Obetix 5

Obeticholic Acid

COMPOSITION

Obetix 5 Tablet: Each film coated tablet contains Obeticholic Acid INN 5 mg.

Therapeutic class: Gastrointestinal Agent.

CLINICAL PHARMACOLOGY

Mechanism of Action

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

PHARMACODYNAMICS

Dose Titration

In Clinical Trial 1, ALP reduction was observed to plateau at approximately 3 months in most patients treated with Obeticholic Acid 5 mg once daily. Increasing the dosage of Obeticholic Acid to 10 mg once daily based on tolerability and response provided additional reduction in ALP in the majority of patients.

Pharmacodynamic Markers

In Clinical Trial 1, administration of Obeticholic Acid 10 mg once daily was associated with a 173% increase in concentrations of FGF-19, an FXR-inducible enterokine involved in bile acid homeostasis, from baseline to month 12. Concentrations of cholic acid and chenodeoxycholic acid were reduced 2.7 micromolar and 1.4 micromolar, respectively, from baseline to month 12. The clinical relevance of these findings is unknown.

Cardiac Electrophysiology

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

Pharmacokinetics

Absorption

Following multiple oral doses of Obeticholic Acid 10 mg once daily, peak plasma concentrations (C_{max}) of Obeticholic Acid occurred at a median time (T_{max}) of approximately 1.5 hours. The median T_{max} for both the glyco- and tauro-conjugates of Obeticholic Acid was 10 hours. Co-administration with food did not alter the extent of absorption of Obeticholic Acid. Following multiple-dose administration of Obeticholic Acid 5, 10, and 25 mg once daily (2.5 times the highest recommend dosage) for 14 days, systemic exposures of Obeticholic Acid increased dose proportionally. Exposures to glyco-obeticholic acid and tauro-obeticholic acid, and total Obeticholic Acid (the sum of Obeticholic Acid and its two active conjugates) increased more than proportionally with dose.

Distribution

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

Elimination

Metabolism

Obeticholic Acid is conjugated with glycine or taurine in the liver and secreted into bile. These glycine and taurine conjugates of Obeticholic Acid are absorbed in the small intestine leading to enterohepatic recirculation. The conjugates can be deconjugated in the ileum and colon by intestinal microbiota, leading to the conversion to Obeticholic Acid that can be reabsorbed or excreted in feces, the principal route of elimination. After daily administration of Obeticholic Acid, there was accumulation of the glycine and taurine conjugates of Obeticholic Acid, which have *in vitro* pharmacological activities similar to the parent drug, Obeticholic Acid. The metabolite-to-parent ratios of the glycine and taurine conjugates of Obeticholic Acid were 13.8 and 12.3 respectively, after daily administration. An additional third Obeticholic Acid metabolite, 3-glucuronide, was formed but was considered to have minimal pharmacologic activity.

Excretion

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

Specific Populations

Age, Sex Race/Ethnicity:

Based on population pharmacokinetic analysis, the pharmacokinetics of Obeticholic Acid would not be expected to be altered based on age, sex, or race/ethnicity.

Renal Impairment:

Obeticholic Acid has not been studied in patients with moderate and severe renal impairment (estimated glomerular filtration rate [eGFR] less than 60 mL/min/1.73 m^2). In the population pharmacokinetic analysis, an eGFR greater than 50 mL/min/1.73 m^2 did not have a meaningful effect on the pharmacokinetics of Obeticholic Acid and its conjugated metabolites.

Hepatic Impairment:

Obeticholic Acid is metabolized in the liver. In subjects with mild, moderate and severe hepatic impairment (Child-Pugh Class A, B, and C, respectively), the mean AUC of total Obeticholic Acid increased by 1.1-, 4- and 17-fold, respectively, compared to subjects with normal hepatic function following single-dose administration of 10 mg Obeticholic Acid.

INDICATIONS

Obeticholic Acid is indicated for the treatment of primary biliary cholangitis (PBC) in combination with Ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA. This indication is approved under accelerated approval based on a reduction in alkaline phosphatase (ALP).

DOSAGE AND ADMINISTRATION

Dosage Regimen

Starting Dosage

The recommended starting dosage of Obeticholic Acid is 5 mg orally once daily in adult patients who have not achieved an adequate biochemical response to an appropriate dosage of UDCA for at least 1 year or are intolerant to UDCA.

Dosage Titration

If an adequate reduction in ALP and/or total bilirubin has not been achieved after 3 months of Obeticholic Acid 5 mg once daily, and the patient is tolerating Obeticholic Acid, increase the dosage of Obeticholic Acid to 10 mg once daily.

Maximum Dosage

The maximum recommended dosage of Obeticholic Acid is 10 mg once daily.

Management of Patients with Intolerable Pruritus on Obeticholic Acid

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

- Add an antihistamine or bile acid binding resin.
- Reduce 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 interrupt Obeticholic Acid dosing for up to 2 weeks followed by restarting at a reduced dosage.

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

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

Dosage Adjustment in Hepatic Impairment

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

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

Monitor patients during treatment with Obeticholic Acid for the occurrence of liver-related adverse reactions. Weigh the potential risks against the benefits of continuing treatment with Obeticholic Acid in patients who have experienced clinically significant liver-related adverse reactions.

Administration Instructions

- Take Obeticholic Acid with or without food.
- For patients taking a bile acid binding resin, take Obeticholic Acid at least 4 hours before or 4 hours after taking the bile acid binding resin, or at as great an interval as possible.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

The limited available human data on the use of Obeticholic Acid during pregnancy are not sufficient to inform a drug-associated risk. In animal reproduction studies, no developmental abnormalities or fetal harm was observed when pregnant rats or rabbits were administered Obeticholic Acid during the period of organogenesis at exposures approximately 13 times and 6 times human exposures, respectively, at the maximum recommended human dose (MRHD) of 10 mg. The estimated background risks of major birth defects and miscarriage for the indicated population are unknown.

Lactation

Risk Summary

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

Pediatric Use

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

Geriatric Use

Of the 201 patients in clinical trials of Obeticholic Acid who received the recommended dosage (5 mg or10 mg once daily), 41 (20%) were 65 years of age and older, while 9 (4%) were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and subjects less than 65 years of age, but greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment

Plasma exposure to Obeticholic Acid and its active conjugates, increases significantly in patients with moderate to severe hepatic impairment (Child-Pugh Classes B and C). Monitor patients during treatment with Obeticholic Acid for elevations in liver biochemical tests and for the development of liver-related adverse reactions. Dosage adjustment of Obeticholic Acid is recommended for patients with moderate and severe hepatic impairment. No dosage adjustment is needed in patients with mild hepatic impairment (Child-Pugh Class A).

CONTRAINDICATION

Obeticholic Acid is contraindicated in patients with complete biliary obstruction.

WARNINGS AND PRECAUTIONS

Liver-Related Adverse Reactions

In two 3-month, placebo-controlled clinical trials a dose-response relationship was observed for the occurrence of liver-related adverse reactions including jaundice, worsening ascites and primary biliary cholangitis flare with dosages of Obeticholic Acid of 10 mg once daily to 50 mg once daily (up to 5-times the highest recommended dosage,the exposure-adjusted incidence rates for all serious and otherwise clinically significant liver-related adverse reactions, and isolated elevations in liver biochemical tests, per 100 patient exposure years (PEY) were: 5.2 in the Obeticholic Acid 10 mg group (highest recommended dosage), 19.8 in the Obeticholic Acid 25 mg group (2.5 times the highest recommended dosage) and 54.5 in the Obeticholic Acid 50 mg group (5 times the highest recommended dosage) compared to 2.4 in the placebo group.

Monitor patients during treatment with Obeticholic Acid for elevations in liver biochemical tests and for the development of liver-related adverse reactions. Weigh the potential risks against the benefits of continuing treatment with Obeticholic Acid in patients who have experienced clinically significant liver-related adverse reactions. The maximum recommended dosage of Obeticholic Acid is 10 mg once daily. Adjust the dosage for patients with moderate or severe hepatic impairment.

Discontinue Obeticholic Acid in patients who develop complete biliary obstruction.

Severe Pruritus

Severe pruritus was reported in 23% of patients in the Obeticholic Acid 10 mg arm, 19% of patients in the Obeticholic Acid titration arm, and 7% of patients in the placebo arm in Clinical trial 1, a 12-month double-blind randomized controlled trial of 216 patients. Severe pruritus was defined as intense or widespread itching, interfering with activities of daily living, or causing severe sleep disturbance, or intolerable discomfort, and typically requiring medical interventions. In the subgroup of patients in the Obeticholic Acid titration arm who increased their dosage from 5 mg once daily to 10 mg once daily after 6 months of treatment (n=33), the incidence of severe pruritus was 0% from Months 0 to 6 and 15% from Months 6 to 12. The median time to onset of severe pruritus was 11, 158, and 75 days for patients in the Obeticholic Acid 10 mg, Obeticholic Acid titration, and placebo arms, respectively.

Management strategies include the addition of bile acid resins or antihistamines, Obeticholic Acid dosage reduction, and/or temporary interruption of Obeticholic Acid dosing.

Reduction in HDL-C

Patients with PBC generally exhibit hyperlipidemia characterized by a significant elevation in total cholesterol primarily due to increased levels of high density lipoprotein-cholesterol (HDL-C). In clinical trial 1, dose-dependent reductions from baseline in mean HDL-C levels were observed at 2 weeks in Obeticholic Acid -treated patients, 20% and 9% in the 10 mg and titration arms, respectively, compared to 2% in the placebo arm. At month 12, the reduction from baseline in mean HDL-C level was 19% in the Obeticholic Acid 10 mg arm, 12% in the Obeticholic Acid titration arm, and 2% in the placebo arm. Nine patients in the Obeticholic Acid 10 mg arm, 6 patients in the Obeticholic Acid titration arm, versus 3 patients in the placebo arm had reductions in HDL-C to less than 40 mg/dL.

Monitor patients for changes in serum lipid levels during treatment. For patients who do not respond to Obeticholic Acid after 1 year at the highest recommended dosage that can be tolerated (maximum of 10 mg once daily), and who experience a reduction in HDL-C, weigh the potential risks against the benefits of continuing treatment.

ADVERSE REACTIONS

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

- Liver-Related Adverse Reactions.
- Severe Pruritus.
- Reduction in HDL-C.

DRUG INTERACTIONS

Bile Acid Binding Resins

Bile acid binding resins such as Cholestyramine, Colestipol, or Colesevelam adsorb and reduce bile acid absorption and may reduce the absorption, systemic exposure, and efficacy of Obeticholic Acid. If taking a bile acid binding resin, take Obeticholic Acid at least 4 hours before or 4 hours after taking the bile acid binding resin, or at as great an interval as possible.

Warfarin

The International Normalized Ratio (INR) decreased following coadministration of Warfarin and Obeticholic Acid. Monitor INR and adjust the dosage of Warfarin, as needed, to maintain the target INR range when co-administering Obeticholic Acid and Warfarin.

CYP1A2 Substrates with Narrow Therapeutic Index

Obeticholic acid may increase the exposure to concomitant drugs that are CYP1A2 substrates. Therapeutic monitoring of CYP1A2 substrates with a narrow therapeutic index (e.g. Theophylline and Tizanidine) is recommended when co-administered with Obeticholic Acid.

PHARMACEUTICAL INFORMATION

Storage condition

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

Presentation and Packaging

Obetix 5 Tablet: Each commercial box contains 30 tablets in HDPE pot.

Only for Export

LF24301

Manufactured By
Beacon Pharmaceuticals Limited
Bhaluka, Mymensingh, Bangladesh

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