SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

Obetix 5 mg film-coated tablets

2. Qualitative and quantitative composition

Obetix 5 mg film-coated tablets

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

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet

4. Clinical particulars

4.1 Therapeutic indications

Obetix 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

Prior to initiation of treatment with obeticholic acid the patient's hepatic status must be known.

The starting dose and dosage titration by PBC patient population is shown in Table 1.

Table 1: Dosage Regimen by PBC Patient Population

Staging/Classification	**Non-Cirrhotic or Child-Pugh Class A**	**Child-Pugh Class B or C or Decompensated Cirrhotic**
Starting Dosage	**5 mg once daily**	**5 mg once weekly**
Dosage Titration	For patients who have not achieved an adequate reduction in alkaline phosphatase (ALP) and/or total bilirubin after **6 months** of treatment and the patient is tolerating obeticholic acid, titrate up to **10 mg once daily**	For patients who have not achieved an adequate reduction in ALP and/or total bilirubin after **3 months** of treatment and the patient is tolerating obeticholic acid, titrate up to **5 mg twice weekly** (at least 3 days apart) and subsequently to **10 mg twice weekly** (at least 3 days apart) based on response and tolerability
Maximum Dosage	**10 mg once daily**	**10 mg twice weekly** (at least 3 days apart)

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:

For Non-Cirrhotic or Child-Pugh Class A patients:

• 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.

For Child-Pugh Class B or C or Decompensated Cirrhotic patients:

• Reducing the dosage of obeticholic acid to:

  ▪ 5 mg once weekly, for patients intolerant to 5 mg twice weekly

  ▪ 10 mg once weekly, for patients intolerant to 10 mg twice weekly

• Temporarily interrupting obeticholic acid dosing for up to 2 weeks followed by restarting at a reduced dosage if applicable.

• Continue to increase the dosage to 10 mg twice weekly, as tolerated, to achieve optimal response.

Consider discontinuing treatment with obeticholic acid for patients who continue to experience persistent, intolerable pruritus.

Special populations

Patients with hepatic impairment

See table 1 for dose recommendations. Further, see sections 4.4 and 5.2.

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).

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). In the post marketing setting, serious liver injury and death have been reported with more frequent dosing of obeticholic acid than recommended in patients with moderate to severe decreases in liver function.

After initiation of therapy, all patients should be monitored for progression of PBC disease with laboratory and clinical assessment to determine whether dosage adjustment is needed. Patients at an increased risk of hepatic decompensation, including those with laboratory evidence of worsening liver function and /or progression to cirrhosis, should be monitored more closely. Dosing frequency should be reduced for patients who progress to advanced disease (i.e. from Child-Pugh Class A to Child-Pugh Class B or C) (see sections 4.2 and 5.2).

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).

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 Obeticholic Acid titration arm and 11% in the Obeticholic Acid 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 Obeticholic Acid 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 2. 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

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, dosage 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 authorization 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 Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 Obeticholic Acid 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 and liver therapy, 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.

Pharmacodynamic effects

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 x ULN but less 2 x 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 3). 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 3. 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 randomized (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 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 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 dosage throughout 12 months. For patients in the Obeticholic Acid titration arm whose Obeticholic Acid 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 Obeticholic Acid 10 mg arm, 138 (102, 174) U/L in the Obeticholic Acid 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 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 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 (Child-Pugh Class B and C, respectively) when compared to healthy controls. Therefore, a modified dose regimen for patients with moderate or severe hepatic impairment is required 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 cores

Pregelatinized Starch (Starch 1500)

Sodium Starch Glycolate (Primojel)

Magnesium Stearate

Colloidal Anhydrous Silica (Aerosil 200)

Sodium Lauryl Sulphate

Erythrosine Lake Color

Microcrystalline Cellulose (Avicel PH 102)

Coating Material

Opadry II Pink

Opadry II White

Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store in cool and dry place, away from light. Keep out of the reach of Children.

6.5 Nature and contents of container

Obetix 5: 30's HDPE Pot

6.6 Special precautions for disposal and other handling

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

7. Marketing authorization holder

Beacon Medicare Limited

9/B/2 Toyenbee Circulaar Road

Motijheel, Dhaka

Bangladesh -1223

8. Marketing authorization number(s)

Obetix 5: 341-338-075

9. Date of first authorization/renewal of the authorization

Obetix 5: 07-10-2018

10. Date of revision of the text

Obetix 5: 06-10-2023