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 (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, 7.6 mm X 7.4 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 (also known as primary biliary cirrhosis) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA.

4.2 **Posology and method of administration**

**Posology**
The starting dose is 5 mg once daily.
Based on an assessment of tolerability after 6 months, the dose should be increased to 10 mg once daily to achieve optimal response.

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.
• Continue to 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.

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

Patients with renal impairment
Limited data exists in patients with mild and moderate renal impairment and no data exists in severe renal impairment. No dose adjustment is required for patients with renal impairment (see section 5.2).

Patients with hepatic impairment
Limited data exists in patients with moderate to severe hepatic impairment. The recommended starting dosage for moderate (Child-Pugh Class B) and severe (Child-Pugh Class C) hepatic impairment is 5 mg once weekly. If an adequate reduction in alkaline phosphatase and/or total bilirubin has not been achieved after 3 months of OCALIVA 5 mg once weekly, and the patient is tolerating the medicinal product, increase the dose of OCALIVA to 5 mg twice weekly (at least three days apart between doses) and subsequently to 10 mg twice weekly (at least three days apart between doses) depending on response and tolerability. No dose adjustment is needed for mild hepatic impairment (Child-Pugh Class A) (see sections 4.4 and 5.2).

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

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

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).

4.3 Contraindications
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Complete biliary obstruction.

4.4 Special warnings and precautions for use

Liver related adverse events
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. Liver-related adverse events have primarily been observed at doses higher than the maximum recommended dose of 10 mg once daily (see section 4.9). Patients should be monitored during treatment with OCALIVA for elevations in liver biochemical tests and for the development of liver-related adverse events. Dosage adjustments are needed for patients with moderate (Child-Pugh Class B) or severe (Child-Pugh Class C) hepatic impairment (see sections 4.2 and 5.2).
Severe pruritus
Severe pruritus was reported in 23% of patients treated with OCALIVA 10 mg arm, 19% of patients in the OCALIVA titration arm, and 7% of patients in the placebo arms. The median time to onset of severe pruritus was 11, 158, and 75 days for patients in the OCALIVA 10 mg, OCALIVA titration, and placebo arms, respectively. Management strategies include the addition of bile acid binding resins or antihistamines, dose reduction, reduced dosing frequency, and/or temporary dose interruption (see sections 4.2 and 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products that are affected by obeticholic acid

*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.

Medicinal products that affect 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.

4.6 Fertility, pregnancy and lactation

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

*Breast-feeding*
It is unknown whether obeticholic acid is excreted in human milk. Based on animal studies and intended pharmacology, obeticholic acid is not expected to interfere with breast-feeding or the growth or development of a breast-fed child. 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 (see section 5.3).

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

*Summary of the safety profile*
The most commonly reported adverse reactions were pruritus (63%) and fatigue (22%). Adverse reactions leading to discontinuation were 1% in the OCALIVA titration arm and 11% in the
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 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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Very common</th>
<th>Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine disorders</td>
<td>Thyroid function abnormality</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td>Dizziness</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td></td>
<td>Palpitations</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td>Oropharyngeal pain</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain and discomfort</td>
<td>Constipation</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Pruritus</td>
<td>Eczema, Rash</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td>Arthralgia</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td>Oedema peripheral, Pyrexia</td>
</tr>
</tbody>
</table>

* 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

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

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

The percentages of patients who required interventions (i.e., 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.

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 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 (e.g., ascites, primary biliary cholangitis flare, new onset jaundice), and transaminase and bilirubin elevations (up to greater than 3-times upper limit of normal [ULN]) were reported. In the case of overdose, patients should be carefully observed and supportive care administered, as appropriate.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bile Acid Preparations, ATC code: A05AA04

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

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

<table>
<thead>
<tr>
<th></th>
<th>OCALIVA 10 mg(^c) (N = 73)</th>
<th>OCALIVA Titration(^c) (N = 70)</th>
<th>Placebo (N=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Month 6</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responders, n (%)</td>
<td>37 (51)</td>
<td>24 (34)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Corresponding 95% CI</td>
<td>39%, 62%</td>
<td>23%, 45%</td>
<td>1%, 13%</td>
</tr>
<tr>
<td>p-value(^d)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Month 12</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responders, n (%)</td>
<td>35 (48)</td>
<td>32 (46)</td>
<td>7 (10)</td>
</tr>
<tr>
<td>Corresponding 95% CI</td>
<td>36%, 60%</td>
<td>34%, 58%</td>
<td>4%, 19%</td>
</tr>
<tr>
<td>p-value(^d)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>NA</td>
</tr>
</tbody>
</table>

**Components of primary endpoint\(^e\)**

<table>
<thead>
<tr>
<th>Component</th>
<th>OCALIVA 10 mg(^c) (N = 73)</th>
<th>OCALIVA Titration(^c) (N = 70)</th>
<th>Placebo (N=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALP less than 1.67-times ULN, n (%)</td>
<td>40 (55)</td>
<td>33 (47)</td>
<td>12 (16)</td>
</tr>
<tr>
<td>Decrease in ALP of at least 15%, n (%)</td>
<td>57 (78)</td>
<td>54 (77)</td>
<td>21 (29)</td>
</tr>
<tr>
<td>Total bilirubin less than or equal to 1-times ULN(^f), n (%)</td>
<td>60 (82)</td>
<td>62 (89)</td>
<td>57 (78)</td>
</tr>
</tbody>
</table>

\(^a\) 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.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with obeticholic acid 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 which may become available 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 volume of distributions of glyco- and tauro- obeticholic acid has 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 increase 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*
Obeticholic acid has minimal renal elimination with less than 3% of the dose recovered in urine. Based on population pharmacokinetic analysis, renal function did not have a meaningful effect on the pharmacokinetics of obeticholic acid.

*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. Therefore, a modified dose regimen for patients with moderate or severe hepatic impairment is recommended to achieve plasma exposure levels similar to patients with no hepatic impairment (see section 4.2).

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

Non-clinical 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 (E460)
- Sodium starch glycolate (Type A)
- Magnesium stearate
6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 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 size: 30 film-coated tablets.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Intercept Pharma Ltd.
2 Pancras Square
London, N1C 4AG
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

OCALIVA 5 mg film-coated tablets
EU/1/16/1139/001

OCALIVA 10 mg film-coated tablets
EU/1/16/1139/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:
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<, and on the website of {name of MS Agency (link)}>.
ANNEX II

A. MANUFACTURER 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 AUTHOURISATION
A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

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

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORIZATION

- Periodic safety update reports

  The requirements for submission of periodic safety update reports 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.

  The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- Risk Management Plan (RMP)

  The 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-AUTHORIZATION MEASURES FOR THE CONDITIONAL MARKETING AUTHORIZATION
This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

<table>
<thead>
<tr>
<th>Description</th>
<th>Due date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interventional study 747-302:</strong></td>
<td>Final report: 2023</td>
</tr>
<tr>
<td>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</td>
<td></td>
</tr>
<tr>
<td><strong>Interventional study 747-401:</strong></td>
<td>Final report: 2020</td>
</tr>
<tr>
<td>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</td>
<td></td>
</tr>
</tbody>
</table>
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

30 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

Intercept Pharma Ltd.
2 Pancras Square
London, N1C 4AG
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1139/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

OCALIVA 5 mg

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

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 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**

   30 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**
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Intercept Pharma Ltd.
2 Pancras Square
London, N1C 4AG
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1139/002

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Lot

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15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

OCALIVA 10 mg

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2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

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SN: {number}
NN: {number}
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<th>1. NAME OF THE MEDICINAL PRODUCT</th>
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<td>obeticholic acid</td>
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<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
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<td>Read the package leaflet before use.</td>
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<th>9. SPECIAL STORAGE CONDITIONS</th>
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PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE 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

30 film-coated tablets

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Oral use

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7. OTHER SPECIAL WARNING(S), IF NECESSARY

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B. PACKAGE LEAFLET
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
2. What you need to know before you take OCALIVA
3. How to take OCALIVA
4. Possible side effects
5. How to store OCALIVA
6. Contents of the pack and other information

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 (also known as primary biliary cirrhosis), 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 a complete blockage of the biliary tract (liver, gall bladder and bile ducts).

Warnings and precautions

Talk to your doctor or pharmacist before taking OCALIVA.

If you experience itching that is difficult to tolerate, talk to your doctor.

Your doctor will do blood tests to monitor the health of your liver when you start treatment and regularly from there on.
**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 4-6 hours before or 4-6 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) 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 and breast-feeding**  
There is little information about the effects of OCALIVA in pregnancy. As a precautionary measure, you should not take OCALIVA if you are pregnant or 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.

### 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.

The recommended dose is one 5 mg film-coated tablet once daily by mouth. 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 4-6 hours before or at least 4-6 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 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 you 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 an increase in the severity of itching while on this medicine. In general itching of the skin is a very common side effect that begins within the first month following the start of treatment with OCALIVA and decreases in severity over time.

**Very common side effects** (may affect more than 1 in 10 people):
- 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
- dry skin, redness of the skin (eczema)
- rash
- pain in your joints
- swelling in the hands and feet
- fever

**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 (E460), sodium starch glycolate (Type A), magnesium stearate.
- Film-coat: Polyvinyl alcohol, part hydrolysed (E1203), titanium dioxide (E171),
  macrogol 3350 (E1521), talc (E553b), iron oxide yellow (E172).

What OCALIVA looks like and contents of the pack
- OCALIVA 5 mg is a yellow, 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, 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 film-coated tablets

Marketing Authorisation Holder
Intercept Pharma Ltd.
2 Pancras Square
London, N1C 4AG
United Kingdom

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

For any information about this medicine, please contact the local representative of the Marketing
Authorisation Holder:

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Netherland/Pays-Bas/Niederlan
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Intercept Pharma UK & Ireland Ltd.
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This leaflet was last revised in \{MM/YYYY\}<~\{month YYYY\}>.

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](http://www.ema.europa.eu). There are also links to other websites about rare diseases and treatments.
Annex IV

Conclusions on the granting of the conditional marketing authorisation and presented by the European Medicines Agency
Conclusions presented by the European Medicines Agency on:

- **Conditional marketing authorisation**

  The CHMP having considered the application is of the opinion that the risk-benefit balance is favourable to recommend the granting of the conditional marketing authorisation as further explained in the European Public Assessment Report.