Obeticholic Acid: First Global Approval

A. Markham¹ · Susan J. Keam¹

Abstract Obeticholic acid (Ocaliva™) is a farnesoid-X receptor (FXR) agonist that is being developed by Intercept Pharmaceuticals for the treatment of various liver diseases, and has recently been granted accelerated approval in the USA for the treatment of primary biliary cholangitis in combination with ursodeoxycholic acid in adults with an inadequate response to ursodeoxycholic acid, or as monotherapy in adults unable to tolerate ursodeoxycholic acid. The drug is in preregistration for this indication in the EU. This article summarizes the milestones in the development of obeticholic acid leading to this first approval for primary biliary cholangitis.

1 Introduction

Obeticholic acid (Ocaliva™) is an orally bioavailable farnesoid-X receptor (FXR) agonist [1]. It is semisynthetic derivative of the primary human bile acid chenodeoxycholic acid, a natural FXR agonist [2]. The drug has been developed by Intercept Pharmaceuticals for the treatment of various liver diseases, including biliary atresia, primary biliary cholangitis, non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, and primary sclerosing cholangitis [3, 4]. FXR is a nuclear receptor expressed in the liver and intestine that is a key regulator of bile acid, inflammatory, fibrotic and metabolic pathways. Activation of FXR suppresses de novo synthesis of bile acids from cholesterol and increases the transport of bile acids out of hepatocytes, thus reducing hepatic exposure to bile acids [1, 5]. FXR activation also promotes insulin sensitivity, decreases circulating triglycerides and reduces hepatic gluconeogenesis and glycogenolysis [2, 6].

Obeticholic acid was granted accelerated approval in the USA in May 2016 for the treatment of primary biliary cholangitis in combination with ursodeoxycholic acid in adults with an inadequate response to ursodeoxycholic acid, or as monotherapy in adults unable to tolerate ursodeoxycholic acid [1, 5], and is awaiting approval in the EU for the same indication [4]. Approval in the USA was based on improvements in alkaline phosphatase (ALP) levels (as a surrogate marker of clinical benefit) seen in a phase III trial in patients with primary biliary cholangitis [5]. The recommended starting dosage of oral obeticholic acid is 5 mg once daily. If adequate reduction in ALP and/or total bilirubin has not been achieved after 3 months’ treatment, and the patient is tolerating the drug, the dosage may be increased to 10 mg once daily [1].

Orphan drug designation for obeticholic acid in primary biliary cholangitis has been granted in the USA and EU; fast track designation in primary biliary cholangitis was granted in the USA in May 2014. In December 2014, a rolling NDA submission for accelerated approval of obeticholic acid in primary biliary cholangitis was initiated and the phase IIIb COBALT confirmatory clinical outcomes trial in patients with advanced disease commenced, in accordance with FDA accelerated approval regulations. Phase II and III trials of obeticholic acid in non-alcoholic steatohepatitis and phase II trials of the drug in alcoholic

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¹ Springer, Private Bag 65901, Mairangi Bay, 0754 Auckland, New Zealand

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hepatitis, primary sclerosing cholangitis, and biliary atresia are underway in several countries.

1.1 Company Agreements

Intercept Pharmaceuticals has granted Dainippon Sumitomo Pharma an exclusive licence to obeticholic acid in Japan, China and Korea for the treatment of chronic liver diseases. Dainippon will focus initially on primary biliary cholangitis and non-alcoholic steatohepatitis. Intercept will receive from Dainippon an initial payment of $US15 million and is eligible to receive approximately $US300 million milestone payment, plus a double-digit royalty on sales. Dainippon has an option to licence in other Asian countries, including Taiwan, and for additional indications. Dainippon is responsible for the costs of developing and commercialising the drug in its territory [3].

1.2 Patent Information

Intercept Pharmaceuticals owns six US patents, four pending US patent applications and corresponding foreign patents and patent applications. Foreign patents covering obeticholic acid are granted in the EU, Switzerland, Liechtenstein, Australia, Canada, China, Israel, Japan and Macao. The composition of matter patent is expected to expire in 2022.

Intercept Pharmaceuticals has patent exclusivity for obeticholic acid, which is expected to expire through 2028. The additional pending composition of matter patent is expected to expire in 2033.

2 Scientific Summary

2.1 Pharmacodynamics

Obeticholic acid is a potent and selective agonist of FXR (EC$_{50}$ 99 nmol/L). It is highly lipophilic, but has no intrinsic cholestatic activity [7]. In rat models of cholestasis [7] and liver fibrosis [8, 9], obeticholic acid demonstrated anticholeretic activity (preventing impairment of bile flow) [7] and reversed fibrosis and cirrhosis and decreased portal hypertension [8, 9].

2.2 Pharmacokinetics

Multiple once daily oral 10 mg doses of obeticholic acid produced maximum plasma concentrations ($C_{max}$) after
The median $t_{\text{max}}$ for two active metabolites, glyco- and tauro-obeticholic acid, was 10 h. Absorption of obeticholic acid was not affected by concomitant administration with food [1]. Systemic exposure to the drug increased in a dose proportional manner after administration of obeticholic acid 5, 10 and 25 mg once daily (2.5 times the highest recommended dosage) for 14 days. Exposure to the glyco- and tauro-obeticholic acid metabolites and total obeticholic acid (obeticholic acid plus the two active metabolites), however, increased more than dose proportionally; after daily administration of obeticholic acid the metabolite-to-parent ratios of glycine- and taurine-obeticholic acid were 13.8 and 12.3, respectively. Human plasma protein binding of obeticholic acid and its conjugates is $\geq 99\%$ and the volume of distribution is 618 L [1]. Obeticholic acid is conjugated with glycine or taurine in the liver to form glyco- and tauro-obeticholic acid, which are secreted into bile. These metabolites may be absorbed in the small intestine, leading to enterohepatic recirculation. Furthermore, microorganisms in the ileum and colon can deconjugate glyco- and tauro-obeticholic acid, converting them into the parent drug, which may then be reabsorbed or excreted in faeces. The latter is the primary route of elimination, accounting for $\approx 87\%$ of a radiolabelled dose of the drug [1].

The pharmacokinetic properties of obeticholic acid are not expected to be altered according to age, gender, ethnicity or renal function based on population pharmacokinetic analyses [1]. Hepatic impairment increases plasma exposure to obeticholic acid and its active metabolites, and dosage adjustment is recommended in patients with moderate to severe (Child–Pugh Classes B and C), but not mild (Child–Pugh Class A), hepatic impairment [1].

### 2.3 Drug Interactions

Obeticholic acid absorption, systemic exposure and efficacy may be reduced by the coadministration of bile acid binding resins (e.g. cholestyramine, colestipol, or colesevelam), which reduce bile acid absorption. On this basis it is recommended that obeticholic acid is taken $\geq 4$ h before or $4$ h after a bile acid binding resin, or at as great an interval as possible [1].

Concomitant administration of obeticholic acid and warfarin decreases the International Normalised Ratio (INR); monitoring of the INR, and warfarin dosage adjustment to maintain the target INR range, is required when these drugs are coadministered. Obeticholic acid may increase exposure to drugs that are CYP1A2 substrates when coadministered; therapeutic monitoring of CYP1A2 substrates that have a narrow therapeutic index (e.g.
theophylline and tizanidine) is recommended during concomitant treatment [1].

2.4 Therapeutic Trials

2.4.1 Primary Biliary Cholangitis

2.4.1.1 Phase III Treatment with obeticholic acid produced a durable improvement in hepatic biochemistry in patients with primary biliary cholangitis who had not responded adequately to, or were not able to tolerate, ursodeoxycholic acid, in the phase III POISE trial (NCT01473524). 217 patients were initially randomised to 12 months’ treatment with once daily obeticholic acid 5–10 mg (dose titrated after 6 months based on response), obeticholic acid 10 mg once daily or placebo. The primary efficacy endpoint was achieving the Global Primary Biliary Cirrhosis Study Group (GPBCSG) ALP/bilirubin goal of ALP levels \(\leq \frac{1.67 \times ULN}{10}\) and normal bilirubin levels and an ALP reduction of \(\geq 15\%\) at 12 months [10]. At the end of this phase of the study, significantly more patients in the obeticholic acid titration and obeticholic acid 10 mg/day groups than placebo recipients (46 and 47 vs 10 %; both \(p < 0.0001\)) reduced from baseline versus placebo in the obeticholic acid titration and obeticholic acid 10 mg/day groups, as were bilirubin levels (\(p < 0.005\)) [10]. Following the double-blind phase, 193 patients entered a long term extension part of the trial; all received obeticholic acid at an initial dose of 5 mg/day with the option to increase this to 10 mg/day after 3 months based on response and tolerability. After an additional 18 months of treatment, improvements in ALP, GGT, ALT and AST levels seen in the obeticholic titration and obeticholic acid 10 mg/day groups at the end of the 12-month double-blind phase were maintained and mean bilirubin levels did not increase [11].

2.4.1.2 Phase II Treatment with obeticholic acid in combination with ursodeoxycholic acid significantly reduced ALP, GGT, ALT and AST levels seen in the obeticholic titration and obeticholic acid 10 mg/day groups at the end of the 12-month double-blind phase were maintained and mean bilirubin levels did not increase [11].

### Key clinical trials of obeticholic acid

<table>
<thead>
<tr>
<th>Drugs(s)</th>
<th>Sponsor/initiator</th>
<th>Indication</th>
<th>Phase</th>
<th>Status</th>
<th>Location(s)</th>
<th>Identifier</th>
</tr>
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<tbody>
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<td>Nonalcoholic steatohepatitis</td>
<td>II</td>
<td>Completed</td>
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<td>Lipodystrophy</td>
<td>II</td>
<td>Planned (not yet recruiting)</td>
<td>US</td>
<td>NCT02430077</td>
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<td>Nonalcoholic steatohepatitis</td>
<td>III</td>
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<td>Multinational</td>
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<td>NCT01625026</td>
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<td>US</td>
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<td>Recruiting</td>
<td>Multinational</td>
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<td>Intercept</td>
<td>Effects on lipoprotein metabolism</td>
<td>II</td>
<td>Ongoing</td>
<td>US</td>
<td>NCT01865812</td>
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<td>Multinational</td>
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In a double-blind, placebo-controlled phase II study (NCT00570765 [201]) in patients with primary biliary cholangitis, 12 weeks’ treatment with obeticholic acid 10 or 50 mg/day as monotherapy reduced ALP levels by 39–45%. In the 28 patients who completed the double-blind phase and were enrolled in an open-label long-term extension trial, obeticholic acid was given either at the dosage received during the double-blind phase, or at a dose of 10 mg/day with the option to titrate up to a maximum dose of 50 mg/day; treatment with ursodeoxycholic acid could also be added. After 4.5 years’ follow up, mean ALP levels were reduced by 244 U/L (p = 0.003 vs baseline) in all 19 patients who remained enrolled, and by 182 U/L in 11 patients who continued to receive obeticholic acid without concomitant ursodeoxycholic acid (p = 0.01 vs baseline). GGT levels were reduced by 317 U/L (p = 0.002 vs baseline) and 235 U/L (p = 0.02 vs baseline) respectively, ALT by 37 U/L (p = 0.001 vs baseline) and 32 U/L (p = 0.005) respectively, and AST by 22 U/L (p = 0.005 vs baseline) and 17 U/L (p = 0.02 vs baseline), respectively [13].

2.4.2 Non-Alcoholic Steatohepatitis

Treatment with obeticholic acid 25 mg once daily improved the histological features of non-alcoholic steatohepatitis compared to placebo in the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-sponsored phase II FLINT trial [6]. After 72 weeks’ treatment, 50 of 110 (45 %) obeticholic acid recipients had improved centrally-scored liver histology (≥2-point decrease in non-alcoholic fatty liver disease activity score, without worsening of fibrosis) compared with 23 of 109 (21 %) recipients in the placebo group (p = 0.0002). Resolution of definite non-alcoholic steatohepatitis was observed in 22 of 102 (22 %) obeticholic acid and 13 of 98 (13 %) placebo recipients who had biopsy specimens taken at baseline and 72 weeks [6].

2.4.2.1 In Patients with Type 2 Diabetes

Six weeks’ treatment with obeticholic acid increased insulin sensitivity and reduced markers of liver inflammation and fibrosis in patients with type 2 diabetes and nonalcoholic fatty liver disease in a placebo-controlled phase II trial (NCT00501592) [2]. All patients underwent a two-step (low and high dose) hyperinsulinaemic-euglycaemic clamp procedure before the first and after the last dose of obeticholic acid or placebo. With low dose insulin, the glucose infusion rate (insulin sensitivity) increased by 28 % (p = 0.19) and 20.1 % (p = 0.06) with obeticholic acid 25 or 50 mg once daily, respectively, compared with a 5.5 % reduction in placebo recipients. With high dose insulin, insulin sensitivity increased by 18.3 % (p = 0.036) and 10.8 % (p = 0.076) after treatment with obeticholic acid 25 or 50 mg once daily, respectively, compared with a 5.4 % decrease in placebo recipients [2].

2.4.3 Chronic Bile Acid Diarrhoea

In the investigator-initiated phase II OBADIAH1 trial (NCT01585025) treatment with obeticholic acid increased levels of FGF19 and reduced bile acid synthesis in patients with primary bile acid diarrhoea (n = 10). Median stool frequency, stool form and diarrhoea index were reduced by 24, 14 and 34 %, respectively (p ≤ 0.05 for each), after 2 weeks treatment with obeticholic acid 25 mg/day. Bile acids reduced from 1.5 to 0.9 µmol/L (p = 0.13; fasting) and 34.5 to 20.9 µmol/L (p = 0.02; 6 h response AUC). Bile acids (6 hour response AUC) decreased from 32 to 22 µmol/L (p = 0.04) in a second group of patients with secondary bile acid diarrhoea (n = 10), however, fasting FGF19 and C4 levels were not significantly improved [14].

2.5 Adverse Events

The most common adverse events in patients with primary biliary cholangitis treated with obeticholic acid in the phase III POISE trial were pruritus (70, 56 and 38 % in obeticholic acid 10 mg/day [n = 73], obeticholic acid titrated [n = 70] and placebo [n = 73] recipients, respectively), fatigue (25, 19 and 15 %) and abdominal pain and discomfort (10, 19 and 14 %). Other adverse events included rash (10, 7 and 8 %), arthralgia (10, 6 and 4 %), oropharyngeal pain (8, 7 and 1 %), dizziness (7, 7 and 5 %), constipation (7, 7 and 5 %), peripheral oedema (7, 3 and 3 %), palpitations (7, 3 and 1 %), pyrexia (7, 0 and 1 %), thyroid function abnormality (4, 6 and 3 %) and eczema (3, 6 and 0 %) [1].

Severe pruritus—defined as intense or widespread itching, interfering with activities of daily living, or causing severe sleep disturbance, or intolerable discomfort, and typically requiring medical intervention—occurred in 23, 19 and 7 % of obeticholic acid 10 mg/day, obeticholic acid titrated and placebo recipients, respectively [1]. Serious or otherwise clinically significant liver-related adverse events included ascites in one patient in the obeticholic acid 10 mg/day group, two episodes of ascites and four episodes of hepatic encephalopathy in one patient in the obeticholic acid titrated group and variceal bleeding in one patient in the placebo group [1].

2.6 Ongoing Clinical Trials

Phase III studies are underway to further investigate the safety and efficacy of obeticholic acid in patients with primary biliary cirrhosis (COBALT [NCT02308111]) and
non-alcoholic steatohepatitis (REGENERATE [NCT02548351]) [15].

Phase II studies are under way to investigate the effects of combined obeticholic acid and atorvastatin in patients with nonalcoholic steatohepatitis (CONTROL [NCT02633956]), the efficacy and safety of obeticholic acid in patients with primary sclerosing cholangitis (AESOP, [NCT02177136]) and the effects of obeticholic acid in paediatric patients with biliary atresia (EudraCT number 2014-004693-42).

3 Current Status

Obeticholic acid received its first global approval on the 27th of May 2016 in the USA for primary biliary cholangitis.

Compliance with ethical standards

Conflict of interest The preparation of this review was not supported by any external funding. During the peer review process the manufacturer of the agent under review was offered an opportunity to comment on the article. Changes resulting from any comments received were made by the authors on the basis of scientific completeness and accuracy. A. Markham is a contracted employee of Adis, Springer SBM. Susan J. Keam is a salaried employee of Adis, Springer SBM.

References