

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OCALIVA® safely and effectively. See full prescribing information for OCALIVA.

OCALIVA® (obeticholic acid) tablets, for oral use
Initial U.S. Approval: 2016

INDICATIONS AND USAGE

OCALIVA, a farnesoid X receptor (FXR) agonist, is indicated for the treatment of primary biliary cholangitis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA.

This indication is approved under accelerated approval based on a reduction in alkaline phosphatase (ALP). An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials. (1)

DOSAGE AND ADMINISTRATION

- **Starting Dosage:** The recommended starting dosage of OCALIVA is 5 mg orally once daily 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. (2.1)
- **Dosage Titration:** If adequate reduction in ALP and/or total bilirubin has not been achieved after 3 months of OCALIVA 5 mg once daily and the patient is tolerating OCALIVA, increase dosage to 10 mg once daily. (2.1)
- **Maximum Dosage:** 10 mg once daily (2.1, 5.1)
- **Management of Patients with Intolerable Pruritus:** See full prescribing information for management options. (2.2)
- **Hepatic Impairment:** See full prescribing information for dosage adjustment in patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). (2.3)

Administration Instructions

- Take with or without food. (2.4)
- For patients taking bile acid binding resins, take OCALIVA at least 4 hours before or 4 hours after taking a bile acid binding resin, or at as great an interval as possible. (2.4, 7.1)

DOSAGE FORMS AND STRENGTHS

Tablets: 5 mg, 10 mg (3)

CONTRAINDICATIONS

Patients with complete biliary obstruction (4)

WARNINGS AND PRECAUTIONS

- **Liver-Related Adverse Reactions:** Monitor for elevations in liver biochemical tests and development of liver-related adverse reactions; weigh the potential risk against the benefits of continuing treatment. Do not exceed 10 mg once daily. Adjust the dosage for patients with moderate or severe hepatic impairment. Discontinue in patients who develop complete biliary obstruction. (2.3, 4, 5.1)
- **Severe Pruritus:** Management strategies include the addition of bile acid binding resins or antihistamines; OCALIVA dosage reduction and/or temporary dosing interruption. (2.2, 5.2)
- **Reduction in HDL-C:** Monitor for changes in serum lipid levels during treatment. (5.3)

ADVERSE REACTIONS

Most common adverse reactions (≥ 5%) are: pruritus, fatigue, abdominal pain and discomfort, rash, oropharyngeal pain, dizziness, constipation, arthralgia, thyroid function abnormality, and eczema. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Intercept Pharmaceuticals at 1-844-782-ICPT or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- **Warfarin:** Potential for decreased INR; monitor INR and adjust the dosage of warfarin, as needed, to maintain the target INR range. (7.2)
- **CYP1A2 Substrates with Narrow Therapeutic Index (e.g., theophylline and tizanidine):** Potential for increased exposure to CYP1A2 substrates; monitor drug concentrations of CYP1A2 substrates with narrow therapeutic index. (7.3)

See 17 for PATIENT COUNSELING INFORMATION.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

This indication is approved under accelerated approval based on a reduction in alkaline phosphatase (ALP) [*see Clinical Studies (14)*]. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage Regimen

Starting Dosage

The recommended starting dosage of OCALIVA is 5 mg orally once daily in adult patients who have not achieved an adequate biochemical response to an appropriate dosage of UDCA for at least 1 year or are intolerant to UDCA [*see Clinical Studies (14)*].

Dosage Titration

If an adequate reduction in ALP and/or total bilirubin has not been achieved after 3 months of OCALIVA 5 mg once daily, and the patient is tolerating OCALIVA, increase the dosage of OCALIVA to 10 mg once daily [*see Clinical Pharmacology (12.2), Clinical Studies (14)*].

Maximum Dosage

The maximum recommended dosage of OCALIVA is 10 mg once daily [*see Warnings and Precautions (5.1)*].

2.2 Management of Patients with Intolerable Pruritus on OCALIVA

For patients with intolerable pruritus on OCALIVA, consider one or more of the following:

- Add an antihistamine or bile acid binding resin [*see Dosage and Administration (2.4), Clinical Studies (14)*].
- Reduce 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 interrupt OCALIVA dosing for up to 2 weeks followed by restarting at a reduced dosage.

Increase the dosage of OCALIVA to 10 mg once daily, as tolerated, to achieve optimal response.

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

2.3 Dosage Adjustment in Hepatic Impairment

Treatment with OCALIVA in patients with moderate and severe hepatic impairment should be initiated and monitored by a healthcare provider with experience managing PBC.

The recommended starting dosage of OCALIVA for moderate (Child-Pugh Class B) and severe (Child-Pugh Class C) hepatic impairment is 5 mg once weekly. If an adequate reduction in ALP and/or total bilirubin has not been achieved after 3 months of OCALIVA 5 mg once weekly, and the patient is tolerating the drug, increase the dosage of OCALIVA to 5 mg twice weekly (at least three days apart) and subsequently to 10 mg twice weekly (at least three days apart) depending on response and tolerability [see *Use in Specific Populations (8.6)*].

Monitor patients during treatment with OCALIVA for the occurrence of liver-related adverse reactions [see *Warnings and Precautions (5.1)*]. Weigh the potential risks against the benefits of continuing treatment with OCALIVA in patients who have experienced clinically significant liver-related adverse reactions.

2.4 Administration Instructions

- Take OCALIVA with or without food.
- 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 *Drug Interactions (7.1)*, *Clinical Studies (14)*].

3 DOSAGE FORMS AND STRENGTHS

OCALIVA is available as:

- 5 mg tablet: Off white to yellow, round tablet debossed with “INT” on one side and “5” on the other side.
- 10 mg tablet: Off white to yellow, triangular tablet debossed with “INT” on one side and “10” on the other side.

4 CONTRAINDICATIONS

OCALIVA is contraindicated in patients with complete biliary obstruction.

5 WARNINGS AND PRECAUTIONS

5.1 Liver-Related Adverse Reactions

In two 3-month, placebo-controlled clinical trials a dose-response relationship was observed for the occurrence of liver-related adverse reactions including jaundice, worsening ascites and primary biliary cholangitis flare 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 [see *Overdosage (10)*].

In a pooled analysis of three placebo-controlled trials in patients with PBC, the exposure-adjusted incidence rates for all serious and otherwise clinically significant liver-related 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.

Monitor patients during treatment with OCALIVA for elevations in liver biochemical tests and for the development of liver-related adverse reactions. Weigh the potential risks against the benefits of continuing treatment with OCALIVA in patients who have experienced clinically significant liver-related adverse reactions. The maximum recommended dosage of OCALIVA is 10 mg once daily [see *Dosage and Administration (2.1)*]. Adjust the dosage for patients with moderate or severe hepatic impairment [see *Dosage and Administration (2.3)*].

Discontinue OCALIVA in patients who develop complete biliary obstruction [see *Contraindications (4)*].

5.2 Severe Pruritus

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 Trial 1, a 12-month double-blind randomized controlled trial of 216 patients [see *Adverse Reactions (6.1)*]. 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 resins or antihistamines, OCALIVA dosage reduction, and/or temporary interruption of OCALIVA dosing [see *Dosage and Administration (2.2)*].

5.3 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 Trial 1, 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 (maximum of 10 mg once daily), and who experience a reduction in HDL-C, weigh the potential risks against the benefits of continuing treatment.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in labeling:

- Liver-Related Adverse Reactions [*see Warnings and Precautions (5.1)*]
- Severe Pruritus [*see Warnings and Precautions (5.2)*]
- Reduction in HDL-C [*see Warnings and Precautions (5.3)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 432 patients with PBC were studied in three double-blind placebo-controlled 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.

In Trial 1, 216 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, in patients who were 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).

During the trial, OCALIVA or placebo was administered in combination with UDCA in 93% of patients and as monotherapy in 7% of patients who were unable to tolerate UDCA. The overall discontinuation rate was 12% in the OCALIVA 10 mg arm, 10% in the OCALIVA titration arm, and 4% in the placebo arm.

The recommended starting dosage of OCALIVA is 5 mg orally once daily for 3 months with titration to 10 mg once daily based upon tolerability and response [*see Dosage and Administration (2.1)*]. Initiation of therapy with OCALIVA 10 mg once daily is not recommended due to an increased risk of pruritus.

The most common adverse reactions in Trial 1 occurring in at least 5% of patients in either OCALIVA treatment arm and at an incidence at least 1% higher than the placebo treatment arm are shown in Table 1.

Table 1: Most Common Adverse Reactions in Adult Patients with PBC in Trial 1 by Treatment Arm with or without UDCA^a

Adverse Reaction ^b	OCALIVA 10 mg N = 73 %	OCALIVA Titration ^c N = 70 %	Placebo N = 73 %
Pruritus ^d	70	56	38
Fatigue ^e	25	19	15
Abdominal pain and discomfort ^f	10	19	14
Rash ^g	10	7	8
Arthralgia	10	6	4
Oropharyngeal pain	8	7	1
Dizziness ^h	7	7	5
Constipation	7	7	5
Peripheral Edema	7	3	3
Palpitations	7	3	1
Pyrexia	7	0	1
Thyroid function abnormality ⁱ	4	6	3
Eczema	3	6	0

^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 Occurring in greater than or equal to 5% of patients in either OCALIVA treatment arm and at an incidence greater than or equal to 1% higher than in the placebo treatment arm.

^c 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.

^d Includes skin eruptions, prurigo, pruritus, pruritus generalized, eye pruritus, ear pruritus, anal pruritus, vulvovaginal pruritus, and rash pruritic.

^e Includes fatigue, tiredness and asthenia.

^f Includes abdominal pain upper, abdominal pain, abdominal discomfort, abdominal pain lower, abdominal tenderness, and gastrointestinal pain.

^g Includes urticaria, rash, rash macular, rash papular, rash maculo-papular, heat rash, urticaria cholinergic.

^h Includes dizziness, syncope, presyncope.

ⁱ Includes thyroxine free decreased, blood thyroid stimulating hormone increased, hypothyroidism.

Liver-Related Adverse Reactions

In Trial 1, the following serious or otherwise clinically significant liver-related 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.

Pruritus

Approximately 60% of patients had a history of pruritus upon enrollment in Trial 1. Treatment-emergent pruritus, including all the terms described in Table 1, 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.

7 DRUG INTERACTIONS

7.1 Bile Acid Binding Resins

Bile acid binding resins such as cholestyramine, colestipol, or colesevelam adsorb and reduce bile acid absorption and may reduce the absorption, systemic exposure, and efficacy of 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 Dosage and Administration (2.4)*].

7.2 Warfarin

The International Normalized Ratio (INR) decreased following coadministration of warfarin and OCALIVA [*see Clinical Pharmacology (12.3)*]. Monitor INR and adjust the dosage of warfarin, as needed, to maintain the target INR range when co-administering OCALIVA and warfarin.

7.3 CYP1A2 Substrates with Narrow Therapeutic Index

Obeticholic acid may increase the exposure to concomitant drugs that are CYP1A2 substrates [*see Clinical Pharmacology (12.3)*]. Therapeutic monitoring of CYP1A2 substrates with a narrow therapeutic index (e.g. theophylline and tizanidine) is recommended when co-administered with OCALIVA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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 Data below*].

The estimated background risks of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

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.

8.2 Lactation

Risk Summary

There is no information on the presence of obeticholic acid in human milk, the effects on the breast-fed infant or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for OCALIVA and any potential adverse effects on the breastfed infant from OCALIVA or from the underlying maternal condition.

8.4 Pediatric Use

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

8.5 Geriatric Use

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.

8.6 Hepatic Impairment

Plasma exposure to obeticholic acid and its active conjugates, increases significantly in patients with moderate to severe hepatic impairment (Child-Pugh Classes B and C) [see *Clinical Pharmacology (12.3)*].

Monitor patients during treatment with OCALIVA for elevations in liver biochemical tests and for the development of liver-related adverse reactions [see *Warnings and Precautions (5.1)*]. Dosage adjustment of OCALIVA is recommended for patients with moderate and severe hepatic impairment [see *Dosage and Administration (2.3)*]. No dosage adjustment is needed in patients with mild hepatic impairment (Child-Pugh Class A).

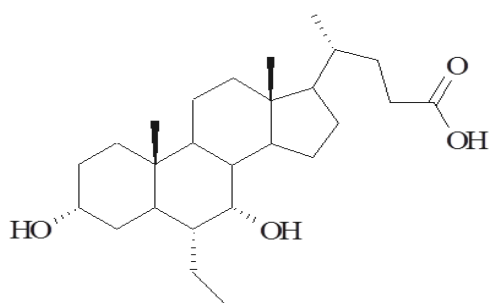
10 OVERDOSAGE

In 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), a dose-dependent increase in the incidence of liver-related adverse reactions, including elevations in liver biochemical tests, ascites, jaundice, portal hypertension, and primary biliary cholangitis flare, was reported [see *Warnings and Precautions (5.1)*].

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

11 DESCRIPTION

OCALIVA is a farnesoid X receptor (FXR) agonist. Chemically, obeticholic acid is 3 α ,7 α -dihydroxy-6 α -ethyl-5 β -cholan-24-oic acid. It 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. Its chemical formula is C₂₆H₄₄O₄, the molecular weight is 420.63 g/mol and the chemical structure is:



OCALIVA tablets are supplied in 5 mg and 10 mg strengths for oral administration. Each tablet contains obeticholic acid as the active ingredient and the following inactive ingredients: microcrystalline cellulose, sodium starch glycolate, and magnesium stearate. The film coating is Opadry II (Yellow) containing polyvinyl alcohol-part hydrolyzed, titanium dioxide, macrogol (polyethylene glycol 3350), talc, and iron oxide yellow.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

Dose Titration

In Trial 1, ALP reduction was observed to plateau at approximately 3 months in most patients treated with OCALIVA 5 mg once daily. Increasing the dosage of OCALIVA to 10 mg once daily based on tolerability and response provided additional reduction in ALP in the majority of patients [see *Dosage and Administration (2.1), Clinical Studies (14)*].

Pharmacodynamic Markers

In Trial 1, 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.

Cardiac Electrophysiology

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

12.3 Pharmacokinetics

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. Coadministration with food did not alter the extent of absorption of obeticholic acid [see *Dosage and Administration (2.4)*].

Following multiple-dose administration of OCALIVA 5, 10, and 25 mg once daily (2.5 times the highest recommend dosage) for 14 days, systemic exposures of obeticholic acid increased dose proportionally. Exposures to glyco-obeticholic acid and tauro-obeticholic acid, and total obeticholic acid (the sum of obeticholic acid and its two active conjugates) increased more than proportionally with dose.

Distribution

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

Elimination

Metabolism

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

After daily administration of obeticholic acid, there was accumulation of the glycine and taurine conjugates of obeticholic acid, which 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.

Excretion

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

Specific Populations

Age, Sex Race/Ethnicity: Based on population pharmacokinetic analysis, the pharmacokinetics of obeticholic acid would not be expected to be altered based on age, sex, or race/ethnicity.

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

Hepatic Impairment: Obeticholic acid is metabolized in the liver. In subjects with mild, moderate and severe hepatic impairment (Child-Pugh Class A, B, and C, respectively), the mean AUC of total obeticholic acid increased by 1.1-, 4- and 17-fold, respectively, compared to subjects with normal hepatic function following single-dose administration of 10 mg OCALIVA [see *Dosage and Administration* (2.3), *Use in Specific Populations* (8.6)].

Drug Interaction Studies

Effect of Obeticholic Acid on Other Drugs

Based on *in vitro* studies, obeticholic acid can inhibit CYP3A4. However, an *in vivo* study indicated no 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.

Warfarin: Concomitant administration of 25 mg warfarin as a single dose with OCALIVA 10 mg once daily resulted in 13% increase in systemic exposure to S-warfarin and 11% decrease in maximum INR [see *Drug Interactions* (7.2)].

Caffeine (CYP1A2 substrate): Concomitant administration of 200 mg caffeine as a single dose with OCALIVA 10 mg once daily resulted in a 42% increase in plasma AUC and 6% increase in C_{max} of caffeine [see *Drug Interactions* (7.3)].

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

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

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

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

Digoxin 0.25 mg (P-gp substrate): 1% increase in AUC and 3% decrease in C_{max} of digoxin.

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

Effect of Other Drugs on Obeticholic Acid

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

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenic potential of obeticholic acid was assessed in carcinogenicity studies of up to 2 years in duration in mice and rats. In mice, there were no drug-related neoplastic findings at doses up to 25 mg/kg/day obeticholic acid, a dose that produced systemic exposures approximately 12 times those in humans at the MRHD of 10 mg. In rats, obeticholic acid was administered at doses of 2, 7, and 20 mg/kg/day. At 20 mg/kg/day (approximately 12 times the human exposure at the MRHD), obeticholic acid caused an increase in the incidence of benign granulosa cell tumors in the ovaries and benign granular cell tumors in the cervix and vagina of female rats. There were no drug-related neoplastic findings in male rats.

Obeticholic acid was not genotoxic in the Ames test, a human peripheral blood lymphocyte chromosomal aberration test, and a mouse micronucleus test. The glycine conjugate of obeticholic acid was also not genotoxic in an Ames test and human peripheral blood lymphocyte chromosome aberration test. The taurine conjugate of obeticholic acid was not genotoxic in an Ames test, and was negative in a

human peripheral blood lymphocyte chromosomal aberration test in the presence of metabolic activation; the findings of the chromosomal aberration assay in the absence of metabolic activation were inconclusive.

Obeticholic acid, administered at oral doses of 5, 25 and 50 mg/kg/day to male rats for 28 days before mating and throughout the mating period, and to female rats from 14 days before mating through mating and until gestation day 7, did not alter male or female fertility or early embryonic development at any dose (the 50 mg/kg/day dose is approximately 13 times the human exposure at the MRHD).

14 CLINICAL STUDIES

The recommended starting dosage of OCALIVA is 5 mg orally once daily for 3 months with titration to 10 mg once daily based upon tolerability and response [*see Dosage and Administration (2.1)*]. Initiation of therapy with a starting dosage OCALIVA 10 mg once daily is not recommended due to an increased risk of pruritus [*see Adverse Reactions (6.1)*].

Trial 1 was a randomized, double-blind, placebo-controlled, 12-month 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. Distribution of patients by Rotterdam disease stage criteria at baseline is shown in Table 2. 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.

Table 2: Rotterdam Disease Stage Criteria at Baseline in Trial 1 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).

Table 3 shows the percentage of patients by treatment arm in Trial 1 who achieved a response to the primary composite endpoint at Month 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 3: Percentage of Adult Patients with PBC Achieving the Primary Composite Endpoint at Month 12 in Trial 1 by Treatment Arm with or without UDCA^a

	OCALIVA 10 mg (N = 73)	OCALIVA Titration ^b (N = 70)	Placebo (N = 73)
Primary Composite Endpoint^c			
Responder rate, (%) ^d [95% CI]	48 [36, 60]	46 [34, 58]	10 [4, 19]
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 ULN ^f , n (%)	60 (82)	62 (89)	57 (78)

^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 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.

^c Percentage of patients achieving a response, defined as an ALP less than 1.67-times the ULN, total bilirubin less than or equal to the ULN, and an ALP decrease of at least 15%. Missing values were considered a non-response. The exact test was used to calculate the 95% CIs.

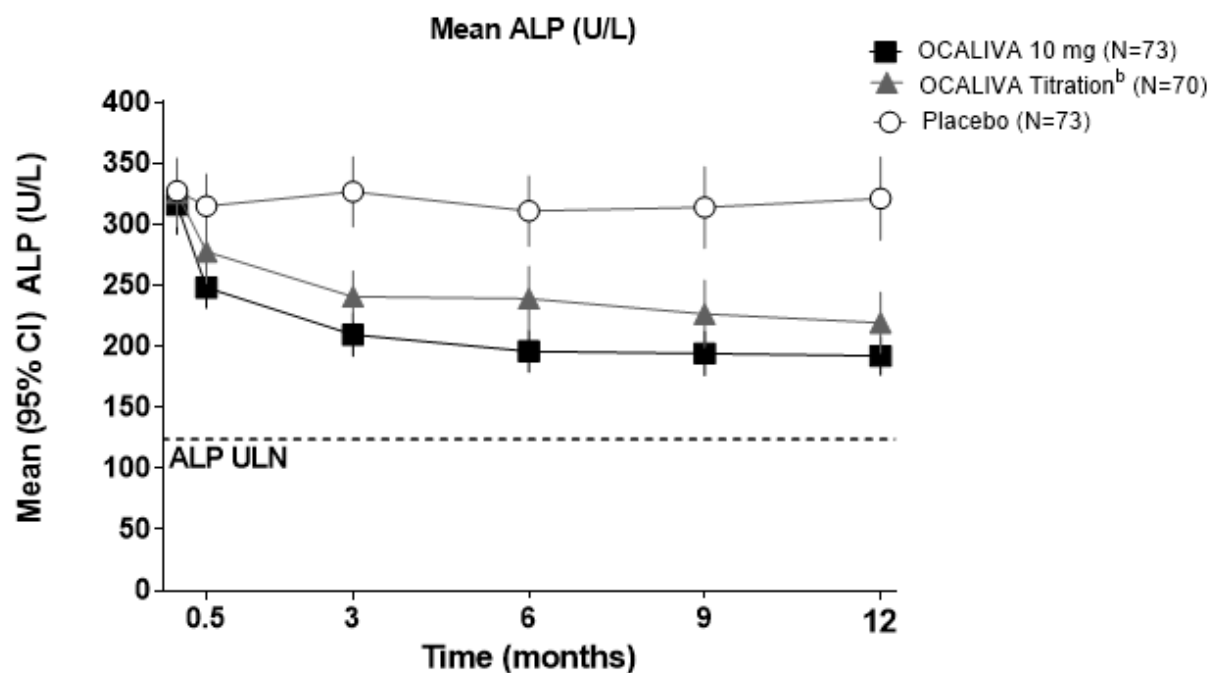
^d $p < 0.0001$ for OCALIVA titration and OCALIVA 10 mg arms versus placebo. P-values are obtained using the Cochran–Mantel–Haenszel General Association test stratified by intolerance to UDCA and pretreatment ALP greater than 3-times ULN and/or AST greater than 2-times ULN and/or total bilirubin greater than ULN.

- ^e Response rates were calculated based on the observed case analysis (i.e., $[n=\text{observed responder}]/[N=\text{ITT population}]$); 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 less than or equal to the ULN in 92% of the enrolled patients.

Mean Reduction in ALP

Figure 1 shows the mean reductions in ALP in OCALIVA-treated patients compared to placebo. Reductions were observed as early as Week 2, plateaued by Month 3 and were maintained through Month 12 for patients who were maintained on the same dosage throughout 12 months. Although Trial 1 studied titration at 6 months, these data are supportive of titration of OCALIVA after 3 months [see *Dosage and Administration (2.1)*]. 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 the patients [see *Clinical Pharmacology (12.2)*].

Figure 1: Mean ALP over 12 Months in Trial 1 by Treatment Arm with or without UDCA^a



- ^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 Trial 1 and from a randomized, double-blind, placebo-controlled, 3-month trial. 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

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 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.

- NDC 69516-005-30 5 mg tablets in a bottle (30 count)

10 mg Tablets

OCALIVA 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.

- NDC 69516-010-30 10 mg tablets in a bottle (30 count)

Storage and Handling

Store at 20°C-25°C (68°F-77°F); excursions permitted to 15°C- 30°C (59°F -86°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Liver-Related Adverse Reactions

- Advise patients to report any symptoms of worsening of liver disease to their healthcare provider immediately and that they may need to undergo laboratory testing periodically while on OCALIVA treatment to assess liver function [see *Warnings and Precautions (5.1)*].
- Advise patients who develop symptoms of complete biliary obstruction to report to their healthcare provider immediately [see *Contraindications (4)*].

Severe Pruritus

- Advise patients to contact their healthcare provider if they experience pruritus or an increase in the severity of pruritus [see *Warnings and Precautions (5.2)*].

Reduction in HDL-C

- Advise patients that they may need to undergo laboratory testing to check for changes in lipid levels while on treatment with OCALIVA [*see Warnings and Precautions (5.3)*].

Administration

Advise patients to take:

- OCALIVA with or without food.
- OCALIVA at least 4 hours before or 4 hours after taking a bile acid binding resin, or at as great an interval as possible [*see Drug Interactions (7.1)*].

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