PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr**OCALIVA®**

Obeticholic acid tablets

Tablets 5 mg and 10 mg, Oral

Farnesoid X Receptor (FXR) Agonist

OCALIVA, 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,

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for OCALIVA please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html

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What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

RECENT MAJOR LABEL CHANGES

2 CONTRAINDICATIONS	08/2022
3 SERIOUS WARNINGS AND PRECAUTIONS BOX	08/2022
4 DOSAGE AND ADMINISTRATION, 4.2 Recommended Dose and Dosage Adjustment	08/2022
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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

OCALIVA® (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.

Marketing authorization with conditions for this indication is based on a randomized, placebo-controlled, phase III study that assessed alkaline phosphatase (ALP) and bilirubin as a composite endpoint [see 14 CLINICAL TRIALS].

Marketing authorization with conditions for the indication for use as monotherapy is based on data from a pooled analysis of data from a randomized, phase III placebo-controlled study, of 12-month duration, and a randomized, double-blind, Phase II placebo-controlled study, of 3-month duration [see 14 CLINICAL TRIALS].

1.1 Pediatrics

Pediatrics (< 16 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Efficacy and safety data in subjects over 65 years of age are limited. Although no overall differences in safety or efficacy were observed between subjects greater than 65 and those less than 65 years of age. The safety and efficacy of OCALIVA as monotherapy in subjects over 65 years of age have not been established.

2 CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING section of the product monograph.
- OCALIVA is contraindicated in patients with decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event [see 7 WARNINGS AND PRECAUTIONS].
- OCALIVA is contraindicated in patients with compensated cirrhosis who have evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia) [see 7 WARNINGS AND PRECAUTIONS].
- OCALIVA is contraindicated in patients with complete biliary obstruction.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

Hepatic decompensation and failure in PBC patients with cirrhosis

- **Hepatic failure, sometimes fatal or resulting in liver transplant, has been reported with OCALIVA treatment in primary biliary cholangitis (PBC) patients with decompensated cirrhosis. In PBC patients with compensated cirrhosis, hepatic decompensation and failure have been reported. Some of these cases resulted in liver transplant [see 7 WARNINGS AND PRECAUTIONS].**
- **OCALIVA is contraindicated in PBC patients with decompensated cirrhosis, or a prior decompensation event, or with compensated cirrhosis who have evidence of portal hypertension [see 2 CONTRAINDICATIONS].**
- **Interrupt treatment during severe intercurrent illness or in patients who experience clinically significant hepatic adverse reactions. Permanently discontinue OCALIVA in patients with laboratory or clinical evidence of hepatic decompensation [see 4 DOSAGE AND ADMINISTRATION, 7 WARNINGS AND PRECAUTIONS].**

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Continuation of OCALIVA treatment in a subject with no improvement in biochemical markers of PBC (ALP and bilirubin) after 1 year on the maximum effective dose (10 mg) should be assessed based on the clinical course of PBC and potential risks and benefits of continued use of OCALIVA.

4.2 Recommended Dose and Dosage Adjustment

- Prior to the initiation of OCALIVA, healthcare providers should determine whether the patient has decompensated cirrhosis (including Child-Pugh Class B or C) or has had a prior decompensation event or has compensated cirrhosis with evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia) because OCALIVA is contraindicated in these patients [see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS].
- The recommended starting dose and titration dosage regimen of OCALIVA in adults who have not achieved an adequate response to an appropriate dosage of UDCA for at least 1 year or are intolerant to UDCA are as follows:
    - The starting dosage of obeticholic acid is 5 mg once daily taken orally for the first 6 months.
    - 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 dosage of 10 mg once daily.

Health Canada has not authorized an indication for pediatric use.

No dosage adjustment required for patients with renal impairment.

Monitoring to Assess Safety, Treatment Interruption or Discontinuation

Routinely monitor patients for progression of PBC including hepatic adverse reactions, with laboratory and clinical assessments to determine whether drug discontinuation is needed. Close monitoring is recommended for patients at increased risk of hepatic decompensation, including those with elevated bilirubin levels, evidence of portal hypertension, concomitant hepatic disease (e.g., autoimmune hepatitis, alcoholic liver disease), and/or severe intercurrent illness to determine whether drug discontinuation is needed.

Interrupt treatment with OCALIVA during severe intercurrent illness or in patients who experience clinically significant hepatic adverse reactions and monitor the patient's liver function. After resolution of the intercurrent illness or clinically significant hepatic adverse reactions, and if there is no laboratory or clinical evidence of hepatic decompensation, consider the potential risks and benefits of restarting OCALIVA treatment.

Permanently discontinue OCALIVA in patients with laboratory or clinical evidence of hepatic decompensation (e.g., ascites, jaundice, variceal bleeding, hepatic encephalopathy, Child-Pugh Class B or C) or in patients who have compensated cirrhosis and develop evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia) [see 2 CONTRAINDICATIONS].

Management of Patients with Intolerable Pruritus on OCALIVA

Management strategies include the addition of bile acid binding resins or antihistamines [see 14 CLINICAL TRIALS].

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

- Reducing the dosage of OCALIVA 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 interrupting OCALIVA dosing for up to 2 weeks followed by restarting at a reduced dosage.
  - Increase the dosage to 10 mg once daily, as tolerated, to achieve optimal response.

Consider discontinuing OCALIVA treatment in patients who continue to experience persistent, intolerable pruritus.

4.4 Administration

Take OCALIVA 30 minutes before breakfast [see 10 CLINICAL PHARMACOLOGY].

For patients taking a bile acid binding resin, take OCALIVA at least 4 hours before or 4 hours after taking the bile acid binding resin, or at as great an interval as possible [see 9 DRUG INTERACTIONS, 14 CLINICAL TRIALS].

4.5 Missed Dose

If a patient misses a dose of OCALIVA at the time it is usually taken, the patient should take OCALIVA as soon as possible, and then take the next dose of OCALIVA at the regularly scheduled time.

5 OVERDOSAGE

In the clinical trials, PBC patients who received OCALIVA 25 mg once daily (2.5-times the highest recommended dosage) or 50 mg once daily (5-times the highest recommended dosage) experienced a dose-dependent increase in the incidence of hepatic adverse reactions, including elevations in liver biochemical tests, ascites, jaundice, portal hypertension, and primary biliary cholangitis flares [see 7 WARNINGS AND PRECAUTIONS].

In the case of overdosage, patients should be carefully observed and supportive care administered, as appropriate.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1: Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form/ Strength/Composition	Non-medicinal Ingredients
oral	tablet 5 mg, 10 mg	Magnesium stearate, microcrystalline cellulose, Opadry II Yellow (polyvinyl alcohol-part hydrolyzed, titanium dioxide, macrogol (polyethylene glycol 3350), talc, and iron oxide yellow), sodium starch glycolate

OCALIVA tablets are supplied in 5 mg and 10 mg strengths for oral administration.

OCALIVA tablets are packaged in a 40 mL high density polyethylene bottle closed with a 33 mm polypropylene child resistant cap containing an induction seal. Each bottle contains 30 tablets.

5 mg Tablets

OCALIVA 5 mg tablets are available as off-white to yellow, round tablets debossed with INT on one side and 5 on the other side. Each tablet contains 5 mg of obeticholic acid.

10 mg Tablets

OCALIVA 10 mg tablets are available as off-white to yellow, triangular tablets debossed with INT on one side and 10 on the other side. Each tablet contains 10 mg of obeticholic acid.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

Carcinogenesis and Mutagenesis

See 16 NON-CLINICAL TOXICOLOGY

Cardiovascular

See 10.2 Pharmacodynamics

Hepatic/Biliary/Pancreatic

Hepatic Adverse Reactions

Hepatic failure, sometimes fatal or resulting in liver transplant, has been reported with OCALIVA treatment in PBC patients with decompensated cirrhosis. OCALIVA has not been adequately studied in patients with hepatic decompensation.

Some of these cases occurred in patients with decompensated cirrhosis when they were treated with higher than the recommended dosage 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 dosage.

In PBC patients with compensated cirrhosis, hepatic decompensation and failure have been reported. Some of these cases resulted in liver transplant.

A dose-response relationship was observed for the occurrence of hepatic adverse reactions including jaundice, worsening ascites and primary biliary cholangitis flares with dosages of OCALIVA of 10 mg once daily to 50 mg once daily (up to 5-times the highest recommended dosage), as early as one month after starting treatment with OCALIVA in two 3-month placebo-controlled clinical trials in patients with primarily early stage PBC [see 5 OVERDOSAGE].

In a pooled analysis of three placebo-controlled clinical trials in patients with PBC, the exposure-adjusted incidence rates for all serious and otherwise clinically significant hepatic adverse reactions, and isolated elevations in liver biochemical tests, per 100 patient exposure years (PEY) were: 5.2 in the OCALIVA 10 mg group (highest recommended dosage), 19.8 in the OCALIVA 25 mg group (2.5-times the highest recommended dosage) and 54.5 in the OCALIVA 50 mg group (5-times the highest recommended dosage) compared to 2.4 in the placebo group.

In mice hepatotoxicity was observed at exposure levels lower than human exposure at therapeutic doses [see 16 NON-CLINICAL TOXICOLOGY].

After initiation of therapy, all patients should be routinely monitored for progression of PBC, including hepatic adverse reactions, with laboratory and clinical assessments to determine whether OCALIVA treatment discontinuation is needed. Patients at increased risk of hepatic decompensation, including those with elevated bilirubin levels, evidence of portal hypertension, concomitant hepatic disease (e.g., autoimmune hepatitis, alcoholic liver disease), and/or severe intercurrent illness should be monitored more closely to determine whether OCALIVA treatment discontinuation in needed [see 4 DOSAGE AND ADMINISTRATION].

Interrupt treatment with OCALIVA during severe intercurrent illness or in patients who experience clinically significant hepatic adverse reactions and monitor the patient's liver function. After resolution of the intercurrent illness or clinically significant hepatic adverse reactions, and if there is no laboratory or clinical evidence of hepatic decompensation, consider the potential risks and benefits of restarting OCALIVA treatment [see 4 DOSAGE AND ADMINISTRATION].

Permanently discontinue OCALIVA in patients with laboratory or clinical evidence of hepatic decompensation (e.g., ascites, jaundice, variceal bleeding, hepatic encephalopathy, Child-Pugh Class B or C) or in patients who have compensated cirrhosis and develop evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia) [see 2 CONTRAINDICATIONS, 4 DOSAGE AND ADMINISTRATION].

Hepatic Impairment

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 by 1.1-, 4- and 17-fold, respectively, compared to subjects with normal hepatic function following single-dose administration of 10 mg OCALIVA.

OCALIVA is contraindicated in patients with decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event, or with compensated cirrhosis who have evidence of portal hypertension [see 2 CONTRAINDICATIONS].

Routinely monitor patients for progression of PBC, including hepatic adverse reactions, with laboratory and clinical assessment to determine whether drug discontinuation is needed [see Hepatic Adverse Reactions].

Treatment with OCALIVA should be initiated and monitored by a healthcare provider with experience managing PBC.

Monitoring and Laboratory Tests

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). In the Phase III trial, dose-dependent reductions from baseline in mean HDL-C levels were observed at 2 weeks in OCALIVA-treated patients, 20% and 9% in the 10 mg and titration arms, respectively, compared to 2% in the placebo arm. At Month 12, the reduction from baseline in mean HDL-C level was 19% in the OCALIVA 10 mg arm, 12% in the OCALIVA titration arm, and 2% in the placebo arm. Nine patients in the OCALIVA 10 mg arm, 6 patients in the OCALIVA titration arm, versus 3 patients in the placebo arm had reductions in HDL-C to less than 40 mg/dL. Monitor patients for changes in serum lipid levels during treatment. For patients who do not respond to OCALIVA after 1 year at the highest recommended dosage that can be tolerated, and who experience a reduction in HDL-C, weigh the potential risks against the benefits of continuing treatment.

Skin

Severe Pruritus

Pruritus was mostly mild to moderate in severity and generally started within the first month following the initiation of treatment with OCALIVA and decreased in severity over time with continued dosing. Severe pruritus was reported in 23% of patients in the OCALIVA 10 mg arm, 19% of patients in the OCALIVA titration arm, and 7% of patients in the placebo arm in the POISE trial, a 12-month double-blind randomized controlled clinical trial of 216 patients [see 8 ADVERSE REACTIONS]. Severe pruritus was defined as intense or widespread itching, interfering with activities of daily living, or causing severe sleep disturbance, or intolerable discomfort, and typically requiring medical interventions. In the subgroup of patients in the OCALIVA titration arm who increased their dosage from 5 mg once daily to 10 mg once daily after 6 months of treatment (n=33), the incidence of severe pruritus was 0% from Months 0 to 6 and 15% from Months 6 to 12. 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, OCALIVA dosage reduction, and/or temporary interruption of OCALIVA dosing [see 4 DOSAGE AND ADMINISTRATION].

7.1 Special Populations

7.1.1 Pregnant Women

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 [see 16 NON-CLINICAL TOXICOLOGY].

7.1.2 Breast-feeding

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 breast-feeding should be considered along with the mother's clinical need for OCALIVA and any potential adverse effects on the breast-fed infant from OCALIVA or from the underlying maternal condition.

7.1.3 Pediatrics (< 16 years of age)

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

7.1.4 Geriatrics (≥ 65 years of age)

Of the 201 patients in clinical trials of OCALIVA who received the recommended dosage (5 mg or 10 mg once daily), 41 (20%) were 65 years of age and older, while 9 (4%) were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and subjects less than 65 years of age, but greater sensitivity of some older individuals cannot be ruled out.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

A total of 432 patients with PBC were studied in three double-blind placebo-controlled Phase II and III clinical trials. Of these patients, 290 were treated with OCALIVA for at least 6 months, 232 were treated for at least 12 months, and 70 were treated for at least 2 years. There were 131 patients who received OCALIVA 10 mg once daily and 70 who received OCALIVA 5 mg once daily.

The most common adverse drug reactions reported in double-blind clinical trials (frequency ≥ 5%) were pruritus, fatigue, constipation, oropharyngeal pain and arthralgia. Pruritus decreased with lower initial doses of OCA, and was manageable with temporary interruptions of treatment, alternate dosing strategies, and/or antipruritic treatments, including antihistamines and bile acid sequestrants [see 7 WARNINGS AND PRECAUTIONS]. Fatigue occurred at a similar incidence in the OCA and placebo treatment arms.

Clinically significant or serious, hepatic findings (including increased transaminases and bilirubin and signs and symptoms of hepatic decompensation such as jaundice) were observed in subjects with PBC mainly at higher doses of OCA (25 to 50 mg/day), and generally within the first 1 to 3 months of treatment [see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX].

Although Health Canada has not authorized an indication for pediatric use, 7 pediatric patients with biliary atresia and successful hepatoportoenterostomy were treated with OCALIVA in an ongoing open label, dose finding Phase II clinical trial. Two patients experienced three serious adverse events, which were assessed as unlikely or not related to the treatment. One 4-year-old female patient, receiving 0.3 mg OCALIVA once daily for three months, experienced sepsis due to pneumococcus. This patient was later hospitalized for a planned liver transplant due to worsening liver function, 34 days after receiving the last dose of OCALIVA. A 3-year-old male patient, with elevated lipase receiving 0.3 mg of OCALIVA for four months was hospitalized with suspected pancreatitis.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The most common adverse reactions in occurring in ≥ 1% of patients in either OCALIVA treatment arm and at an incidence greater than the placebo treatment arm in the Phase II and Phase III clinical trials are shown in Table 2.

Table 2: Most Common Treatment-Emergent Adverse Reactions [1] by System Organ Class in Adult Patients with PBC in the Phase II and Phase III Clinical Trials

System Organ Class/ Preferred Term, n (%)	Total OCA (N=306) Subjects[2]	Placebo (N=134) Subjects[2]
All TE Adverse Events		
Skin and subcutaneous tissue disorders		
Pruritus	209 (68%)	54 (40%)
Rash	11 (4%)	4 (3%)
Dry skin	7 (2%)	2 (1%)
Eczema	6 (2%)	1 (<1%)
Erythema	5 (2%)	0
Gastrointestinal disorders		
Constipation	22 (7%)	7 (5%)
Abdominal discomfort	6 (2%)	1 (<1%)
Faeces discoloured	4 (1%)	1 (<1%)
Infections and infestations		
Influenza	12 (4%)	4 (3%)
Sinusitis	8 (3%)	2 (1%)
Bronchitis	7 (2%)	0
Cystitis	5 (2%)	0
Tooth abscess	5 (2%)	0
General disorders and administration site conditions		
Fatigue	44 (14%)	18 (13%)
Oedema peripheral	11 (4%)	2 (1%)
Pyrexia	8 (3%)	3 (2%)
Chills	6 (2%)	1 (<1%)
Chest pain	5 (2%)	1 (<1%)
Asthenia	4 (1%)	1 (<1%)
Musculoskeletal and connective tissue disorders		
Arthralgia	15 (5%)	6 (4%)
Pain in extremity	9 (3%)	3 (2%)
Myalgia	7 (2%)	2 (1%)
Osteoarthritis	4 (1%)	1 (<1%)
Nervous system disorders		
Syncope	5 (2%)	1 (<1%)
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	18 (6%)	3 (2%)
Injury, poisoning and procedural complications		
Contusion	8 (3%)	3 (2%)
Procedural pain	6 (2%)	1 (<1%)
Scratch	4 (1%)	0
Psychiatric disorders		
Sleep disorder	4 (1%)	0
Ear and labyrinth disorder		

System Organ Class/ Preferred Term, n (%)	Total OCA (N=306) Subjects[2]	Placebo (N=134) Subjects[2]
Ear pain	5 (2%)	1 (<1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Hypothyroidism	5 (2%)	1 (<1%)

[1] Common treatment-emergent adverse reactions are defined as AEs occurring in ≥ 1% of patients treated with OCALIVA and at an incidence greater than the placebo

[2] At each level of summation (overall, system organ class, preferred term), subjects reporting more than one TEAE are counted only once.

Note: A TEAE is defined as any AE that newly appeared, increased in frequency, or worsened in severity following initiation of study drug

Adverse Events are displayed by system organ class and preferred terms, ordered by descending order of incidence of system organ class and preferred term within each system organ class in the total OCA group. If tie in incidence, alphabetical ordering is done.

Phase III Double-Blind Clinical Trial (POISE)

Approximately 60% of patients had a history of pruritus upon enrollment in POISE. Treatment-emergent pruritus generally started within the first month following the initiation of treatment with OCALIVA. The incidence of pruritus was higher in patients who started on OCALIVA 10 mg once daily relative to the OCALIVA titration arm, 70% and 56%, respectively. Discontinuation rates due to pruritus were also higher in patients who started on OCALIVA 10 mg once daily relative to the OCALIVA titration arm, 10% and 1%, respectively. The number of patients with pruritus who required an intervention (e.g., dosage adjustment, treatment interruption, or initiation of bile acid binding resin or antihistamine) was 30 of 51 patients (59%) in the OCALIVA 10 mg arm, 24 of 39 patients (62%) in the OCALIVA titration arm, and 14 of 28 patients (50%) in the placebo arm. Other AEs occurring at a frequency ≥ 5% and at a greater frequency in the either OCA treatment arm compared to placebo were fatigue, abdominal pain and discomfort, rash, arthralgia, oropharyngeal pain, dizziness, constipation, peripheral edema, palpitations, pyrexia, thyroid function abnormality and eczema.

In the POISE trial, the following serious or otherwise clinically significant hepatic adverse reactions were reported at the recommended dosage of OCALIVA: one patient in the OCALIVA 10 mg treatment arm experienced ascites; one patient in the OCALIVA titration treatment arm experienced two episodes of ascites and four episodes of hepatic encephalopathy; one patient in the placebo treatment arm experienced variceal bleeding.

Phase II Double-Blind, Clinical Trials

Pruritus was the most frequently reported TEAE in the Phase II trials across OCA doses of 10 mg, 25 mg, and 50 mg. The incidence of pruritus increased with increasing dose and was highest at the 25 mg and 50 mg doses. Except for the higher incidence, greater severity, and earlier onset of pruritus events in the OCA 25 mg and 50 mg groups, there were no notable differences in the treatment-related TEAEs across treatment groups. Other AEs occurring at a greater frequency in the total OCA group compared to placebo included oropharyngeal pain and oedema peripheral.

In the Phase II trials, a total of 6 SAEs occurred in the total OCA group compared to two SAEs in

the placebo group. Three SAEs were reported from the SOC “Hepatobiliary Disorders” or “Gastrointestinal Disorders” including GI hemorrhage, jaundice, and biliary cirrhosis primary (PBC flare), all of which occurred in the OCA 50 mg treatment group. No other notable differences in SAEs were observed.

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post approval use of OCALIVA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure, particularly in PBC patients who have progressive liver disease.

Hepatobiliary Disorders: liver failure, new onset cirrhosis, increased direct and total bilirubin, new or worsening of jaundice [see 7 WARNINGS AND PRECAUTIONS].

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Based on *in vitro* studies, obeticholic acid can inhibit CYP3A4. However, an *in vivo* study did not detect inhibition of CYP3A4 by obeticholic acid at the recommended dose of OCALIVA. 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 OCALIVA. 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 OCALIVA.

In vitro data suggest that obeticholic acid is not metabolized to any significant extent by CYP450 enzymes.

9.3 Drug-Behavioural Interactions

There have been no adequate, well-controlled studies regarding drug-behavioural interactions.

9.4 Drug-Drug Interactions

The drugs listed below are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3: Established or Potential Drug-Drug Interactions

Common name	Source of Evidence	Effect	Clinical comment
Pharmacokinetic Interactions (Effects of Other Drugs on OCALIVA)			

Common name	Source of Evidence	Effect	Clinical comment
Bile acid binding resins (such as cholestyramine, colestipol, or colesevelam)	T	Predicted to decrease OCALIVA concentration.	Bile acid binding resins adsorb and reduce bile acid absorption and may reduce the absorption, systemic exposure, and efficacy of OCALIVA. If taking a bile acid binding resin, take OCALIVA at least 4 hours before or 4 hours after taking the bile acid binding resin, or at as great an interval as possible [see 4 DOSAGE AND ADMINISTRATION].
Omeprazole 20 mg (acid reducing agent)	CT	16% increase in AUC and 19% increase in C_{max} of OCALIVA.	No OCALIVA dose adjustment is recommended. Concomitant administration of 40 mg omeprazole once daily with OCALIVA 10 mg once daily has not been studied.
Pharmacokinetic Interactions (Effects of OCALIVA 10 mg once daily on Other Drugs)			
Warfarin 25 mg (anticoagulant)	CT	13% increase in systemic exposure to S-warfarin and 11% decrease in maximum INR.	Monitor INR and adjust the dosage of warfarin, as needed, to maintain the target INR range when co-administering OCALIVA and warfarin.
Caffeine 200 mg (CYP1A2 substrate)	CT	42% increase in plasma AUC and 6% increase in C_{max} of caffeine.	Therapeutic monitoring of CYP1A2 substrates with a narrow therapeutic index (e.g., theophylline and tizanidine) is recommended when co-administered with OCALIVA.
Omeprazole 20 mg (CYP2C19 substrate)	CT	32% increase in AUC and a 33% increase in C_{max} of omeprazole.	No OCALIVA dose adjustment is recommended.
Rosuvastatin 20 mg (BCRP, OATP1B1, OATP1B3 substrate)	CT	22% increase in AUC and a 27% increase in C_{max} of rosuvastatin.	No OCALIVA dose adjustment is recommended.
Midazolam 2 mg (CYP3A4 substrate)	CT	2% increase in AUC and 2% increase in C_{max} of midazolam.	No OCALIVA dose adjustment is recommended.
Dextromethorphan 30 mg (CYP2D6 substrate)	CT	11% decrease in AUC and 12% decrease in C_{max} of dextromethorphan.	No OCALIVA dose adjustment is recommended.
Digoxin 0.25 mg (P-gp substrate)	CT	1% increase in AUC and 3% decrease in C_{max} of digoxin.	No OCALIVA dose adjustment is recommended.

Legend: CT = Clinical Trial; T = Theoretical

9.5 Drug-Food Interactions

A study was conducted to assess the pharmacokinetics of obeticholic acid following a single 10 mg tablet under fed and fasted conditions. When OCALIVA 10 mg tablets were administered following consumption of a high fat, high calorie meal, there was an increase in AUC_{0-72} by approximately 20% while there was no significant effect on C_{max} when compared to administration under fasting conditions [see 4 DOSAGE AND ADMINISTRATION].

9.6 Drug-Herb Interactions

There have been no adequate, well-controlled studies regarding drug-herb interactions.

9.7 Drug-Laboratory Test Interactions

There have been no adequate, well-controlled studies regarding drug-laboratory interactions.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Obeticholic acid is an agonist for farnesoid X receptor (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.

10.2 Pharmacodynamics

Pharmacodynamic Markers

In the Phase III study, administration of OCALIVA 10 mg once daily was associated with a 173% increase in concentrations of FGF-19, an FXR-inducible enterokine involved in bile acid homeostasis, from baseline to Month 12. Concentrations of cholic acid and chenodeoxycholic acid were reduced 2.7 micromolar and 1.4 micromolar, respectively, from baseline to Month 12. The clinical relevance of these findings is unknown.

In clinical studies with PBC patients, obeticholic acid decreased c-reactive protein (CRP), immunoglobin M (IgM), and cytokeratin 18 (CK 18) markers of inflammation and apoptosis.

Cardiac Electrophysiology: In a randomized, double-blind, placebo- and positive-controlled, parallel group ECG assessment study performed in healthy subjects (N=62-63/treatment arm), OCALIVA 100 mg/day (10-times maximum recommended therapeutic dose) administered for 5 days was not associated with any treatment-related pattern of effects on the QTcF interval, the QRS duration, the PR interval, or heart rate.

10.3 Pharmacokinetics

Table 4: Summary of Obeticholic Acid Pharmacokinetic Parameters in Healthy Subjects

Single dose mean (SD)	C_{max} (ng/mL)	t_{max}[a] (h)	$t_{1/2}$ (h)	AUC_{0-168} (ng·h/mL)	$AUC_{0-\infty}$ (ng·h/mL)	CL/F (L/h)	Vd/F (L)
Study #1[b] (n=157)	65.1 (28.6)	3.0 (0.3, 36.0)	43.7 (33.9)	1762 (939)	1930 (1080)	6.61 (3.54)	381 (385)
Study #2[b] (n=152)	60.6 (28.1)	2.0 (0.3, 36.0)	36.0 (14.3)	1565 (770)	1671 (826)	NC	NC

AUC = area under the plasma concentration-time curve; $AUC_{0-\infty}$ = AUC from time 0 to infinity; AUC_{0-168} = AUC from time 0 to 168 hours; C_{max} = maximum concentration (observed); NC = not calculated; OCA = obeticholic acid; SD = standard deviation; t_{max} = time to C_{max}

[a] Median (Min-Max).

[b] Study #1: 747-115; Study #2: 747-116 Commercial image tablet only

Absorption:

Following multiple oral doses of OCALIVA 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. When OCALIVA 10 mg tablets were administered following consumption of a high fat, high calorie meal, there was an increase in AUC_{0-72} by approximately 20% while there was no significant effect on C_{max} when compared to administration under fasting conditions [see 4 DOSAGE AND ADMINISTRATION].

Following multiple-dose administration of OCALIVA 5, 10, and 25 mg once daily 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 (AUC_{0-24h}) achieved on Day 14 of total obeticholic acid was 4.2-, 6.6-, and 7.8-fold the systemic exposure (AUC_{0-24h}) achieved on Day 1 after 5, 10, and 25 mg once daily dosing, respectively.

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.

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.

After daily administration of obeticholic acid for 14 days, there was accumulation of the

glycine and taurine conjugates of obeticholic acid, which have *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.

Elimination:

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.

Special Populations and Conditions

- **Pediatrics**: The safety and effectiveness of OCALIVA in pediatric patients have not been established.
- **Geriatrics**: No overall differences in safety or effectiveness were observed between subjects greater than 65 and those less than 65 years of age, but greater sensitivity of some older individuals cannot be ruled out.
- **Sex**: Based on population pharmacokinetic analysis, the pharmacokinetics of obeticholic acid would not be expected to be altered based on gender.
- **Ethnic Origin:** Based on population pharmacokinetic analysis, the pharmacokinetics of obeticholic acid would not be expected to be altered based on race/ethnicity.
- **Hepatic Insufficiency**: 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 by 1.1-, 4- and 17-fold, respectively, compared to subjects with normal hepatic function following single-dose administration of 10 mg OCALIVA [see 2 CONTRAINDICATIONS, 7 WARNINGS AND PRECAUTIONS].
- **Renal Insufficiency:** 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.
- **Obesity:** The Population PK model predicted that body weight was demonstrated to be negatively correlated with AUC. The median AUC in a typical 40-kg subject is expected to be 50% higher than that of a typical 67.4-kg subject. Conversely, the median AUC in a typical 134-kg subject is expected to be 42.6% lower than that in a typical 67.4-kg subject. However, the results of the pivotal clinical trial do not support this finding [see 14 CLINICAL TRIALS]. Body weight effect is not expected to have a meaningful impact on efficacy.

11 STORAGE, STABILITY AND DISPOSAL

Store OCALIVA tablets at room temperature (15°C - 30°C).

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

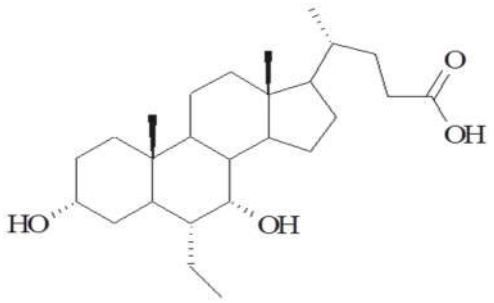
Drug Substance

Proper name: Obeticholic acid

Chemical name: 3α,7α-dihydroxy-6α-ethyl-5β-cholan-24-oic acid

Molecular formula and molecular mass: $C_{26}H_{44}O_4$ and 420.63 g/mol

Structural formula:



Physicochemical properties: Obeticholic acid is a white to off-white powder. It is soluble in methanol, acetone and ethyl acetate. Its solubility in water is pH dependent. It is slightly soluble at low pH and very soluble at high pH.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Table 5: Summary of Patient Demographics for Clinical Trials in PBC

Study #	Study design and duration	Dosage and route of administration	Study subjects (n)	Mean age (Range)	Sex
747-301	Phase III, randomized, double-blind, placebo-controlled, 12-month trial	10 mg once daily, orally	73	56 years (29-86 years)	91% female and 9% male
		OCALIVA titration, orally	70		
		Placebo, orally	73		

The POISE trial was a Phase III, randomized, double-blind, placebo-controlled, 12-month clinical trial which evaluated the safety and efficacy of OCALIVA in 216 patients with PBC who were taking UDCA for at least 12 months (on a stable dosage for at least 3 months), or who were unable to tolerate UDCA and did not receive UDCA for at least 3 months. Patients were included in the trial if the ALP was 1.67-times upper limit of normal (ULN) or greater and/or if total bilirubin was greater than 1-times ULN but less than 2-times ULN. Patients were excluded from the trial if they had other liver disease, presence of clinically significant hepatic decompensation events (i.e., portal hypertension and its complications, cirrhosis with

complications, or hepato-renal syndrome), severe pruritus, or Model for End Stage Liver Disease (MELD) score of 15 or greater.

Patients were randomized (1:1:1) to receive either OCALIVA 10 mg once daily for the entire 12 months of the trial, (n=73); 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 ULN or greater, and/or total bilirubin greater than ULN, or less than 15% ALP reduction) (n=70); or placebo (n=73). OCALIVA or placebo was administered in combination with UDCA in 93% of patients during the trial and as monotherapy in 7% of patients who were unable to tolerate UDCA.

The primary endpoint was a responder analysis at Month 12, where response was defined as a composite of three criteria: ALP less than 1.67-times the ULN, total bilirubin less than or equal to ULN, and an ALP decrease of at least 15%. The ULN for ALP was defined as 118 U/L for females and 124 U/L for males. The ULN for total bilirubin was defined as 1.1 mg/dL for females and 1.5 mg/dL for males.

The study population was 91% female and 94% white. The mean age was 56 years (range 29 to 86 years). The mean baseline ALP concentration was 323.2 U/L, corresponding to 2.74-times ULN. Approximately 29% of the patients had ALP concentration levels greater than 3-times the ULN. The mean baseline total bilirubin concentration was 0.65 mg/dL, and was less than or equal to the ULN in 92% of the enrolled patients. Cirrhosis was present at baseline in 4 patients (5%) in the OCALIVA 10 mg arm, 7 patients (10%) in the OCALIVA titration arm, and 9 patients (12%) in the placebo arm. Distribution of patients by Rotterdam disease stage criteria at baseline is shown in Table 6.

Table 6: Rotterdam Disease Stage Criteria at Baseline in the POISE Trial by Treatment Arm with or without UDCA[a]

Disease Stage[b]	OCALIVA 10 mg (N=73)	OCALIVA Titration (N=70)	Placebo (N=73)
Early, n (%)	66 (90)	64 (91)	65 (89)
Moderately Advanced, n (%)	7 (10)	6 (9)	8 (11)
Advanced, n (%)	0 (0)	0 (0)	0 (0)

Percentages are based on non-missing values for each time point.

[a] 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.

[b] Early: normal total bilirubin and normal albumin (values less than or equal to ULN and greater than or equal to the lower limit of normal (LLN), respectively), Moderately advanced: abnormal total bilirubin or abnormal albumin, Advanced: abnormal total bilirubin and abnormal albumin. Total bilirubin ULN: 1.1 mg/dL (females) and 1.5 mg/dL (males). Albumin LLN: 35 g/L (females and males).

14.2 Study Results

Table 7 shows the percentage of patients by treatment arm in POISE who achieved a response to the primary composite endpoint at Month 6 and 12, and to the individual components of the primary endpoint (i.e., ALP less than 1.67-times the ULN, total bilirubin less than or equal to ULN, and an ALP decrease of at least 15%). A total of 33 patients in the OCALIVA titration arm, who did not achieve a response at 6 months and tolerated OCALIVA, had their dosage

increased from 5 mg once daily to 10 mg once daily. Of these 33 patients, 13 (39%) achieved the primary composite endpoint at 12 months.

Table 7: Percentage of Adult Patients with PBC Achieving the Primary Composite Endpoint at Month 6 and 12 in the POISE trial by Treatment Arm with or without UDCA[a]

	OCALIVA + UDCA[b]		Placebo + UDCA[b] (N=73)
	OCALIVA 10 mg (N=73)	OCALIVA Titration (N=70)	
Month 6			
Responders, n (%) Corresponding 95% CI	37 (51) 39%, 62%	24 (34) 23%, 45%	5 (7) 1%, 13%
p-value[c]	<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[c]	<0.0001	<0.0001	NA
Components of Primary Endpoint			
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[d], 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.

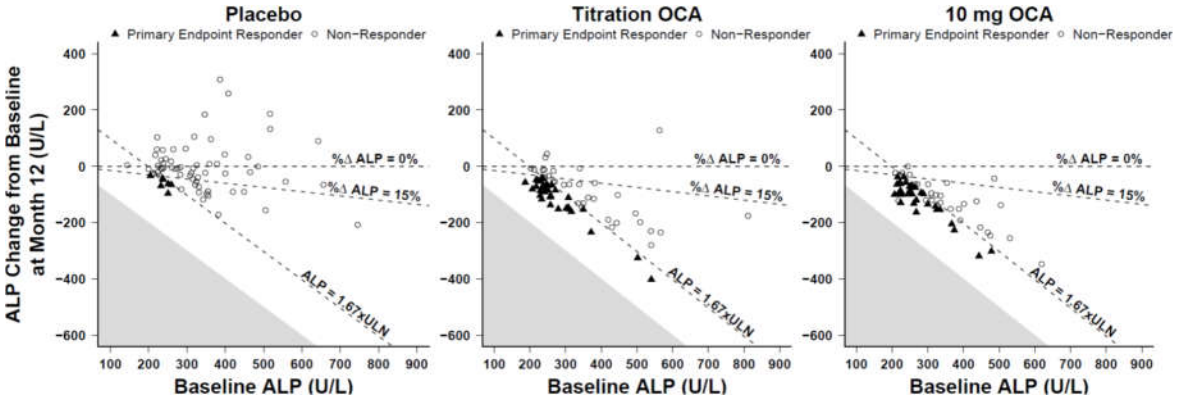
[b] Patients were randomized (1:1:1) to receive OCALIVA 10 mg once daily for the entire 12 months of the trial, or OCALIVA titration (5 mg once daily for the initial 6 months, with the option to increase to 10 mg once daily for the last 6 months, if the patient was tolerating OCALIVA but had ALP 1.67-times the ULN or greater, and/or total bilirubin above the ULN, or less than 15% ALP reduction) or placebo. 16 patients (7%) were intolerant to UDCA and received OCALIVA as monotherapy or placebo.

[c] p-values for comparing OCALIVA versus placebo are obtained using the CMH General Association test stratified by randomization factor.

[d] 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.

In the Phase III POISE trial, 77% (110/143) of patients on both titration and OCALIVA 10 mg achieved a reduction of at least 15% in ALP after 12 months of treatment compared to 29% (21/73) of patients on placebo (see Figure 1). In addition, 36% (26/73) of patients treated with placebo experienced an increase in ALP, which is associated with worsening of disease, compared to 5% (3/70) of patients on OCALIVA titration and 2% (1/73) on OCALIVA 10 mg.

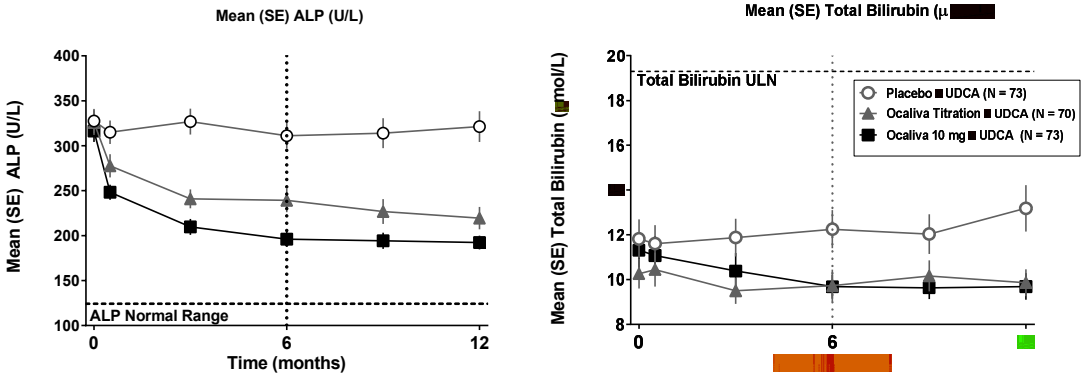
Figure 1: Observed Individual Patient Level Change in ALP from Baseline at Month 12 for Responders versus Non-Responders, by Treatment Group



Mean Reduction in ALP and Total Bilirubin

Figure 2 shows the mean reductions in ALP in OCALIVA-treated patients compared to placebo. Reductions were observed as early as Week 2, and were maintained through Month 12 for patients who were maintained on the same dosage throughout 12 months. For patients in the OCALIVA titration arm whose OCALIVA dosage 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 [see 10 CLINICAL PHARMACOLOGY]. During the double-blind, 12 month period, bilirubin levels increased in the placebo patients and remained stable in patients taking OCALIVA.

Figure 2: Mean ALP and Total Bilirubin over 12 Months in Poise by Treatment Arm with or without UDCA[a,b]



[a] 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.
[b] Patients randomized to OCALIVA titration received OCALIVA 5 mg once daily for the initial 6 month period. At Month 6, patients who were tolerating OCALIVA, but had an ALP 1.67-times ULN or greater, and/or total bilirubin greater than ULN, or less than 15% ALP reduction were eligible for titration from 5 mg once daily to 10 mg once daily for the final 6 months of the trial.

Mean Reduction in GGT

The mean (95% CI) reduction in gamma-glutamyl transferase (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.

OCALIVA 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 POISE trial and from a randomized, double-blind, placebo-controlled, 3-month clinical trial. At Month 3, 9 (38%) OCALIVA-treated patients achieved a response to the composite endpoint, compared to 1 (4%) placebo-treated patients. 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.

Long-term efficacy of OCALIVA as monotherapy has not been established. Efficacy of OCALIVA as monotherapy in elderly patients (> 65 years of age) has not been established.

Body Mass Index (BMI)

In the Phase III POISE trial, 177 patients had a baseline BMI < 30 kg/m^2 and 39 patients had a baseline BMI ≥ 30 kg/m^2. For patients with a baseline BMI < 30 kg/m^2, 48% (28/58) of patients on titration and 49% (30/61) of patients on OCALIVA 10 mg achieved the primary composite endpoint compared to 7% (4/58) of patients on placebo following 12 months of treatment. For patients with a baseline BMI ≥ 30 kg/m^2, 33% (4/12) of patients on titration and 33% (4/12) of patients on OCALIVA 10 mg achieved the primary composite endpoint compared to 20% (3/15) of patients on placebo following 12 months of treatment [see 10 CLINICAL PHARMACOLOGY].

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology:

Obeticholic acid is an FXR agonist and modified bile acid developed for the treatment of PBC. The nonclinical data package demonstrates mechanistic rationale for the target indication, provides evidence of the similarity of PK and metabolism to that of endogenous bile acids, and underwrites the safety of obeticholic acid in a predictable pattern of toxicity, and adequate safety margins in animal species compared to human subjects.

Pharmacodynamic studies demonstrated important features of obeticholic acid-mediated FXR activation within *in vitro* models and *in vivo* disease models. The primary pharmacology of obeticholic acid that is likely responsible for the beneficial actions in human cholestasis is FXR-mediated activation of the enteric release of FGF-19, induction of the transcription factor SHP, and repression in CYP7A1 expression and bile acid synthesis. Reduction of bile acid

synthesis is complemented by the effects of OCA to increase expression of bile acid transporters BSEP, OST, and MDR3 thus promoting choleresis. The unique combination of decreased bile acid synthesis and increased transport of bile acids out of the hepatocyte serves to combat the toxic burden of hepatic bile acid accumulation in cholestasis. In line with these findings, serum FGF-19 concentrations increased in a dose-related manner and both C4 (a bile acid precursor and a plasma marker whose level correlates with bile acid synthesis) and endogenous bile acid concentrations were decreased when obeticholic acid was administered to patients with PBC, on top of UDCA therapy or as a monotherapy. These data link the mechanism of FXR activation to FGF-19 production and reduced levels of endogenous bile acids, confirming FXR target engagement in PBC patients.

Obeticholic acid pharmacodynamic effects include the ability to exert anti-inflammatory and antifibrotic effects as demonstrated across a variety of *in vitro* and *in vivo* models. Anti-inflammatory effects were demonstrated in hepatocyte cell models with notable improvements in the induced transcriptional expression of inflammatory markers, including that of TNF-α, COX-2, and iNOS. These effects were extended to extra-hepatic *in vitro* models, including those of atherosclerosis (VSMCs) and intestinal disease (LPMCs from colonic and ileal biopsies obtained from individuals with IBD), at the protein level. Evidence for direct antifibrotic effects was obtained in immortalized human HSCs.

Importantly, using *in vivo* disease models, cholestasis-associated inflammation and fibrosis were improved with obeticholic acid administration. Collectively, the results of these studies indicated that obeticholic acid counteracts hepatic inflammation with data supporting a mechanism involving interaction with inflammatory pathways in hepatocytes, non-parenchymal hepatic (stellate) cells, and immune cells in the intestine. Obeticholic acid administration was also shown in preliminary data to inhibit progression to fibrosis and to partially reverse established fibrosis and cirrhosis in a rodent model of thioacetamide (TAA)-induced fibrosis. This observation is consistent with obeticholic acid regulation of key proteins in fibrotic pathways.

Two noteworthy pharmacodynamic observations indirectly supporting the indication of PBC include (1) a reduction in portal hypertension observed in bile duct-ligation BDL and TAA rodent models and, (2) general improvements in metabolic profile (e.g., improved glucose metabolism, decreased adiposity) and hepatic homeostasis (e.g., anti-steatotic effects) in animal models of obesity and diabetes. These studies corroborate observations from clinical studies with obeticholic acid that show a trend to reduce portal venous pressure gradient in patients with cirrhosis, as well as to improve glucose tolerance, and induce weight loss in patients with type 2 diabetes.

In a randomized, double-blind, placebo- and positive-controlled, parallel group ECG assessment study performed in healthy subjects (N=62-63/treatment arm), OCALIVA 100 mg/day (10-times maximum recommended therapeutic dose) administered for 5 days was not associated with any treatment-related pattern of effects on the QTcF interval, the QRS duration, the PR interval, or heart rate.

Carcinogenicity:

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.

Genotoxicity:

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.

Hepatotoxicity:

In all three nonclinical species, mouse, rat, and dog, obeticholic acid exerted its primary toxicologic adverse effects on the liver, its hepatocellular and hepatobiliary systems, at the dose levels which multifold exceeded the MRHD. These effects presented as increases in liver weights, increases in liver function enzymes, and microscopic findings consistent with liver injury.

The findings in nonclinical species (hepatobiliary injury), are similar to those of human patients with PBC dosed at 25 to 50 mg/kg (2.5-times to 5-times higher than the MRHD), where a dose dependent increase in the incidence of hepatic adverse reactions, including the elevation of activity of liver enzymes was observed.

Based on the AUC (total OCA equivalents) the safety margins in nonclinical species exceeded the MRHD in the range between 6.1 to 9.2-fold in rats (dosed up to 26-weeks) and at the magnitude of 7.9 to 16.2-fold in dogs dosed up to 9-months. In mice, the systemic exposure relative to that of humans was only about 0.5 to 0.9-fold. Because the margins of safety in mice were suboptimal, any potential hepatotoxicity in humans, should be monitored through the results of activity of hepatobiliary enzyme activity.

Reproductive and Developmental Toxicology:

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).

In an embryo-fetal development study in rats, obeticholic acid was administered orally during

the period of organogenesis at doses of 5, 25, and 75 mg/kg/day. At 25 mg/kg/day (a dose that produced systemic exposures approximately 13-times those in humans at the MRHD of 10 mg), there was no maternal or developmental toxicity. At 75 mg/kg/day (approximately 40-times the human exposure at the MRHD), decreased fetal body weights and increased numbers of early or late resorptions and nonviable fetuses were observed. In maternal animals, mortality, fetal loss, decreased body weight and food consumption as well as decreased body weight gain were observed at 75 mg/kg/day. Thus, the developmental toxicity observed at this dose may be secondary to maternal toxicity. In rabbits, obeticholic acid was administered orally during the period of organogenesis at doses of 3, 9, and 20 mg/kg/day. Obeticholic acid administered at doses up to 20 mg/kg/day (approximately 6-times the human exposure at the MRHD) was not teratogenic and did not produce any evidence of fetal harm.

In a pre- and post-natal development study, administration of obeticholic acid in rats during organogenesis through lactation at doses of 5, 25, and 40 mg/kg/day did not produce effects on pregnancy, parturition or postnatal development at any dose (the 40 mg/kg/day dose is approximately 21-times the human exposure at the MRHD).

Obeticholic acid exposure margins were calculated using systemic exposure (AUC) values of obeticholic acid plus obeticholic acid's active metabolite conjugates (tauro-obeticholic acid and glyco-obeticholic acid) in animals (at the indicated doses) and in humans at the MRHD of 10 mg.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrOCALIVA®

Obeticholic acid tablets

Read this carefully before you start taking **OCALIVA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **OCALIVA**.

Serious Warnings and Precautions

- Your healthcare professional will check your liver before you take OCALIVA and while you are taking it.
- These liver tests will help your healthcare professional decide if it is safe for you to start taking OCALIVA and safe for you to continue taking OCALIVA.
- Worsening of liver problems or liver failure has happened in people with primary biliary cholangitis (PBC) with liver cirrhosis when taking OCALIVA. This can lead to liver transplant or death.
- Do not take OCALIVA if you have PBC with liver cirrhosis with symptoms such as blood in your stool or vomiting blood, developing fluid in your stomach area, confusion or if your healthcare professional found abnormalities in certain tests that check your liver.

What is OCALIVA used for?

OCALIVA is used to treat primary biliary cholangitis (PBC). PBC is a disease of the liver causing destruction of the bile ducts.

For the following indication(s) OCALIVA has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

- 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.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does OCALIVA work?

Obeticholic acid decreases the production of bile acids in your liver and increases the removal of bile from the liver. This may slow or prevent progression of the disease.

What are the ingredients in OCALIVA?

Medicinal ingredients: obeticholic acid

Non-medicinal ingredients: magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The film coating is Opadry II (Yellow) containing polyvinyl alcohol-part hydrolyzed, titanium dioxide, macrogol (polyethylene glycol 3350), talc, and iron oxide yellow.

OCALIVA comes in the following dosage forms:

5 mg and 10 mg tablets

Do not use OCALIVA if:

- You have an allergy to obeticholic acid or to any other ingredient in OCALIVA (see "What are the Ingredients in OCALIVA?").
- You have late stage liver cirrhosis (decompensated cirrhosis) or have previously experienced a prior decompensation event with symptoms such as blood in your stool or vomiting blood, developing fluid in your stomach area, or confusion.
- You have liver cirrhosis (compensated cirrhosis) and show signs of portal hypertension (high blood pressure in the veins in your liver).
- You have complete blockage of bile flow.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take OCALIVA. Talk about any health conditions or problems you may have, including if you:

- Are pregnant or planning to become pregnant.
- Are breast-feeding or planning to breast-feed.
- See any signs of liver disease or biliary obstruction getting worse:
  - Tiredness.
  - Yellowish skin.
  - Stomach or abdominal pain.

Talk to your healthcare professional if the following occurs while taking OCALIVA:

- You develop severe, intense, widespread or persistent itching or itching that causes discomfort and sleep loss.
- You develop any of the following symptoms of worsening liver problems such as:
  - swelling of your stomach-area from a build-up of fluid
  - yellowing of your skin or the whites of your eyes
  - black, tarry, or bloody stools
  - coughing up or vomiting blood
  - mental changes
- You develop any of the following symptoms and they are severe or do not go away:
  - stomach-area pain
  - nausea, vomiting, or diarrhea
  - loss of appetite or weight loss
  - new or worsening fatigue
  - weakness
  - fever and chills
  - light-headedness
  - less frequent urination

Other warnings you should know about:

Patients with PBC may have high blood fat (lipid) levels. While you are taking OCALIVA, your healthcare professional may order tests to check your blood lipid levels.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with OCALIVA:

- Cholestyramine
- Colestipol
- Colesevelam
- Warfarin

- Theophylline
- Tizanidine
- Caffeine

You may feel the effects of caffeine for longer while taking OCALIVA.

How to take OCALIVA:

- Take OCALIVA 30 minutes before breakfast.
- Take OCALIVA more than 4 hours before or after taking any of the following drugs:
    - Cholestyramine
    - Colesevelam
    - Colestipol

Usual dose:

- The recommended starting dosage of OCALIVA is 5 mg orally once daily.
- Before you start OCALIVA, and while you are taking it, your healthcare professional will do tests to check your liver. These tests will help them decide if it is safe for you to start taking OCALIVA and safe for you to continue taking OCALIVA.
- Do not exceed the dosage that your healthcare professional prescribes for you.
- If your healthcare professional feels your liver function tests are not improving enough, they may increase the dosage.

Overdose:

If you think you, or a person you are caring for, have taken too much OCALIVA, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you do miss a dose of OCALIVA, take the tablet as soon as possible. Then take the next dose as usual.

If it is nearly time for your next dose, wait and take the next dose at your usual time. Do not take a double dose (two doses close together).

What are possible side effects from using OCALIVA?

These are not all the possible side effects you may have when taking OCALIVA. If you experience any side effects not listed here, tell your healthcare professional.

Some patients may experience side effects including the following:

Very common side effects (may affect more than 1 in 10 people):

- Stomach pain
- Itching of the skin
- Feeling tired

Common side effects (may affect up to 1 in 10 people):

- Thyroid hormone difficulty
- Dizziness
- Fast or irregular heart beat (palpitations)
- Pain in the mouth
- Constipation
- Dry skin, redness of the skin (eczema)
- Rash
- Pain in your joints
- Swelling in the hands and feet
- Fever

While you are taking OCALIVA, lab tests will be run by your healthcare professional every so often. This is to assess liver function.

Tell your healthcare professional right away if you have new onset or worsening of these conditions.

Serious side effects and what to do about them			
Symptom/effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
COMMON Itching of the skin		X	
RARE Yellowing of the skin		X	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at controlled room temperature 15°to 30°.

Keep out of reach and sight of children.

If you want more information about OCALIVA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website, www.advanzpharma.com, or by calling 1-800-982-0340.

This leaflet was prepared by Advanz Pharma Canada Inc.

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