SUMMARY OF RISK MANAGEMENT PLAN

OCALIVA®

obeticholic acid (OCA)

Version 2.1

Date: 22-September-2023

Advanz Pharma Specialty Medicine Switzerland GmbH

Disclaimer:

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of OCALIVA is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le médicament” approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of OCALIVA in Switzerland is the “Arzneimittelinformation / Information sur le médicament” (see www.swissmedic.ch) approved and authorized by Swissmedic. Advanz Pharma Specialty Medicine Switzerland GmbH is fully responsible for the accuracy and correctness of the content of the published summary RMP of OCALIVA.

Part VI: Summary of the risk management plan

Summary of risk management plan for OCALIVA (obeticholic acid)

This is a summary of the risk management plan (RMP) for OCALIVA. The RMP details important risks of OCALIVA, how these risks can be minimised, and how more information will be obtained about OCALIVA's risks and uncertainties (missing information).

OCALIVA's summaries of product characteristics (SmPC) and package leaflets give essential information to healthcare professionals and patients on how OCALIVA should be used.

This summary of the RMP for OCALIVA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Reports (EPARs).

Important new concerns or changes to the current ones will be included in updates of OCALIVA's RMP.

I. The medicine and what it is used for

OCALIVA is authorised for the treatment of primary biliary cholangitis (also known as PBC) in combination with ursodeoxycholic acid (UDCA) in adults with an inadequate response to UDCA or as monotherapy in adults unable to tolerate UDCA (see OCALIVA SmPC for the full indication). It contains OCA as the active substance and it is given by mouth.

Further information about the evaluation of OCALIVA's benefits can be found in OCALIVA's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines/human/EPAR/ocaliva.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of OCALIVA, together with measures to minimise such risks and the proposed studies for learning more about OCALIVA's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

If important information that may affect the safe use of OCALIVA is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of OCALIVA are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of OCALIVA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Liver injury
Important potential risks	Atherosclerotic cardiovascular events secondary to changes in lipids
Missing information	Use in patients with other concomitant liver diseases Use in patients with HCC Use post liver transplantation Long-term safety

II.B Summary of important risks

Important identified risk: Liver injury	
Evidence for linking the risk to the medicine	**Non-clinical studies**: Hepatobiliary toxicity in animal models included mild transient elevations in liver enzymes and/or bilirubin as well as a mild increase in liver weight. **Clinical trials**: Cases of hepatic events were observed in clinical trials. From study 747-302 it was observed that of the 168 patients in the Ocaliva group, 2 patients (1.2%) developed drug-induced liver injury, 5 patients (3.0%) developed jaundice, 2 patients (1.2%) devolped hepatic failure From study 747-401 it was observed that of the 10 patients in the Ocaliva group, 1 patient (10%) developed Hepatic failure and 1 patient (10%) developed Blood bilirubin increased which was deemed to have 'definite', 'probable', or 'possible' relationship to Ocaliva treatment. During the period (27 May 2021 - 26 May 2022), a total of 40 reports with liver related AEs were identified from clinical trials. Six initial reports were received from clinical studies in patients with PBC and 15 initial reports were received in patients in ongoing NASH studies. In the six cases from patients with PBC, the events of hepatocellular carcinoma, hepatic failure (n=2 each), oesophageal varices haemorrhage and hepatic cirrhosis (n=1 each) were reported. In 15 initial cases from patients with NASH, the events of hepatic failure, hepatic encephalopathy (n=6 each), hepatocellular carcinoma (n=5), hyperbilirubinaemia, hepatic lesion, hepatic cirrhosis, ascites, blood bilirubin increased (n=2 each), and hepatectomy (n=1) were reported. **Post-marketing experience**: Cases of hepatic events were observed post-marketing During the period (27 May 2021 - 26 May 2022), a total of 505 post-marketing reports were received. Of the 360 initial reports, 140 were serious and 220 were non-serious. Of the 140 serious reports, 139 cases included AEs with non-fatal outcomes and the remaining one report with a fatal outcome.
Risk factors and risk groups	Risk factors for drug-induced hepatic effects are in general poorly understood in patients with chronic liver disease. Pre-existing liver disease is not likely to increase the risk of developing drug induced liver-related AEs, however, if liver-related AEs occurs it might be more severe.

Important identified risk: Liver injury	
Risk minimisation measures	**Routine risk minimisation measures**: SmPC section 4.2, 4.4, 4.8 PL section 2,3, 4 Contraindication for use of drug in patients with PBC with either compensated or decompensated cirrhosis is included in SmPC section 4.2, 4.3 and 4.4. . Prescription only medicine **Additional risk minimisation measures**: None

Important potential risk: Atherosclerotic cardiovascular events secondary to changes in lipids	
Evidence for linking the risk to the medicine	**Clinical trials**: Atherosclerotic cardiovascular events secondary to changes in lipids were reported in clinical trials. During 27 May 2021 to 26 May 2022, 36 clinical trial reports (28 initial and 8 follow up cases) were received. Two initial reports were received from clinical studies in patients with PBC and 26 were received from patients in ongoing NASH studies. **Post-marketing experience**: Atherosclerotic cardiovascular events secondary to changes in lipids were reported post-marketing. During 27 May 2021 to 26 May 2022, 26 post-marketing reports (21 initial and 5 follow-ups) were received reporting 13 ADRs of Atherosclerotic CV Events Secondary to Changes in Lipids.
Risk factors and risk groups	In the general population, hyperlipidaemia is an established risk factor for increased mortality from CVD, the leading cause of death in the US. However, elevated cholesterol levels in patients with PBC are not known to be associated with increased cardiovascular risk. An Italian study found that hypertension significantly increased the risk of cardiovascular events in a PBC population.
Risk minimisation measures	**Routine risk minimisation measures**: SmPC section 4.8 PL section 4 Prescription only medicine **Additional risk minimisation measures**: None

Missing information: Use in patients with other concomitant liver diseases	
Risk minimisation measures	**Routine risk minimisation measures**: Prescription only medicine **Additional risk minimisation measures**: None

Missing information: Use in patients with hepatocellular carcinoma (HCC)	
Risk minimisation measures	**Routine risk minimisation measures**: Prescription only medicine **Additional risk minimisation measures**: None

Missing information: Use post liver transplantation	
Risk minimisation measures	**Routine risk minimisation measures**: Prescription only medicine **Additional risk minimisation measures**: None

Missing information: Long-term safety	
Risk minimisation measures	**Routine risk minimisation measures**: Prescription only medicine **Additional risk minimisation measures**: None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

Study short name	**Purpose of the study**
Study 747-302	**Primary objectives**: To assess the effect of OCA compared to placebo, in conjunction with established local standard of care, on clinical outcomes in subjects with PBC as measured by time to first occurrence of any of the following adjudicated events, derived as a composite event endpoint: Death (all-cause), liver transplant, MELD score ≥15, hospitalisation for variceal bleed, hepatic encephalopathy, spontaneous bacterial peritonitis, uncontrolled ascites **Secondary objectives**: To assess the effect of OCA compared to placebo on time to first occurrence of each individual component of the primary endpoint as listed above. To assess the effect of OCA compared to placebo on time to occurrence of liver related death. To assess the effect of OCA compared to placebo on progression to cirrhosis. To assess the effect of OCA compared to placebo on time to occurrence of HCC. To assess the effect of OCA compared to placebo on disease progression via the following: Liver biochemistry and markers of inflammation and fibrosis To assess the effect of OCA compared to historical controls on liver-related clinical outcomes. To characterise the PK of OCA and its conjugates in a subset of subjects.

	To assess health outcomes and pharmacoeconomics including cost-effectiveness, resource utilisation, and quality of life measures in subjects treated with OCA compared to placebo. To assess the safety and tolerability in subjects treated with OCA compared to placebo. **Summary/Conclusion:** Overall, administration of OCA was generally well tolerated in subjects with PBC, including subjects with predominantly cirrhotic liver disease. The overall incidence of treatment emergent adverse event was similar between OCA and placebo groups. The incidence of treatment-emergent serious adverse event was generally similar across treatment groups: 31.5% in the OCA group and 31.9% in the placebo group. Seven subjects had a treatment emergent adverse event leading to death (5 in OCA-treated subjects: acute respiratory failure, respiratory failure, subarachnoid hemorrhage, sepsis, and lower respiratory tract infection; and 2 in placebo-treated subjects: sarcopenia and hepatocellular carcinoma). All TEAEs leading to death were considered not related or unlikely related to the investigational product. The incidence of severe treatment-emergent serious adverse event, treatment-emergent serious adverse events, deaths, and treatment-emergent serious adverse event leading to discontinuation of investigational product was higher in OCA-treated subjects with more advanced stage PBC than subjects with earlier stage PBC. The pharmacokinetic profile of total-OCA was relatively consistent overtime (having reached steady state) with multiple moderate peaking, characteristic of enterohepatic recycling of bile acids in general at steady state. Due to the limited sample size in each dose regimen and the high variability, no clear conclusions were determined from the mean PK parameters for total OCA plasma concentrations. Overall, the safety data remain consistent with the known safety profile of OCA and anticipated for subjects with PBC.
Study 747-401	**Primary objectives**: To evaluate the PK of OCA and its conjugates, glyco-OCA and tauro-OCA, and metabolite OCA glucuronide compared with placebo To evaluate the safety and tolerability of OCA treatment compared with placebo **Secondary objectives**: To evaluate the effect of OCA treatment compared to placebo on: The MELD score and its components, Child-Pugh score and its components, liver biochemistry including total and direct bilirubin, ALP, and aminotransferases (ALT, AST, and GGT), INR, creatinine, albumin, platelets, biomarkers of bile acid synthesis and homeostasis including FGF19, 7α hydroxy-4-cholesten-3-one, and plasma bile acids **Additional Objectives**: To evaluate the effect of OCA treatment compared to placebo on: Noninvasive markers of liver fibrosis (ELF™ score), noninvasive measurement of liver stiffness (TE) To assess the PK/PD relationship of OCA with: PK parameters compared to PD parameters and safety and tolerability assessments To assess patient reported outcomes (Pruritus VAS, PBC-40, EQ 5D-5L, CLDQ) To assess clinical events consistent with end-stage liver disease: Death (all-cause), liver transplant, MELD score ≥15 (for patients with MELD ≤12 at baseline), hospitalization (as defined by a stay of 24 hours or greater) for new onset or recurrence of: variceal bleed, hepatic encephalopathy (as defined by a West Haven score of ≥2), spontaneous bacterial peritonitis, uncontrolled ascites (diuretic resistant ascites requiring therapeutic paracentesis at a frequency of at least twice in a month), HCC. **Summary/Conclusion:** Twenty-two subjects of a planned 50 subjects were randomized into the study: 10 in the OCA and 12 in the placebo groups. PK information was limited with only 6 subjects having adequate plasma concentration data to derive PK parameters for OCA 5 mg once weekly; 4 subjects titrated to OCA 5 mg twice weekly and of the 4 subjects, 2

	subjects titrated to OCA 10 mg twice weekly. Despite these limitations, and as expected, total OCA exposure was consistent with the expectation that exposure is higher in subjects with moderate hepatic impairment (CP-B) versus subjects without hepatic impairment. The The PK results of this study demonstrated the accuracy of the simulation to predict total OCA exposure, at steady-state, following OCA 5 mg once weekly. The observed mean AUC0-24h (2970 ng·h/mL) and Cmax (293 ng/mL) for total OCA at Week 12 (i.e., steady-state) were similar to the simulated predicted mean AUC0-24h (2633 ng·h/mL) and Cmax (300 to 330 ng/mL) of values from the simulation for the OCA 5 mg once weekly dose demonstrating that the modified OCA dose regimen of 5 mg once weekly achieved targeted OCA exposure. Following dose titration to OCA 5 mg twice weekly and 10 mg twice weekly dose proportional increases were observed. It should be noted that PK was not assessed in subjects with severe hepatic impairment (CP-C) as originally planned. Based on previous studies in hepatic impairment exposure to total OCA would be higher in subjects with CP-C than subjects with moderate hepatic impairment (CP-B). No clear efficacy conclusions could be drawn in this study given that the number of subjects was small, and the study was not designed to detect differences between treatments for efficacy endpoints. No clinically meaningful differences were noted between OCA and placebo for composite outcome of death, including liver-related death, liver transplant, MELD score, refractory ascites, and hospitalizations for decompensating events. Variceal bleeding was the only individual component with a nominal p-value of <0.05. No clear differences were detected between OCA and placebo over time for MELD-Na, CP score, or clinical liver biochemistry results. A trend towards improving LSM over time among OCA compared to placebo-treated subjects was noted. Overall, the administration of OCA was generally well tolerated in this population of patients with PBC with moderate to advanced cirrhosis. Reported TEAEs were, in general, consistent with the known safety profile of OCA and anticipated for subjects with advanced PBC. The most commonly reported TEAEs in OCA-treated subjects were ascites, pruritus, anemia, esophageal varices hemorrhage, pneumonia, and urinary tract infection. The frequency of SAEs in the study was similar among placebo- and OCA-treated subjects. Five deaths were reported in the study, 3 in placebo and 2 in the OCA arm; all were considered unlikely or not related to study treatment. Hepatic-related safety findings were consistent with that reported in previous studies with OCA, and no new relevant safety findings were noted. Based on a broad set of highly sensitive pre-specified triggers, a total of 20 subjects had events assessed by the Hepatic Safety Adjudication Committee as potential hepatic injury for further assessment of causality to drug and event severity. Of the 20 subjects, 2 subjects (1 placebo, 1 OCA) had events assessed as possibly related to study treatment. Due to limited availability of clinical data in patients with PBC with more advanced liver disease, the CCDS and product information was revised to contraindicate use of OCA in patients with decompensated cirrhosis or a prior decompensation event and those with compensated cirrhosis with evidence of portal hypertension. Acknowledging the limitations of the small sample size in the study and based on clinical outcomes, biochemistry results, predictor models (i.e., MELD, MELD-NA, and CP score), and markers of fibrosis, OCA demonstrated no clear clinical benefit or new safety concern in this advanced patient population compared to placebo.

II.C.2 Other studies in post-authorisation development plan

None.