ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Ocaliva 5 mg film-coated tablets

Ocaliva 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Ocaliva 5 mg film-coated tablets

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

Ocaliva 10 mg film-coated tablets

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

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Ocaliva 5 mg film-coated tablets

Yellow, 8 mm round tablet debossed with 'INT' on one side and '5' on the other side.

Ocaliva 10 mg film-coated tablets

Yellow, 8 mm × 7 mm 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 Posology and method of administration

Posology

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

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

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

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

Management and dose adjustment for severe pruritus

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

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

- The dose of obeticholic acid may be reduced to:
  - 5 mg every other day, for patients intolerant to 5 mg once daily
  - 5 mg once daily, for patients intolerant to 10 mg once daily
- The dose of obeticholic acid may be temporarily interrupted for up to 2 weeks followed by restarting at a reduced dose.
- The dose may be increased to 10 mg once daily, as tolerated, to achieve optimal response.

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

Bile acid binding resins

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

Missed dose

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

Special populations

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

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

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

Paediatric population
There is no relevant use of obeticholic acid in the paediatric population in the treatment of PBC.

Method of administration

The tablet should be taken orally with or without food.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Hepatic adverse events

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

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

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

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

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

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

Severe pruritus

Severe pruritus was reported in 23% of patients treated with obeticholic acid 10 mg arm, 19% of patients in the obeticholic acid 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 obeticholic acid 10 mg, obeticholic acid titration, and placebo arms, respectively. Management strategies include the addition of bile acid binding resins or antihistamines, dose reduction, reduced dosing frequency, and/or temporary dose interruption (see sections 4.2 and 4.8).

Excipients

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

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on obeticholic acid

Bile acid binding resins

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

Effect of obeticholic acid on other medicinal products

Warfarin

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

Interaction with CYP1A2 substrates with narrow therapeutic index

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding

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

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

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

Tabulated list of adverse reactions

The adverse reactions reported with obeticholic acid are listed in the table below by MedDRA system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000) and not known (cannot be estimated from the available data).

Table 1. Frequency of adverse reactions in PBC patients

System organ class	Very common	Common	Not known
Endocrine disorders		Thyroid function abnormality	
Nervous system disorders		Dizziness	
Cardiac disorders		Palpitations	
Respiratory, thoracic and mediastinal disorders		Oropharyngeal pain	
Gastrointestinal disorders	Abdominal pain and discomfort	Constipation	
Hepatobiliary disorders			Hepatic failure, Blood bilirubin increased, Jaundice, Hepatic cirrhosis
Skin and subcutaneous tissue disorders	Pruritus	Eczema, Rash	
Musculoskeletal and connective tissue disorders		Arthralgia	
General disorders and administration site conditions	Fatigue	Oedema peripheral, Pyrexia	

Description of selected adverse reactions

Discontinuation of treatment

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

Pruritus

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

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

The highest single dose exposure of obeticholic acid in healthy volunteers has been at the 500 mg dose. Repeated doses of 250 mg have been administered for 12 consecutive days and some subjects experienced pruritus and reversible transaminase liver elevations. In the clinical trials, PBC patients who received obeticholic acid 25 mg once daily (2.5-times the highest recommended dose) or 50 mg once daily (5-times the highest recommended dose), experienced a dose-dependent increase in the incidence of hepatic adverse reactions (e.g., ascites, primary biliary cholangitis flare, new onset jaundice), and transaminase and bilirubin elevations (up to greater than 3-times upper limit of normal [ULN]). In the case of overdose, patients should be carefully observed and supportive care administered, as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

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

Clinical efficacy and safety

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

	Obeticholic acid 10 mg[c] (N=73)	**Obeticholic acid 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 obeticholic acid 10 mg arm, 5 patients (7%) in the obeticholic acid titration arm, and 5 patients (7%) in the placebo arm.
[c] Patients were randomised (1:1:1) to receive obeticholic acid 10 mg once daily for the entire 12 months of the trial, or obeticholic acid 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 obeticholic acid 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] Obeticholic acid titration and obeticholic acid 10 mg versus placebo. P-values are obtained using the Cochran-Mantel-Haenszel General Association test stratified by intolerance to UDCA and pre-treatment ALP greater than 3-times ULN and/or AST greater than 2-times ULN and/or total bilirubin greater than ULN.
[e] Response rates were calculated based on the observed case analysis (i.e., [n=observed responder]/[N=intention to treat (ITT) population]); percentage of patients with month 12 values are 86%, 91% and 96% for the obeticholic acid 10 mg, obeticholic acid titration and placebo arms, respectively.
[f] The mean baseline total bilirubin value was 0.65 mg/dL, and was within the normal range (i.e., less than or equal to the ULN) in 92% of the enrolled patients.

Mean reduction in ALP

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

Mean reduction in gamma-glutamyl transferase (GGT)

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

Monotherapy

Fifty-one PBC patients with baseline ALP 1.67-times ULN or greater and/or total bilirubin greater than ULN were evaluated for a biochemical response to obeticholic acid as monotherapy (24 patients received obeticholic acid 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%) obeticholic acid-treated patients achieved a response to the composite endpoint, compared to 1 (4%) placebo-treated patient. The mean (95% CI) reduction in ALP in obeticholic acid-treated patients was 246 (165, 327) U/L compared to an increase of 17 (-7, 42) U/L in the placebo-treated patients.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Ocaliva in all subsets of the paediatric population in PBC (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.
The European Medicines Agency will review any new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Absorption

Obeticholic acid is absorbed with peak plasma concentrations (C_{max}) occurring at a median time (t_{max}) of approximately 2 hours. Co-administration with food does not alter the extent of absorption of obeticholic acid.

Distribution

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

Biotransformation

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

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

Elimination

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

Dose/Time proportionality

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

Special populations

Elderly

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

Paediatric population

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

Gender

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

Race

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

Renal impairment

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

Hepatic impairment

Obeticholic acid is metabolised in the liver and intestines. The systemic exposure of obeticholic acid, its active conjugates, and endogenous bile acids is increased in patients with moderate and severe hepatic impairment (Child-Pugh Class B and C, respectively) when compared to healthy controls (see sections 4.2, 4.3 and 4.4).

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

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

5.3 Preclinical safety data

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

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

Tablet coating

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

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

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 sizes: 30 or 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

ADVANZ PHARMA Limited
Suite 17, Northwood House,
Northwood Avenue, Santry,
Dublin 9
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1139/001

EU/1/16/1139/002

EU/1/16/1139/003

EU/1/16/1139/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 12 December 2016
Date of latest renewal: 15 November 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Almac Pharma Services (Ireland) Limited
Finnabair Industrial Estate
Dundalk
Co. Louth
A91 P9KD
Ireland

Almac Pharma Services
Seagoe Industrial Estate
Portadown
Craigavon
BT63 5UA
United Kingdom

Millmount Healthcare Limited
Block-7, City North Business Campus
Stamullen
Co. Meath
K32 YD60
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORISATION

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
Interventional study 747-302: Description: In order to confirm the efficacy and safety of Ocaliva, the MAH should conduct and submit the results of study 747-302, a confirmatory double-blind, randomised, placebo-controlled multicentre study investigating the clinical benefit associated with Ocaliva treatment in patients with PBC who are either unresponsive or intolerant to UDCA treatment based on clinical endpoints. Rationale: to investigate the effect of obeticholic acid on clinical outcomes in subjects with PBC	Final report: 2023
Interventional study 747-401: Description: In order to confirm the efficacy and safety of Ocaliva, the MAH should conduct and submit the results of study 747-401, a double-blind, randomised, placebo-controlled study evaluating the efficacy, safety and pharmacokinetics of Ocaliva in patients with PBC and moderate to severe hepatic impairment. Rationale: to investigate the uncertainties related to the lack of data in a population with more advanced liver disease	Final report: 2023

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 5 mg

1. NAME OF THE MEDICINAL PRODUCT

Ocaliva 5 mg film-coated tablets
obeticholic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablet

30 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ADVANZ PHARMA Limited
Suite 17, Northwood House,
Northwood Avenue, Santry,
Dublin 9
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1139/001 30 film-coated tablets
EU/1/16/1139/003 100 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ocaliva 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL 5 mg

1. NAME OF THE MEDICINAL PRODUCT

Ocaliva 5 mg film-coated tablets
obeticholic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablet

30 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

ADVANZ PHARMA Limited
Suite 17, Northwood House,
Northwood Avenue, Santry,
Dublin 9
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1139/001 30 film-coated tablets
EU/1/16/1139/003 100 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON 10 mg

1. NAME OF THE MEDICINAL PRODUCT

Ocaliva 10 mg film-coated tablets
obeticholic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablet

30 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1139/002 30 film-coated tablets
EU/1/16/1139/004 100 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Ocaliva 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL 10 mg

1. NAME OF THE MEDICINAL PRODUCT

Ocaliva 10 mg film-coated tablets
obeticholic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablet

30 film-coated tablets
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1139/002 30 film-coated tablets
EU/1/16/1139/004 100 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Ocaliva 5 mg film-coated tablets
Ocaliva 10 mg film-coated tablets
obeticholic acid

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Ocaliva is and what it is used for

Ocaliva contains the active substance obeticholic acid (farnesoid X-receptor agonist) which helps to improve how your liver works by reducing the production and build up of bile in the liver and also reducing inflammation.

This medicine is used to treat adult patients with a type of liver disease known as primary biliary cholangitis, either by itself or together with another medicine, ursodeoxycholic acid.

2. What you need to know before you take Ocaliva

Do not take Ocaliva
- if you are allergic to obeticholic acid or any of the other ingredients of this medicine (listed in section 6).
- if you have primary biliary cholangitis with liver cirrhosis with symptoms such as fluid in the belly or confusion (decompensated liver cirrhosis).
- if you have a complete blockage of the biliary tract (liver, gallbladder and bile ducts).

Warnings and precautions
Talk to your doctor or pharmacist before taking Ocaliva.

Your doctor may need to interrupt or discontinue Ocaliva if your liver function gets worse. Your doctor will do blood tests to monitor the health of your liver when you start treatment and regularly from there on.

Itching may occur when taking Ocaliva and may sometimes become severe (intense itching or itching over much of your body). Your doctor may prescribe other medicines for treatment of itching or adjust your dose of Ocaliva. If you experience itching that is difficult to tolerate, talk to your doctor.

Children and adolescents
This medicine is not for use in children or adolescents.

Other medicines and Ocaliva
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In particular, tell your doctor if you are taking so-called bile acid binding resins (cholestyramine, colestipol, colesevelam) used to lower blood cholesterol levels as they may lessen the effect of Ocaliva. If you take any of these medicines, take Ocaliva at least 4 to 6 hours before or 4 to 6 hours after taking bile acid binding resin, giving as much time as possible.

The levels of some medicines such as theophylline (a medicine to help breathing) or tizanidine (a medicine to relieve the stiffness and restriction of muscles) may be increased and need to be monitored by your doctor while taking Ocaliva. Your doctor may need to monitor how well your blood clots when taking medicines such as warfarin (a medicine to help your blood flow) with Ocaliva.

Pregnancy
There is no experience using Ocaliva in pregnancy. As a precautionary measure, you should not take Ocaliva if you are pregnant.

Breast-feeding
It is not known if this medicine passes into human milk. Your doctor will determine whether you should discontinue breast-feeding or discontinue/abstain from Ocaliva therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for you.

Driving and using machines
This medicine has no or negligible influence on your ability to drive or use machines.

Ocaliva contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

3. How to take Ocaliva

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Prior to initiation of treatment with Ocaliva, your hepatic status must be known. If you have primary biliary cholangitis with liver cirrhosis with symptoms such as fluid in the belly or confusion (decompensated liver cirrhosis) or if you have a complete blockage of the biliary tract (liver, gallbladder and bile ducts) this should be determined (see section 2, Do not take Ocaliva, Warnings and precautions).

The recommended starting dose is one 5 mg film-coated tablet once daily.

Your doctor may adjust your dose depending on your liver function or if you experience itching that is difficult to tolerate.

Depending on your body’s response after 6 months, your doctor may increase your dose to 10 mg once daily. Your doctor will discuss any change of dose with you.

You can take Ocaliva with or without food. If you take bile acid binding resins, take this medicine at least 4 to 6 hours before or at least 4 to 6 hours after the bile acid binding resin (see section "Other medicines and Ocaliva").

If you take more Ocaliva than you should
If you accidentally take too many tablets, you may experience itching or liver-related side effects such as yellowing of the skin. Contact a doctor or go to a hospital for advice immediately.

If you forget to take Ocaliva
Skip the missed dose and take your next dose when you would normally take it. Do not take a double dose to make up for a forgotten tablet.

If you stop taking Ocaliva
You should continue to take Ocaliva for as long as your doctor tells you to. Do not stop taking the medicine without talking to your doctor first.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor or pharmacist if you experience itching of the skin (pruritus) or if the itch gets worse while on this medicine. In general itching of the skin is a very common (may affect more than 1 in 10 people) side effect that begins within the first month following the start of treatment with Ocaliva and usually becomes less severe over time.

Other possible side effects may be:

Very common side effects
- stomach pain
- feeling tired

Common side effects (may affect up to 1 in 10 people)
- thyroid hormone irregularity
- dizziness
- fast or irregular heart beat (palpitations)
- pain in the mouth and throat
- constipation
- itchy, dry and/or red skin (eczema)
- rash
- pain in your joints
- swelling in the hands and feet
- fever

Not known (frequency cannot be estimated from the available data)
The following side effects have been reported since the marketing of Ocaliva, but how often they occur is not known:
- liver failure
- increase in bilirubin (liver blood test)
- yellowing of eyes or skin (jaundice)
- scarring of the liver (cirrhosis)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Ocaliva

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and bottle after "EXP". The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Ocaliva contains
- The active substance is obeticholic acid.
  - Ocaliva 5 mg film-coated tablets: Each film-coated tablet contains 5 mg of obeticholic acid.
  - Ocaliva 10 mg film-coated tablets: Each film-coated tablet contains 10 mg of obeticholic acid.

- The other ingredients are:
  - Tablet core: Microcrystalline cellulose (E 460), sodium starch glycolate (Type A) (see section 2 "Ocaliva contains sodium"), magnesium stearate.
  - Film-coat: Polyvinyl alcohol, part hydrolysed (E 1203), titanium dioxide (E 171), macrogol (3350) (E 1521), talc (E 553b), iron oxide yellow (E 172).

What Ocaliva looks like and contents of the pack
- Ocaliva 5 mg is a yellow, 8 mm round film-coated tablet with 'INT' on one side and '5' on the other side of the film-coated tablet.
- Ocaliva 10 mg is a yellow, 8 mm × 7 mm triangular film-coated tablet with 'INT' on one side and '10' on the other side of the film-coated tablet.

Pack sizes

1 bottle with 30 or 100 film-coated tablets.

Not all pack sizes may be marketed.

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This leaflet was last revised in

This medicine has been given ‘conditional approval’. This means that there is more evidence to come about this medicine.

The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.