1. NAME OF THE MEDICINAL PRODUCT

OCALIVA™ 5 mg

OCALIVA™ 10 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

OCALIVA 5 mg film-coated tablets
Each film-coated tablet contains 5 mg of obeticholic acid.

OCALIVA 10 mg film-coated tablets
Each film-coated tablet contains 10 mg of obeticholic acid.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet

OCALIVA 5 mg film-coated tablets
Off white to yellow, round tablet debossed with 'INT' on one side and '5' on the other side.

OCALIVA 10 mg film-coated tablets
Off white to yellow, triangular tablet, debossed with 'INT' on one side and '10' on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

OCALIVA is indicated for the treatment of primary biliary cholangitis (also known as primary biliary cirrhosis) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA.

4.2 Posology and method of administration

Posology
Prior to initiation of treatment with obeticholic acid the patient's hepatic status must be known. Whether the patient has decompensated cirrhosis (including Child-Pugh Class B or C) or has had a prior decompensation event should be determined prior to initiation of treatment because obeticholic acid is contraindicated in these patients (see sections 4.3 and 4.4).

The starting dose of obeticholic acid is 5 mg once daily for the first 6 months.

Limited data is available on Ocaliva as monotherapy.

After the first 6 months, for patients who have not achieved an adequate reduction in alkaline phosphatase (ALP) and/or total bilirubin and who are tolerating obeticholic acid, increase to a maximum dose of 10 mg once daily.

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

Management and dose adjustment for severe pruritus
Management strategies include the addition of bile acid binding resins or antihistamines.

For patients experiencing severe intolerability due to pruritus, one or more of the following should be considered:

- The dose of obeticholic acid may be reduced 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
- The dose of obeticholic acid may be temporarily interrupted for up to 2 weeks followed by restarting at a reduced dose.
- The dose may be increased to 10 mg once daily, as tolerated, to achieve optimal response.

Discontinuing treatment with obeticholic acid may be considered for patients who continue to experience persistent intolerable pruritus.

Bile acid binding resins
For patients taking bile acid binding resins, obeticholic acid should be administered at least 4 to 6 hours before or 4 to 6 hours after taking a bile acid binding resin, or at as great an interval as possible (see section 4.5).

Missed dose
If a dose is missed, the missed dose should be skipped and the normal schedule should be resumed for the following dose. A double dose should not be taken to make up for the missed dose.

Special populations

Hepatic impairment
Obeticholic acid is contraindicated in patients with decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event (see sections 4.3 and 4.4).

Elderly (≥ 65 years)
Limited data exists in elderly patients. No dose adjustment is required for elderly patients (see section 5.2).

Renal impairment
No dose adjustment is required for patients with renal impairment (see section 5.2).

Paediatric population
There is no relevant use of obeticholic acid in the paediatric population in the treatment of primary biliary cholangitis (PBC).

Method of administration
The tablet should be taken orally with or without food.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Patients with decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event (see section 4.4).
- Patients with complete biliary obstruction.

4.4 Special warnings and precautions for use

Hepatic adverse events

Hepatic failure, sometimes fatal or resulting in liver transplant, has been reported with obeticholic acid treatment in PBC patients with either compensated or decompensated cirrhosis.

Some of these cases occurred in patients with decompensated cirrhosis when they were treated with higher than the recommended dose for that patient population; however, cases of hepatic decompensation and failure have continued to be reported in patients with decompensated cirrhosis even when they received the recommended dose.

Elevations in alanine amino transferase (ALT) and aspartate aminotransferase (AST) have been observed in patients taking obeticholic acid. Clinical signs and symptoms of hepatic decompensation have also been observed. These events have occurred as early as within the first month of treatment. Hepatic adverse events have primarily been observed at doses higher than the maximum recommended dose of 10 mg once daily (see section 4.9).

All patients should be routinely monitored for progression of PBC, including hepatic adverse reactions, with laboratory and clinical assessments to determine whether obeticholic acid treatment discontinuation is needed. Patients at increased risk of hepatic decompensation, including those with elevated bilirubin levels, evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia), concomitant hepatic disease (e.g., autoimmune hepatitis, alcoholic liver disease), and/or severe intercurrent illness should be closely monitored to determine whether obeticholic acid treatment discontinuation is needed.

Treatment with obeticholic acid in patients with laboratory or clinical evidence of hepatic decompensation (e.g., ascites, jaundice, variceal bleeding, hepatic encephalopathy), including progression to Child-Pugh Class B or C, should be permanently discontinued (see section 4.3).

Treatment with obeticholic acid should be interrupted during severe intercurrent illness or in patients who experience clinically significant hepatic adverse reactions and the patient's liver function should be monitored. After resolution and if there is no laboratory or clinical evidence of hepatic decompensation, the potential risks and benefits of restarting obeticholic acid treatment should be considered.

Severe pruritus
Severe pruritus was reported in 23% of patients treated with OCALIVA 10 mg arm, 19% of patients in the OCALIVA titration arm, and 7% of patients in the placebo arms. The median time to onset of severe pruritus was 11, 158, and 75 days for patients in the OCALIVA 10 mg, OCALIVA titration, and placebo arms, respectively. Management strategies include the addition of bile acid binding resins or antihistamines, dose reduction, reduced dosing frequency, and/or temporary dose interruption (see sections 4.2 and 4.8).

Excipients
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on obeticholic acid

Bile acid binding resins
Bile acid binding resins such as cholestyramine, colestipol, or colesevelam adsorb and reduce bile acid absorption and may reduce efficacy of obeticholic acid. When concomitant bile acid binding resins are administered, obeticholic acid should be taken at least 4 to 6 hours before or 4 to 6 hours after taking a bile acid binding resin, or at as great an interval as possible.

Effect of obeticholic acid on other medicinal products

Warfarin
International normalised ratio (INR) is decreased following co-administration of warfarin and obeticholic acid. INR should be monitored and the dose of warfarin adjusted, if needed, to maintain the target INR range when co-administering obeticholic acid and warfarin.

Interaction with CYP1A2 substrates with narrow therapeutic index
Obeticholic acid may increase the exposure to concomitant medicinal products that are CYP1A2 substrates. Therapeutic monitoring of CYP1A2 substrates with narrow therapeutic index (e.g., theophylline and tizanidine) is recommended.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no data on the use of obeticholic acid in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of obeticholic acid during pregnancy.

Breast-feeding
It is unknown whether obeticholic acid is excreted in human milk. Based on animal studies and intended pharmacology, obeticholic acid is not expected to interfere with breast-feeding or the growth or development of a breast-fed child (see section 5.3). A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from obeticholic acid therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
No fertility data is available in humans. Animal studies do not indicate any direct or indirect effects on fertility or reproduction (see section 5.3).

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

Summary of the safety profile
The most commonly reported adverse reactions were pruritus (63%) and fatigue (22%). 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 reported with OCALIVA are listed in the table below by MedDRA system organ class and by frequency. 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).

Table 1. Frequency of adverse reactions in PBC patients

System organ class	Very common	Common	Not known
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	
Hepatobiliary disorders			Hepatic failure, Blood bilirubin increased, Jaundice, Hepatic cirrhosis
Skin and subcutaneous tissue disorders	Pruritus	Eczema, Rash	
Musculoskeletal and connective tissue disorders		Arthralgia	
General disorders and administration site conditions	Fatigue	Oedema peripheral, Pyrexia	

Description of selected adverse reactions

Discontinuation of treatment

Adverse reactions leading to discontinuation of treatment were 1% (pruritus) in the obeticholic acid titration arm and 11% (pruritus and fatigue) in the obeticholic acid 10 mg arm.

Pruritus

Approximately 60% of patients had a history of pruritus upon enrollment in the phase III study. Treatment-emergent pruritus generally started within the first month following the initiation of treatment.

Relative to patients who started on 10 mg once daily in the OCALIVA 10 mg arm, patients in the OCALIVA titration arm had a lower incidence of pruritus (70% and 56% respectively) and a lower discontinuation rate due to pruritus (10% and 1%, respectively).

The percentages of patients who required interventions (i.e., dose adjustments, treatment interruptions, or initiation of antihistamines or bile acid binding resins) were 41% in the OCALIVA 10 mg arm, 34% in the OCALIVA titration group, and 19% in the placebo group.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il
and additionally emailed to the Registration Holder's Patient Safety Unit at:
drugsafety@neopharmgroup.com

4.9 Overdose

The highest single dose exposure of obeticholic acid in healthy volunteers has been at the 500 mg dose. Repeated doses of 250 mg have been administered for 12 consecutive days and some subjects experienced pruritus and reversible transaminase liver elevations. In PBC patients who received OCALIVA 25 mg once daily (2.5-times the highest recommended dose) or 50 mg once daily (5-times the highest recommended dose), experienced 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 Pharmacodynamic properties

Pharmacotherapeutic group: Bile and liver therapy, bile acids and derivatives. ATC code: A05AA04

Mechanism of action
Obeticholic acid is a selective and potent agonist for the farnesoid X receptor (FXR), a nuclear receptor expressed at high levels in the liver and intestine. FXR is thought to be 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 increasing 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.

Clinical efficacy and safety
A phase III, randomised, double-blind, placebo-controlled, parallel-group, 12-month study (POISE) evaluated the safety and efficacy of OCALIVA in 216 patients with PBC who were taking UDCA for at least 12 months (stable dose for ≥ 3 months) or who were unable to tolerate UDCA and did not receive UDCA for ≥ 3 months. Patients were included in the trial if the alkaline phosphatase (ALP) was greater than or equal to 1.67 times upper limit of normal (ULN) and/or if total bilirubin was greater than 1 × ULN but less 2 × ULN. Patients were randomised (1:1:1) to receive once daily placebo, OCALIVA 10 mg, or OCALIVA titration (5 mg titrated to 10 mg at 6 months dependent on therapeutic response/tolerability).

The majority (93%) of patients received treatment in combination with UDCA and a small number of patients (7%) unable to tolerate UDCA received placebo, OCALIVA (10 mg) or OCALIVA titration (5 mg to 10 mg) as monotherapy. ALP and total bilirubin were assessed as categorical variables in the primary composite endpoint, as well as continuous variables over time.

The study population was predominantly female (91%) and white (94%). The mean age was 56 years, with the majority of patients less than 65 years old. Mean baseline ALP values ranged from 316 U/L to 327 U/L. Mean baseline total bilirubin values ranged from 10 µmol/L to 12 µmol/L across treatment arms, with 92% of patients within normal range.

Treatment with OCALIVA 10 mg or OCALIVA titration (5 mg to 10 mg) resulted in clinically and statistically significant increases ($p<0.0001$) relative to placebo in the number of patients achieving the primary composite endpoint at all study time points (see Table 2). Responses occurred as early as 2 weeks and were dose dependent (OCALIVA 5 mg compared with 10 mg at 6 months, $p=0.0358$).

Table 2. Percentage of PBC patients achieving the primary composite endpoint[a] at month 6 and month 12 with or without UDCA[b]

	OCALIVA 10 mg[c] (N=73)	**OCALIVA Titration[c] (N=70)**	**Placebo (N=73)**
Month 6			
Responders, n (%) Corresponding 95% CI	37 (51) 39%, 62%	24 (34) 23%, 45%	5 (7) 1%, 13%
p-value[d]	<0.0001	<0.0001	NA
Month 12			
Responders, n (%) Corresponding 95% CI	35 (48) 36%, 60%	32 (46) 34%, 58%	7 (10) 4%, 19%
p-value[d]	<0.0001	<0.0001	NA
Components of primary endpoint[e]			
ALP less than 1.67-times ULN, n (%)	40 (55)	33 (47)	12 (16)
Decrease in ALP of at least 15%, n (%)	57 (78)	54 (77)	21 (29)
Total bilirubin less than or equal to 1-times ULN[f], n (%)	60 (82)	62 (89)	57 (78)

[a] Percentage of subjects achieving a response, defined as an ALP less than 1.67-times the ULN, total bilirubin within the normal range, and an ALP decrease of at least 15%. Missing values were considered a non-response. The Fisher's exact test was used to calculate the 95% confidence intervals (CIs).
[b] In the trial there were 16 patients (7%) who were intolerant and did not receive concomitant UDCA: 6 patients (8%) in the OCALIVA 10 mg arm, 5 patients (7%) in the OCALIVA titration arm, and 5 patients (7%) in the placebo arm.
[c] Patients were randomised (1:1:1) to receive OCALIVA 10 mg once daily for the entire 12 months of the trial, or OCALIVA titration (5 mg once daily for the initial 6 months, with the option to increase to 10 mg once daily for the last 6 months, if the patient was tolerating OCALIVA but had ALP 1.67-times the ULN or greater, and/or total bilirubin above the ULN, or less than 15% ALP reduction) or placebo.
[d]OCALIVA titration and OCALIVA 10 mg versus placebo. P-values are obtained using the Cochran-Mantel-Haenszel General Association test stratified by intolerance to UDCA and pre-treatment ALP greater than 3-times ULN and/or AST greater than 2-times ULN and/or total bilirubin greater than ULN.
[e] Response rates were calculated based on the observed case analysis (i.e., [n=observed responder]/[N=intention to treat (ITT) population]); percentage of patients with month 12 values are 86%, 91% and 96% for the OCALIVA 10 mg, OCALIVA titration and placebo arms, respectively.
[f] The mean baseline total bilirubin value was 0.65 mg/dL, and was within the normal range (i.e., less than or equal to the ULN) in 92% of the enrolled patients.

Mean reduction in ALP
Mean reductions in ALP were observed as early as week 2 and were maintained through month 12 for patients who were maintained on the same dose throughout 12 months. For patients in the OCALIVA titration arm whose OCALIVA dose was increased from 5 mg once daily to 10 mg once daily, additional reductions in ALP were observed at month 12 in the majority of patients.

Mean reduction in gamma-glutamyl transferase (GGT)
The mean (95% CI) reduction in GGT was 178 (137, 219) U/L in the OCALIVA 10 mg arm, 138 (102, 174) U/L in the OCALIVA titration arm, and 8 (-32, 48) U/L in the placebo arm**.**

Monotherapy
Fifty-one PBC patients with baseline ALP 1.67-times ULN or greater and/or total bilirubin greater than ULN were evaluated for a biochemical response to OCALIVA as monotherapy (24 patients received OCALIVA 10 mg once daily and 27 patients received placebo) in a pooled analysis of data from the phase III randomised, double-blind, placebo-controlled 12-month study (POISE) and from a randomised, double-blind, placebo-controlled, 3-month study. At month 3, 9 (38%) OCALIVA-treated patients achieved a response to the composite endpoint, compared to 1 (4%) placebo-treated patient. The mean (95% CI) reduction in ALP in OCALIVA-treated patients was 246 (165, 327) U/L compared to an increase of 17 (-7, 42) U/L in the placebo-treated patients.

5.2 Pharmacokinetic properties

Absorption
Obeticholic acid is absorbed with peak plasma concentrations (C_{max}) occurring at a median time (t_{max}) of approximately 2 hours. Co-administration with food does 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.

Biotransformation
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 faeces, the principal route of elimination.

After daily administration of obeticholic acid, there was accumulation of the glycine and taurine conjugates of obeticholic acid which have *in vitro* pharmacological activities similar to the parent drug. 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 is formed but is considered to have minimal pharmacologic activity.

Elimination
After administration of radiolabeled obeticholic acid, greater than 87% is excreted in faeces. Urinary excretion is less than 3%.

Dose/Time proportionality
Following multiple-dose administration of 5, 10, and 25 mg once daily for 14 days, systemic exposures of obeticholic acid increased dose proportionally. Exposures of glyco- and tauro-obeticholic acid, and total obeticholic acid increase more than proportionally with dose.

Special populations
Elderly
There are limited pharmacokinetic data in elderly patients (≥ 65 years). Population pharmacokinetic analysis, developed using data from patients up to 65 years old, indicated that age is not expected to significantly influence obeticholic acid clearance from the circulation.

Paediatric population
No pharmacokinetic studies were performed with obeticholic acid in patients less than 18 years of age.

Gender
Population pharmacokinetic analysis indicated that gender does not influence obeticholic acid pharmacokinetics.

Race
Population pharmacokinetic analysis indicated that race is not expected to influence obeticholic acid pharmacokinetics.

Renal impairment
In a dedicated single-dose pharmacokinetic study using 25 mg of obeticholic acid, plasma exposures to obeticholic acid and its conjugates were increased by approximately 1.4- to 1.6-fold in subjects with mild (modification of diet in renal disease [MDRD] eGFR ≥ 60 and < 90 mL/min/1.73 m^2), moderate (MDRD eGFR ≥ 30 and < 60 mL/min/1.73 m^2) and severe (MDRD eGFR ≥ 15 and < 30 mL/min/1.73 m^2) renal impairment compared to subjects with normal renal function. This modest increase is not considered to be clinically meaningful.

Hepatic impairment
Obeticholic acid is metabolised in the liver and intestines. The systemic exposure of obeticholic acid, its active conjugates, and endogenous bile acids is increased in patients with moderate and severe hepatic

impairment (Child-Pugh Class B and C, respectively) when compared to healthy controls (see sections 4.2, 4.3 and 4.4).

The impact of mild hepatic impairment (Child-Pugh Class A) on the pharmacokinetics of obeticholic acid was negligible, therefore, no dose adjustment is necessary for patients with mild hepatic impairment.

In subjects with mild, moderate and severe hepatic impairment (Child-Pugh Class A, B, and C, respectively), mean AUC of total obeticholic acid, the sum of obeticholic acid and its two active conjugates, increased by 1.13-, 4- and 17-fold, respectively, compared to subjects with normal hepatic function following single-dose administration of 10 mg obeticholic acid.

5.3 Preclinical safety data

Nonclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, and toxicity to fertility, reproduction and development.

Oral administration of obeticholic acid above the NOAEL to mice, rats, and dogs in pivotal, repeat dose toxicity studies resulted primarily in effects on the hepatobiliary system. These included increased liver weights, alterations in serum chemistry parameters (ALT, AST, LDH, ALP, GGT, and/or bilirubin), and macroscopic/microscopic alterations. All changes were reversible with discontinued dosing, and are consistent with and predict the dose-limiting toxicity in humans (systemic exposure at NOAEL was up to 24-fold higher than that seen at the maximum recommended human dose). In a pre- and post-natal toxicity study in rats, the tauro-conjugate of obeticholic acid was found in pups nursing from dams dosed with obeticholic acid.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Microcrystalline cellulose (E 460)
Sodium starch glycolate (Type A)
Magnesium stearate

Tablet coating
Poly(vinyl alcohol), partially hydrolysed (E 1203)
Titanium dioxide (E 171)
Macrogol (3350) (E 1521)
Talc (E 553b)
Iron oxide yellow (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

High-density polyethylene (HDPE) bottles with a child resistant polypropylene closure and an aluminium foil induction seal.

Pack size: 30 film-coated tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

Intercept Pharma Ltd.
Two Pancras Square
Kings Cross N1C 4AG
London
United Kingdom

8. REGISTRATION HOLDER

Neopharm Ltd.
6 Hashiloach St.
Petach-Tikva, 4951439
Israel

9. REGISTRATION NUMBERS

OCALIVA™ 5 mg: 160-32-35217-00
OCALIVA™ 10 mg: 160-33-35218-00

Revised in December 2022 according to MOH guidelines