Obeliva

Obeticholic Acid

Everest

COMPOSITION

OBELIVA tablets: Each film coated tablet contains Obeticholic Acid INN 5 mg.

INDICATIONS AND USAGE

Obeticholic Acid is indicated for the treatment of primary biliary cholangitis (also known as primary biliary cirrhosis) in combination with ursodeoxycholic acid in adults with an inadequate response to ursodeoxycholic acid or as monotherapy in adults unable to tolerate ursodeoxycholic acid.

DOSAGE AND ADMINISTRATION

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

Staging/ Classification	Non-Cirrhotic or Child-Pugh Class A	Child-Pugh Class B or C or Decompensated Cirrhotic[a]
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 3 months of treatment and the patient is tolerating obeticholic acid, titrate up to 10 mg once daily.[b]	5 mg twice weekly (at least 3 days apart) Titrate 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)

[a]Gastroesophageal variceal bleeding, new or worsening jaundice, spontaneous bacterial peritonitis, etc.

[b]Prior to dosage adjustment, re-calculate the Child-Pugh classification.

CONTRAINDICATION

Hypersensitivity to the active substance complete biliary obstruction.

WARNINGS AND PRECAUTIONS

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. 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. 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)

SIDE EFFECTS

The most commonly reported adverse reactions were pruritus and fatigue. 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.

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).

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) [Prothrombin time] 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.

USE IN SPECIFIC POPULATION
Pregnancy
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.

Lactation
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.

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

Geriatric Use
No overall differences in safety or effectiveness were observed between these patients and patients less than 65 years of age, but greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment
Hepatic decompensation and failure, in some cases fatal, have been reported postmarketing in PBC patients with decompensated cirrhosis or Child-Pugh B or C hepatic impairment when Obeticholic Acid was dosed more frequently than recommended. In PBC clinical trials, a dose-response relationship was observed for the occurrence of liver-related adverse reactions with Obeticholic Acid.

OVERDOSAGE
The highest single dose exposure of obeticholic acid in healthy volunteers has been at the 500 mg dose. In the case of overdose, patients should be carefully observed and supportive care administered, as appropriate.

PHARMACEUTICAL INFORMATION
How Supplied
OBELIVA tablet: Each HDPE container of **OBELIVA** contains 30 film-coated tablets (each tablet contains Obeticholic Acid INN 5 mg.), a silica gel desiccant and polyester coil with a child-resistant closure.

Storage
Store below 30°C, in a cool and dry place. Keep away from light. Keep out of the reach of children.

Manufactured by
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