



**Cost-effectiveness of obeticholic acid (Ocaliva®) for the treatment of primary biliary cholangitis in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA**

The NCPE has issued a recommendation regarding the cost-effectiveness of obeticholic acid (Ocaliva®). Following NCPE assessment of the applicant's submission, obeticholic acid (Ocaliva®) is not considered cost-effective 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 and therefore is not recommended for reimbursement at the submitted price.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Intercept Pharma) economic dossier on the cost effectiveness of obeticholic acid (Ocaliva®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

**About the National Centre for Pharmacoeconomics**

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

## Summary

In June 2017, Intercept Pharma submitted a pharmacoeconomic assessment to the National Centre for Pharmacoeconomics (NCPE) to support the use of obeticholic acid (OCA) 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. Primary biliary cholangitis (PBC) is a rare, progressive, debilitating autoimmune non-viral liver disease that leads to complications, such as fibrosis, cirrhosis, liver transplantation and death. PBC affects mostly women with most cases being diagnosed in those aged between 40 and 60 years. There are no data on the prevalence of PBC in Ireland, however the estimated prevalence in the UK is approximately 3.9 per 10,000. The incidence of PBC in the UK is 0.58 per 10,000 population.

Current clinical practice for PBC relies on one approved therapy – ursodeoxycholic acid (UDCA). However, up to 40% of patients treat with UDA do no respond and there are also a small number of patients who are unable to tolerate UDCA. Obeticholic acid (OCA) is a farnesoid X receptor agonist. Farnesoid receptors are a novel pharmacological target and stimulation of these receptors appears to have multiple effects; in PBC the most notable is the reduction in hepatocellular concentration of bile acids. The recommended starting dose of OCA is 5mg by mouth daily, however patients may up titrate to 10 mg daily after 6 months if an adequate reduction in serum alkaline phosphatase (ALP) or total bilirubin has not been achieved.

### **1. Comparative effectiveness of obeticholic acid**

Data from the POISE trial was used as clinical evidence to support the economic evaluation. The POISE trial was a multicentre international trial with 217 participants comparing OCA in combination with UDCA compared to UDCA alone in patients with an inadequate response to UDCA and comparing OCA to no treatment in patients intolerant to UDCA. The trial was conducted over 12 months covering an extensive range of surrogate outcomes. The primary outcome was a composite outcome that reflected the proportion of patients reaching targets for both ALP and bilirubin after 12 months of therapy.

Results from the POISE trial showed that a larger proportion of OCA treat patients achieved the composite outcome of ALP less than 1.67 times the upper limit of normal (ULN) and total bilirubin at ULN or lower, and decrease in ALP of 15% or more from baseline at 12

months compared with placebo (46% vs 10% of participants), and this difference was statistically significant (odds ratio 9.1; 95% CI, 3.6 to 23.3:  $p < 0.0001$ ). There was one death in the study, in a patient receiving OCA titration. There were no events for other clinical outcomes; morbidity, cirrhosis and transplant. The lack of clinical outcomes and subsequent reliance on surrogate markers is a limitation of the efficacy results in POISE. However, the key surrogates used; ALP and bilirubin, appear to be accepted surrogate biomarkers in PBC and any elevation above the ULN is considered likely to be clinically relevant.

## **2. Safety of obeticholic acid**

From the clinical trial programme a total of 1507 subjects have been exposed to at least a single dose of OCA. The majority of subjects in the overall population had OCA exposure <3 months, consistent with the extensive Phase 1 program. The mean (SD) number of days on OCA was 141.1 (279.60), the mean exposure was 0.42 (0.797) years, and the mean daily OCA dose received was 22.7 mg (range of mean daily dose 10.8 mg to 28.0 mg). The mean daily OCA dose was predominantly driven by the higher doses evaluated in the Phase 2 programs (up to 50 mg).

Of the 217 randomised patients, 216 received at least one dose of the study treatments and 198 of them completed the 12-month DB period (70, 64 and 64 patients in the placebo, OCA titration and OCA 10 mg groups, respectively). The main reason for discontinuation was AE ( $n=15$ ), followed by consent withdrawal ( $n=4$ ).

Over 90% of patients on any of the treatment groups experienced at least one treatment emergent AE (TEAE), with over half of the TEAEs considered as treatment-related (52% in placebo, 60% in OCA titration group and 74% in the OCA 10 mg).

The most frequent TEAE across all treatment groups was pruritus. Over half of the patients on any of the treatment groups reported on-going pruritus at baseline (64%, 53% and 60% in the placebo, OCA titration and OCA 10 mg groups, respectively). TEAEs of pruritus, defined as new onset or increasing intensity pruritus, were more frequently reported in OCA-treated patients than in placebo-treated patients (38%, 56% and 70%, in the placebo, OCA titration and OCA 10 mg groups, respectively). Most of them required an intervention for pruritus (50%, 62% and 59% in the placebo, OCA titration and OCA 10mg groups, respectively).

Pruritus was the main reason for discontinuation in a total of 8 patients, 1 in the OCA titration group and 7 in the OCA 10 mg. Discontinuations due to pruritus occurred in approximately 10% of patients. The SmPC lists pruritus as a very common adverse reaction and provides guidance on dose adjustment / treatment discontinuation for the management of pruritus. Overall, the incidence of treatment discontinuation was low, suggesting that OCA treatment is reasonably tolerated.

FDA Warning: On 21<sup>st</sup> September 2017 the FDA warned that OCA is being incorrectly dosed in some patients with moderate to severe decreases in liver function, resulting in an increased risk of serious liver injury and death. These patients are receiving excessive dosing, particularly a higher frequency of dosing than is recommended in the drug label for them. They are working with the manufacturer to address these safety concerns.

### **3. Cost effectiveness of obeticholic acid**

#### *Methods*

A cost utility analysis was conducted to assess the cost effectiveness of OCA in combination with UDCA compared to UDCA alone in UDCA inadequate responders and of OCA monotherapy compared to no treatment in UDCA intolerant patients. The treatment considered in the intervention group was OCA dose titration (5mg for the first six months of treatment, followed by 10 mg for the subsequent months). The comparator considered in the UDCA inadequate responder group was oral UDCA at 13mg/kg/day to 15mg/kg/day. In the UDCA intolerant patient group the comparator considered was placebo (no treatment). The outcome considered was the QALY. The base case analysis was conducted from the Irish healthcare payer's perspective over a lifetime horizon (i.e. 50 years). The applicant developed a Markov model which consisted of 10 health states with transitions taking place every three months, capturing patient progression over time. The model captured the two components of the natural history of the disease: the PBC-specific liver disease component, representing the progression of PBC based on ALP and bilirubin biomarkers (three health states), and the liver disease clinical outcome component (seven health states), which is entered once patients progress to decompensated cirrhosis or hepatocellular carcinoma. For the OCA groups and UDCA group, results from the pivotal phase III POISE study were used to inform health state

transitions for each three-month cycle for the first year. After year 1, PBC-specific health state transitions were calculated based on data from the Global and UK PBC study cohorts. Utility data specific to cholangitis patients were used for PBC-specific health states, and Irish data were used for liver disease clinical outcome states. Resource use and costs were collected from the published literature and expert opinion.

### *Results*

Using the NCPE's preferred set of model assumptions, OCA dose titration therapy was associated with incremental costs of €454,067 and incremental QALYs of 3.096 compared with placebo, resulting in a deterministic ICER of €146,659/QALY for the UDCA inadequate responder population. In the UDCA intolerant population, OCA dose titration therapy was associated with incremental costs of €425,275 and incremental QALYs of 3.9 compared with placebo, resulting in an ICER of €108,094 /QALY.

### *Sensitivity analysis*

Using the RG's preferred set of model assumptions (in the inadequate responder population) OCA dose titration therapy was associated with incremental costs of €450,0874 and incremental QALYs of 3.01 compared with placebo, resulting in a probabilistic ICER of €149,540/QALY (in the inadequate responder population). The probability of cost effectiveness for both the UDCA inadequate responders and the UDCA intolerant population was 0% at €45,000/QALY.

## **4. Budget impact of obeticholic acid**

The list price of obeticholic acid (5mg and 10mg) is €2,981. The cost per patient per year is calculated as €38,021.12. The estimated numbers of eligible patients that could be treated per year could range between 22 and 141. Based on these numbers and including a half yearly cost for those who discontinue, the estimated gross budget impact ranges from €1m in year 1 to €6.6m in year 5. The applicant estimates the cumulative 5 year gross budget impact to be approximately €21.5million.

## **5. Patient submissions**

No patient submissions were received during the course of this appraisal.

## **6. Conclusion**

Following NCPE assessment of the company submission, which is based on the current level of evidence available, obeticholic acid (Ocaliva®) is not considered cost-effective for the treatment of primary biliary cirrhosis (PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA and therefore is not recommended for reimbursement at the submitted price. RG would advise that this product be reassessed when it receives its licence in full, i.e. when data on clinical outcomes become available.