in the small intestine leading to enterohepatic recirculation. The conjugates can be deconjugated in the ileum and colon by intestinal microbiota, leading to the conversion to obeticholic acid that can be reabsorbed or excreted in feces, the principal route of elimination.

After daily administration of obeticholic acid, there was accumulation of the glycine and taurine conjugates of obeticholic acid, which has *in vitro* pharmacological activities similar to the parent drug, obeticholic acid. The metabolite-to-parent ratios of the glycine and taurine conjugates of obeticholic acid were 13.8 and 12.3 respectively, after daily administration. An additional third obeticholic acid metabolite, 3-glucuronide, was formed but was considered to have minimal pharmacologic activity.

Excretion
After administration of radiolabeled obeticholic acid, about 87% of the dose was excreted in feces through biliary secretion. Less than 3% of the dose was excreted in the urine with no detection of obeticholic acid.

Specific Populations
Body weight, Age, Sex Race/Ethnicity: Based on population pharmacokinetic analysis, body weight was a significant predictor of obeticholic acid pharmacokinetics with lower obeticholic acid exposure expected with higher body weight. The body weight effect is not expected to cause a meaningful impact on efficacy. The pharmacokinetics of obeticholic acid would not be expected to be altered based on age, sex, or race/ethnicity

Renal Impairment: Obeticholic acid has not been studied in patients with moderate and severe renal impairment (estimated glomerular filtration rate [eGFR] less than 60 mL/min/1.73 m2). In the population pharmacokinetic analysis, an eGFR greater than 50 mL/min/1.73 m2 did not have a meaningful effect on the pharmacokinetics of obeticholic acid and its conjugated metabolites.

Hepatic Impairment: Obeticholic acid is metabolized in the liver. In subjects with mild, moderate and severe hepatic impairment (Child-Pugh Class A, B, and C, respectively), the mean AUC of total obeticholic acid increased 1.1-, 4-and 17-fold, respectively, compared to subjects with normal hepatic function following single-dose administration of 10 mg obeticholic acid.

Drug Interaction Studies

Effect of Obeticholic Acid on Other Drugs
Obeticholic acid can inhibit CYP3A4. Obeticholic acid is not expected to inhibit CYPs 2B6, 2C8, 2C9, 2C19, and 2D6, or induce CYPs 1A2, 2B6, 2C8, 2C9, 2C19, and 3A4 at the recommended dose of Obeticholic acid. Down-regulation of mRNA was observed in a concentration-dependent fashion for CYP1A2 and CYP3A4 by obeticholic acid and its glycine and taurine conjugates.

In vitro studies suggest that there is potential for obeticholic acid and its glycine and taurine conjugates to inhibit OATP1B1 and OATP1B3 (the clinical significance of which is unknown), but not P-gp, BCRP, OAT1, OAT3, OCT2, and MATE transporters, at the recommended dose of obeticholic acid.

In vitro studies showed that obeticholic acid and its glycine and taurine conjugates inhibit BSEP in a dose dependent manner. However, an in vivo drug interaction due to inhibition of BSEP in patients using the recommended dosage regimen appears unlikely.

Induction of BSEP can occur by FXR activation by obeticholic acid and its conjugates, which are FXR agonists.

Warfarin: Concomitant administration of 25 mg warfarin as a single dose with Obeticholic acid 10 mg once daily resulted in 13% increase in systemic exposure to S-warfarin and 11% decrease in maximum INR.

Caffeine (CYP1A2 substrate): Concomitant administration of 200 mg caffeine as a single dose with Obeticholic acid 10 mg once daily resulted in a 42% increase in plasma AUC and 6% increase in C_{max} of caffeine.

Omeprazole (CYP2C19 substrate): Concomitant administration of 20 mg omeprazole as a single dose with Obeticholic acid 10 mg once daily resulted in a 32% increase in AUC and a 33% increase in C_{max} of omeprazole. The clinical significance is unknown.

No clinically relevant interactions were seen when the following drugs were administered as single doses concomitantly with Obeticholic acid 10 mg once daily:

Midazolam 2 mg (CYP3A4 substrate): 2% increase in AUC and C_{max} of midazolam.

Dextromethorphan 30 mg (CYP2D6 substrate): 11% decrease in AUC and 12% decrease in C_{max} of dextromethorphan.

Rosuvastatin 20 mg (BCRP, OATP1B1, OATP1B3 substrate): 22% increase in AUC and a 27% increase in C_{max} of rosuvastatin.

Effect of Other Drugs on Obeticholic Acid
In vitro data suggest that obeticholic acid is not metabolized to any significant extent by CYP450 enzymes.

Proton Pump Inhibitors (omeprazole): Concomitant administration of 20 mg omeprazole once daily with Obeticholic acid 10 mg once daily resulted in a less than 1.2-fold increase in obeticholic acid exposure. This increase is not expected to be clinically relevant. Concomitant administration of 40 mg omeprazole once daily with Obeticholic acid 10 mg once daily was not studied.

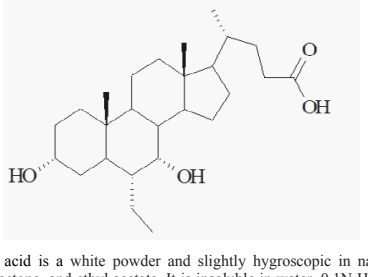
BSEP inhibitors: In vitro data indicate that tauro-obeticholic acid is a substrate of BSEP.

6. NONCLINICAL PROPERTIES

6.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenic potential of obeticholic acid was assessed in carcinogenicity studies of up to 2 years in duration in mice and rats. In mice, there were no drug-related neoplastic findings at doses up to 25 mg/kg/day obeticholic acid, a dose that produced systemic exposures approximately 12 times those in humans at the MRHD of 10 mg. In rats, obeticholic acid was administered at doses of 2, 7, and 20 mg/kg/day. At 20 mg/kg/day (approximately 12 times the human exposure at the MRHD), obeticholic acid caused an increase in the incidence of benign granulosa cell tumors in the ovaries and benign granular cell tumors in the cervix and vagina of female rats. There were no drug-related neoplastic findings in male rats. Obeticholic acid was not genotoxic in the Ames test, a human peripheral blood lymphocyte chromosomal aberration test, and a mouse micronucleus test. The glycine conjugate of obeticholic acid was also not genotoxic in an Ames test and human peripheral blood lymphocyte chromosome aberration test. The taurine conjugate of obeticholic acid was not genotoxic in an Ames test, and was negative in a human peripheral blood lymphocyte chromosomal aberration test in the presence of metabolic activation; the findings of the chromosomal aberration assay in the absence of metabolic activation were inconclusive. Obeticholic acid, administered at oral doses of 5, 25 and 50 mg/kg/day to male rats for 28 days before mating and throughout the mating period, and to female rats from 14 days before mating through mating and until gestation day 7, did not alter male or female fertility or early embryonic development at any dose (the 50 mg/kg/day dose is approximately 13 times the human exposure at the MRHD) *[Reference OCALIVA USFDA label, dated Feb-2018]*.

7. DESCRIPTION
Obeticholic Acid is a farnesoid X receptor (FXR) agonist. Chemically, obeticholic acid is 3α, 7α-dihydroxy-6α-ethyl-5β-cholan-24-oic acid. The molecular formula is $C_{26}H_{44}O_4$ and the molecular weight is 420.63 g/mol.

The chemical structure of Obeticholic Acid is:



Obeticholic acid is a white powder and slightly hygroscopic in nature. It is soluble in methanol, acetone, and ethyl acetate. It is insoluble in water, 0.1N HCl, Hydrochloric acid buffer (pH 1.2), Acid Phthalate buffer (pH 3.0), Acetate buffer (pH 4.5) and Phosphate buffer (pH 6.8, 7.2 and 8.0).

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities
None

8.2 Packing Information
10's Alu-Alu blister pack.

8.3 Storage and Handling Instructions
Do not store above 30^0C.

KEEP OUT OF REACH OF CHILDREN

9. PATIENT COUNSELING INFORMATION
Advise the patient to read package insert.

Hepatic Decompensation and Failure in Incorrectly Dosed PBC Patients with Child-Pugh Class B or C or Decompensated Cirrhosis

- Instruct patients and caregivers to immediately contact their healthcare provider if they experience:
  - Symptoms of disease progression or worsening liver function, such as ascites, jaundice, gastrointestinal bleeding or worsening of hepatic encephalopathy.
  - Symptoms of complete biliary obstruction.
- Instruct patients and caregivers to immediately contact their healthcare provider if they experience severe or persistent non-specific signs and symptoms of impaired health: nausea, vomiting, abdominal pain, diarrhea, weight loss, fever and chills, worsening or new fatigue, weakness, loss of appetite or dehydration.
- Inform patients that they will need to undergo laboratory testing periodically while on Obeticholic acid treatment to assess liver function.

Severe Pruritus
- Advise patients to contact their healthcare provider if they experience new onset or worsening severe pruritus.

Reduction in HDL-C
- Advise patients to contact their healthcare provider if they experience new onset or worsening severe pruritus.

Administration

Advise patients to take:
- Obeticholic acid with or without food.
- Obeticholic acid at least 4 hours before or 4 hours after taking a bile acid binding resin, or at as great an interval as possible

10. DETAILS OF MANUFACTURER
MSN Laboratories Private Limited
(Formulations Division), Plot No. 42, Anrich Industrial Estate, Bollaram,
Sangareddy District - 502 325, Telangana, INDIA.

11. DETAILS OF MANUFACTURING LICENCE NUMBER

38/MD/AP/2007/F/CC

12. DATE OF REVISION

August 2020.

B32683-00