▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – OCALIVA® (OBETICHOLIC ACID) TABLETS

1 NAME OF THE MEDICINE

Obeticholic acid

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each OCALIVA tablet contains the active ingredient obeticholic acid 5 mg or 10 mg. For the full list of excipients, see section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

OCALIVA 5 mg film-coated tablets

Yellow round tablet debossed with 'INT' on one side and '5' on the other side.

OCALIVA 10 mg film-coated tablets

Yellow triangular tablet debossed with 'INT' on one side and '10' on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

Prior to the initiation of obeticholic acid, healthcare professionals 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 obeticholic acid is contraindicated in these patients (see section 4.3 CONTRAINDICATIONS and section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

The starting dosage of obeticholic acid is 5 mg once daily 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.

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

Management and dose adjustment for severe pruritus

Management strategies include the addition of bile acid binding resins or antihistamines.

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

- Reducing the dosage of obeticholic acid to:
  - 5 mg every other day, for patients intolerant to 5 mg once daily.
  - 5 mg once daily, for patients intolerant to 10 mg once daily.
- Temporarily interrupting obeticholic acid 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 treatment with obeticholic acid for patients who continue to experience persistent intolerable pruritus.

Bile acid binding resins

For patients taking bile acid binding resins, obeticholic acid should be administered at least 4-6 hours before or 4-6 hours after taking a bile acid binding resin, or at as great an interval as possible (see section 4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Special populations

Elderly (≥ 65 years)

Limited data exists in elderly patients. No dose adjustment is required for elderly patients (see section 5.2 PHARMACOKINETIC PROPERTIES).

Renal impairment

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

Hepatic impairment

Obeticholic acid is contraindicated in patients with decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event, or compensated cirrhosis with evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia) (see section 4.3 CONTRAINDICATIONS and section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). No dose adjustment is needed for mild hepatic impairment (Child-Pugh Class A) (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE and section 5.2 PHARMACOKINETIC PROPERTIES).

Routinely monitor patients during obeticholic acid treatment 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 progression to cirrhosis and/or hepatic decompensation, including those with laboratory evidence of worsening liver function (e.g., 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 obeticholic acid treatment discontinuation is needed (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Permanently discontinue in patients with laboratory or clinical evidence of hepatic decompensation (see section 4.3 CONTRAINDICATIONS and 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Discontinue in patients who develop complete biliary obstruction (see section 4.3 CONTRAINDICATIONS).

Paediatric population

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

Method of administration

The tablet should be taken orally with or without food.

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients
- Patients with decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
- Patients with compensated cirrhosis who have evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia) (see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE)
- Patients with complete biliary obstruction.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hepatic adverse events

Hepatic failure, sometimes fatal or resulting in liver transplant, has been reported with obeticholic acid treatment in PBC patients with either compensated or decompensated cirrhosis. Obeticholic acid 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 recommended doses (e.g., started on OCALIVA 5 mg once daily); however, cases of hepatic decompensation and failure have continued to be reported in patients with decompensated cirrhosis even when they received lower doses (e.g., 5 mg once weekly). See section 4.3 CONTRAINDICATIONS.

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

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

Liver tests should be obtained before initiating treatment with OCALIVA, within the first 6 months after initiation of treatment, and as clinically indicated thereafter.

After initiation of therapy, all patients should be routinely monitored for progression of PBC, including hepatic adverse reactions, with laboratory and clinical assessment to determine whether obeticholic acid treatment discontinuation is needed. Closely monitor patients at increased risk of compensated cirrhosis, concomitant hepatic disease (e.g., autoimmune hepatitis, alcohol-associated liver disease), and/or intercurrent illness (including hospitalisations) for new evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia) or increases above the upper limit of normal in total bilirubin, direct bilirubin, or prothrombin time, to determine whether drug interruption or discontinuation is needed.

Treatment with obeticholic acid should be promptly interrupted in patients with suspected liver injury based on clinical signs or symptoms (e.g., anorexia, right upper abdominal discomfort, dark urine, jaundice, or new onset or worsening of fatigue), symptomatic cholelithiasis and/or cholecystitis (particularly with any suspicion of biliary obstruction) and clinically significant changes in laboratory results (e.g., rise in ALT, ALP, total bilirubin, or International Normalised Ratio (INR); decrease in albumin or platelets). After resolution of the suspected liver injury, obeticholic acid treatment can be resumed if an alternative probable cause has been found.

Treatment with obeticholic acid should be permanently discontinued in patients who develop laboratory or clinical evidence of hepatic decompensation (e.g., ascites, jaundice, variceal bleeding, hepatic encephalopathy), have compensated cirrhosis and develop evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia), experience clinically significant liver injury, or develop complete biliary obstruction (see section 4.3 CONTRAINDICATIONS).

Severe pruritus

Severe pruritus was reported in 23% of patients treated with OCALIVA 10 mg arm, 19% of patients in the OCALIVA titration arm, and 7% of patients in the placebo arms. The median time to onset of severe pruritus was 11, 158, and 75 days for patients in the OCALIVA 10 mg, OCALIVA titration, and placebo arms, respectively.

Management strategies include the addition of bile acid binding resins or antihistamines, dose reduction, reduced dosing frequency, and/or temporary dose interruption (see section 4.2 DOSE AND METHOD OF ADMINISTRATION and section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

Consider clinical evaluation of patients with new onset or worsening severe pruritus.

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 clinical study, 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.

Use in the elderly

Limited data exists in elderly patients. No dose adjustment is required for elderly patients (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

Paediatric use

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

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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.

Effect of obeticholic acid on other medicinal products

Warfarin

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

CYP1A2 substrates with narrow therapeutic index

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

Effect of other medicinal products on obeticholic acid

Bile acid binding resins

Bile acid binding resins such as cholestyramine, colestipol, or colesevelam adsorb and reduce bile acid absorption and may reduce efficacy of obeticholic acid. When concomitant bile acid binding resins are administered, obeticholic acid should be taken at least 4-6 hours before or

4-6 hours after taking a bile acid binding resin, or at as great an interval as possible.

Inhibitors of bile salt efflux pump

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No fertility data is available in humans. 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).

Use in pregnancy – Pregnancy Category B1

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.

Use in lactation

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Obeticholic acid has no or negligible influence on the ability to drive and use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The most commonly reported adverse reactions were pruritus (63%) and fatigue (22%). Adverse reactions leading to discontinuation were 1% in the OCALIVA titration arm and 11% in the OCALIVA 10 mg arm. The most common adverse reaction leading to discontinuation was pruritus. The majority of pruritus occurred within the first month of treatment and tended to resolve over time with continued dosing.

Tabulated list of adverse reactions

The adverse reactions reported with OCALIVA in the phase III clinical study are listed in Table 1 by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10),

common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

Table 1: Frequency of adverse reactions in PBC patients*

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

* Adverse reactions are defined as events occurring at a rate of greater than or equal to 5% of patients on obeticholic acid treatment arm and at an incidence greater than or equal to 1% higher than in the placebo treatment arm.

Description of selected adverse reactions

Hepatic adverse events

Hepatic failure, sometimes fatal or resulting in liver transplant, has been reported in patients with obeticholic acid treatment in PBC patients with decompensated cirrhosis (e.g., Child-Pugh Class B or C) (see section 4.3 CONTRAINDICATIONS and section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Pruritus

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

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

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

Post-marketing experience

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: hepatic failure, bilirubin increase, jaundice, cirrhosis.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

The highest single dose exposure of obeticholic acid in healthy volunteers has been at the 500 mg dose. Repeated doses of 250 mg have been administered for 12 consecutive days and some subjects experienced pruritus and reversible transaminase liver elevations. In 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 (e.g., ascites, primary biliary cholangitis flares, new onset jaundice), and transaminase and bilirubin elevations (up to greater than 3-times upper limit of normal [ULN]).

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

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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

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

Clinical trials

A phase III, randomised, double-blind, placebo-controlled, parallel-group, 12-month study (POISE) evaluated the safety and efficacy of OCALIVA in 216 patients with PBC who were taking UDCA for at least 12 months (stable dose for ≥ 3 months) or who were unable to tolerate UDCA and did not receive UDCA for ≥ 3 months. Patients were included in the trial if the alkaline phosphatase (ALP) was greater than or equal to 1.67 times upper limit of normal (ULN) and/or if total bilirubin was greater than 1 x ULN but less 2 x ULN. Patients were randomised (1:1:1) to receive once daily placebo, OCALIVA 10 mg, or OCALIVA titration (5 mg titrated to 10 mg at 6 months dependent on therapeutic response/tolerability). The majority (93%) of patients received treatment in combination with UDCA and a small number of patients (7%) unable to tolerate UDCA received placebo, OCALIVA (10 mg) or OCALIVA titration (5 mg to 10 mg) as

monotherapy. ALP and total bilirubin were assessed as categorical variables in the primary composite endpoint, as well as continuous variables over time.

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

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

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

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

[a] Percentage of subjects achieving a response, defined as an ALP less than 1.67-times the ULN, total bilirubin within the normal range, and an ALP decrease of at least 15%. Missing values were considered a non-response. The Fisher's exact test was used to calculate the 95% Confidence Intervals (Cis).

[b] In the trial there were 16 patients (7%) who were intolerant and did not receive concomitant UDCA: 6 patients (8%) in the OCALIVA 10 mg arm, 5 patients (7%) in the OCALIVA titration arm, and 5 patients (7%) in the placebo arm.

[c] Patients were 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.

[d] OCALIVA titration and OCALIVA 10 mg versus placebo. P-values are obtained using the Cochran-Mantel-Haenszel General Association test stratified by intolerance to UDCA and 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=observed responder]/[N=Intention to Treat (ITT) population]); percentage of patients with Month 12 values are 86%, 91% and 96% for the OCALIVA 10 mg, OCALIVA titration and placebo arms, respectively.

[f] The mean baseline total bilirubin value was 0.65 mg/dL, and was within the normal range (i.e., less than or equal to the ULN) in 92% of the enrolled patients.

Mean reduction in ALP

Mean reductions in ALP were observed as early as Week 2 and were maintained through Month 12 for patients who were maintained on the same 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.

Mean reduction in gamma-glutamyl transferase (GGT)

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

Monotherapy

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

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Obeticholic acid is absorbed with peak plasma concentrations (C_{max}) occurring at a median time (t_{max}) of approximately 2 hours. Peak plasma exposure of total obeticholic acid (sum of obeticholic acid and its two active conjugates, glyco- and tauro-obeticholic acid) occur after a meal similar to endogenous bile acids.

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.

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 faeces, the principal route of elimination.

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

Excretion

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

Dose/time proportionality

Following multiple-dose administration of 5, 10, and 25 mg once daily for 14 days, systemic exposures of obeticholic acid increased dose proportionally. Exposures of glyco- and tauro-obeticholic acid, and total obeticholic acid increase more than proportionally with dose. The steady-state systemic exposure ($AUC_{0\text{-}24h}$) achieved on Day 14 of total obeticholic acid was 4.2-, 6.6-, and 7.8- fold the systemic exposure ($AUC_{0\text{-}24h}$) achieved on Day 1 after 5, 10, and 25 mg once daily dosing, respectively. There was high variability in the C_{max} and AUC of obeticholic acid in a limited number of PBC patients.

Special populations

Elderly

There are limited pharmacokinetic data in elderly patients (≥ 65 years). Population pharmacokinetic analysis, developed using data from patients up to 65 years old, indicated that age is not expected to significantly influence obeticholic acid clearance from the circulation. There are insufficient data to make dosing recommendations for patients 75 years of age and older.

Paediatric population

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

Body weight

Based on population pharmacokinetic analysis, body weight was a significant predictor of obeticholic acid pharmacokinetics with lower obeticholic acid plasma exposure expected with higher body weight. Body weight is not expected to have a meaningful impact on efficacy.

Sex

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

Race

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

Renal impairment

In a single-dose pharmacokinetic study using 25 mg of obeticholic acid, plasma exposures to obeticholic acid and its conjugates were increased by approximately 1.6 to 2.5-fold in subjects with

mild (modification of diet in renal disease [MDRD] eGFR 60 -<90 mL/min), moderate (MDRD eGFR 30 - <60 mL/min) and severe (MDRD eGFR <30 mL/min) renal impairment compared to subjects with normal renal function. This modest increase is not considered to be clinically meaningful.

Hepatic impairment

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

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

In subjects with mild, moderate and severe hepatic impairment (Child-Pugh Class A, B, and C, respectively), mean AUC of total obeticholic acid, the sum of obeticholic acid and its two active conjugates, increased by 1.13-, 4- and 17-fold, respectively, compared to subjects with normal hepatic function following single-dose administration of 10 mg obeticholic acid. There is no clinical data to guide the effects of a 4- to 17-fold increase in systemic exposure of obeticholic acid in patients with moderate or severe hepatic impairment.

5.3 PRECLINICAL SAFETY DATA

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.

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 tumours in the ovaries and benign granular cell tumours in the cervix and vagina of female rats. There were no drug-related neoplastic findings in male rats.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Microcrystalline cellulose
Sodium starch glycollate type A
Magnesium stearate
Opadry II complete film coating system 85F32351 YELLOW

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

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

Pack size: 30 or 100 film-coated tablets. Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

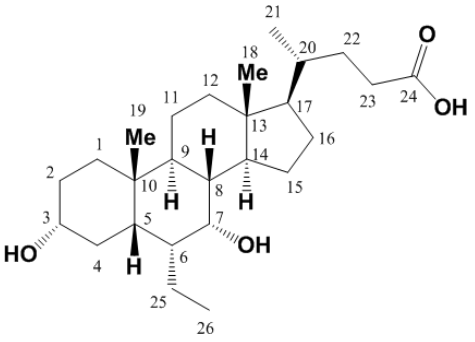
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Obeticholic acid (OCA) is a 6-ethyl derivative of the human bile acid chenodeoxycholic acid. It is a poorly soluble and highly permeable white to off-white powder.

Chemical structure

6α-ethylchenodeoxycholic acid



Empirical formula: $C_{26}H_{44}O_4$ MW: 420.63 g/mol

CAS number

459789-99-2

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

Chiesi Australia Pty Ltd
Suite 3, 22 Gillman Street,
Hawthorn East, VIC 3123.
Email: medinfo.au@chiesi.com

Under licence from the Advanz Pharma group of companies.

9 DATE OF FIRST APPROVAL

21 September 2018

10 DATE OF REVISION

11 February 2025

Summary table of changes

Section changed	Summary of new information
4.2	Align with the revised contraindications
4.3	Addition of contraindication in patients with compensated cirrhosis who have evidence of portal hypertension
4.4	Clarification of recommendations for monitoring and interruption or discontinuation of treatment
8	Update to contact details