NOTIFICATION TO THE CHMP/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 20 OF REGULATION (EC) 726/2004

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This notification is a referral under Article 20 of Regulation (EC) 726/2004 to the Committee for Human Medicinal Products (CHMP) made by the European Commission (EC):

Product(s) Name(s)	Ocaliva
Active substance(s)	Obeticholic acid
Pharmaceutical form(s)	All
Strength(s)	All
Route(s) of Administration	All
Marketing Authorisation Holder(s)	Advanz Pharma Limited

Background

Ocaliva is a film-coated tablet containing obeticholic acid. Obeticholic acid (OCA) 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.

Ocaliva is a centrally authorised product 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 product was granted a conditional marketing authorisation (CMA) in 2016 mainly based on results from a pivotal phase III, randomised, double-blind, placebo-controlled, parallel-group study (747-301, also POISE), showing superiority to placebo on the primary endpoints (percentage of patients reaching alkaline phosphatase and bilirubin levels below predefined cut-off values).

At the time of the initial marketing authorisation (MA), uncertainty remained as to the extent to which the observed changes in those laboratory parameters correlated with clinical liver outcomes. In order to alleviate this uncertainty, the marketing authorisation holder (MAH) was requested to conduct and submit the results of study 747-302 (also COBALT), a confirmatory double-blind, randomised, placebo-controlled multicentre study investigating the clinical benefit associated with Ocaliva treatment in patients with PBC who are either unresponsive or intolerant to UDCA treatment based on clinical endpoints. In addition, in order to investigate the uncertainties related to the lack of data in a population with more advances liver disease, the MAH was requested to conduct and submit the results of study 747-401, a double-blind, randomised, placebo-controlled study evaluating the efficacy, safety and pharmacokinetics of Ocaliva in patients with PBC and moderate to severe hepatic impairment.

In the post-authorisation phase the MAH reported enrolment and retention difficulties for study 747-302, and a transition to an open label design versus historic control was proposed, or a revision of the composite primary endpoint. Neither proposal was deemed acceptable at the time to the CHMP.

In 2020, based on a review of a protocol-specified interim analysis of the primary efficacy endpoint of study 747-302, and of *ad hoc* safety and pharmacokinetic data from studies 747-302 and 747-401, the independent data monitoring committee (IDMC) concluded that "*Study 747-302 (COBALT) is unlikely to provide evidence of efficacy for the enrolled PBC population as an aggregate or in any subpopulation*". The IDMC also recommended that there be no further enrolment in either study (747-302 and 747-401), based on feasibility concerns. The MAH considered that it would be no longer feasible to establish the safety and efficacy of Ocaliva in PBC patients with decompensated cirrhosis or a prior decompensation event, from studies 747-302 and 747-401 (the later having been imposed to this aim). Therefore, taking also into account post-marketing data suggesting an association between hepatic events and this treatment in patients with decompensated cirrhosis or a prior decompensation event, a variation was submitted to contraindicate Ocaliva in those patients (EMEA/H/C/004093/II/0030), and study 747-401 was prematurely terminated. Study 747-302 was also prematurely terminated.

Issues to be considered

In December 2022, the MAH submitted the final results from studies 747-302 and 747-401 in a type II variation requesting the switch of the type of marketing authorisation from CMA to a full MA (EMEA/H/C/004093/II/0038). Final results from the long-term safety extension of study 747-301 together with results of three real-world evidence studies were also included in this variation application as supportive information.

With 67% of the planned events, study 747-302 failed to show a difference between treatment arms (Ocaliva vs. placebo) for the primary composite endpoint of death, liver transplant, or hepatic decompensation for the intention-to-treat (ITT) population: hazard ratio (HR) 1.01 (95% confidence interval (CI) 0.68, 1.51), p value 0.954. Likewise, in the subgroup of compensated PBC patients (79% of participants) the results were the following: 21.3% OCA vs 21.7% placebo, HR 0.98 (0.58, 1.64). For decompensated patients (at present excluded from the authorised indication) a numerical imbalance in favour of placebo was observed:59.4% OCA vs 54.1% in placebo, HR 1.22 (0.65, 2.28).

In addition, compared to placebo, OCA treated patients showed a higher incidence of treatment-emergent adverse events (TEAEs), severe TEAEs, TEAEs leading to discontinuation, and TEAEs leading to death, both in the general safety population and the subset of patients with compensated liver disease.

In October 2023, the CHMP considered that study 747-302 had failed to demonstrate the clinical benefit of Ocaliva across the spectrum of PBC patients and considered the request to switch to a full MA not acceptable. In this context, the CHMP further considered that the proposed risk minimisation measures, including the restriction of indication to patient with less severe disease, proposed by the MAH, were insufficient at this stage. These results showing a potential lack of efficacy and worsen safety profile raise serious concerns as to whether the benefit of Ocaliva still outweighs its risks in its authorised indication.

In light of these new data, there is a need to review the findings in the context of all available data and assess their potential impact on the benefit-risk of Ocaliva in its approved indication.

In view of the above, the EC initiates a procedure under Article 20 of Regulation (EC) No 726/2004 and requests the Agency/CHMP to assess the above concerns and their impact on the benefit risk balance for the centrally authorised medicinal product Ocaliva (obeticholic

acid). The EC requests the Agency/CHMP to give its opinion by June 2024 on whether the marketing authorisation for this product should be maintained, varied, suspended or revoked.

In addition, the EC requests the Agency/CHMP to give its opinion, as soon as possible, as to whether temporary measures are necessary to ensure the safe and effective use of this medicinal product taking into account amongst other elements the findings from the type II variation procedure.

Signed Date
Olga Solomon
Head of Unit - Medicines: policy, authorisation and monitoring
Health and Food Safety Directorate General