Ocaliva

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
II/0039	Submission of an updated RMP version 2.0 in order to change to EU Qualified Person for Pharmacovigilance (QPPV), update the list of safety concerns and study data for 747-302 and 747-401. C.I.11.b - Introduction of, or change(s) to, the	16/03/2023	n/a		Reclassification of 'Liver injury' as Important identified risk following variation procedure EMEA/H/C/004093/II/0030 in which section 4.4 of the SmPC was updated to include a new warning on monitoring and management of patients for possible progression of PBC and other hepatic adverse reactions and the adverse events of hepatic failure, blood

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				bilirubin increased, jaundice, and hepatic cirrhosis with the frequency unknown were added as adverse reactions to section 4.8 of the SmPC in the system organ class (SOC) Hepatobiliary disorders. Removal of Missing information 'Use in patients with moderate to severe hepatic impairment following the update of section 4.3 of the SmPC in the same variation procedure that included a contraindication in patients with decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event.
PSUSA/10555 /202205	Periodic Safety Update EU Single assessment - obeticholic acid	12/01/2023	n/a		PRAC Recommendation - maintenance
T/0037	Transfer of Marketing Authorisation	07/11/2022	16/12/2022	SmPC, Labelling and PL	
R/0034	Renewal of the marketing authorisation.	15/09/2022	09/11/2022		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Ocaliva, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
II/0035	B.I.a.1.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant update to the relevant AS section in the dossier	15/09/2022	n/a		

II/0030	Update of section 4.3 of the SmPC in order to include a contraindication in patients with decompensated cirrhosis (e.g., Child-Pugh Class B or C) or a prior decompensation event based on interim analyses from the ongoing studies 747-302 and 747-401 listed as Specific Obligations in Annex II and on post marketing data. Consequently, dosing instructions for patients with CP-B and CP-C cirrhosis were removed from Section 4.2, and the wording in sections 4.2, 4.4 and 5.2 of the SmPC have been updated accordingly. In addition, section 4.4 of the SmPC has been updated to include a new warning on monitoring and management of patients for possible progression of PBC and other hepatic adverse reactions. Furthermore, the adverse events of hepatic failure, blood bilirubin increased, jaundice, and hepatic cirrhosis with the frequency unknown were added to section 4.8 of the SmPC in the system organ class (SOC) Hepatobiliary disorders. The MAH has also taken the opportunity to remove the outdated term "primary biliary cirrhosis" from section 4.1 and to make editorial changes to sections 4.9, 5.1 and Annex IIE to improve clarity and correct typographical errors. The Package Leaflet is updated accordingly. Also, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.2. C.I.4 - Change(s) in the SPC, Labelling or PL due to	19/05/2022	24/06/2022	SmPC, Annex II, Labelling and PL	During a pre-planned unblinded interim analysis (IA) that took place in September 2020 for studies 747-401 and 747-302 that both enrolled primary biliary cholangitis (PBC) population including patients with decompensated cirrhosis, the independent data monitoring committee (DMC) determined in their blinded report that it does not appear to be feasible to establish the safety and efficacy of Ocaliva in this patient population. Further, whilst stronger evidence from the well-controlled blinded clinical trials indicates no difference in the occurrence of decompensation events in Ocaliva vs placebo, post-marketing data suggest an association between hepatic events and PBC patients taking Ocaliva, particularly in cirrhosis patients (CP-B and C). It was acknowledged by the CHMP that reporting rates observed in post-market data are still lower than the background rates observed in PBC cohorts in epidemiologic studies but considering that it will no longer be feasible to establish the safety and efficacy of Ocaliva in this patient population, the CHMP agreed to add a contraindication in patients with decompensated cirrhosis (e.g. Child-Pugh Class B or C) or prior decompensation event. Further, post-marketing research revealed an increased risk in patients with concomitant liver disease e.g. autoimmune hepatitis and alcoholic liver disease. Accordingly, section 4.4 of the SmPC emphasizes now that patients with an increased risk of hepatic decompensation should be closely monitored. in total 45.2% of the 186 post-marketing cases of hepatic adverse events could not be classified to a CP class and of them 14.3% were described in patients presumed to be

	new quality, preclinical, clinical or pharmacovigilance data				non-cirrhotic; considering the contraindication in case of progression and the risk of hepatic decompensation all patients should be routinely (i.e. not only at treatment initiation) monitored for progression of PBC including hepatic adverse reaction with laboratory and clinical assessments if treatment needs to be discontinued as now reflected in Section 4.4. of the SmPC. For more information, please refer to the Summary of Product Characteristics.
IB/0033	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	26/01/2022	n/a		
PSUSA/10555 /202105	Periodic Safety Update EU Single assessment - obeticholic acid	13/01/2022	n/a		PRAC Recommendation - maintenance
R/0027	Renewal of the marketing authorisation.	11/11/2021	12/01/2022		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for OCALIVA, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
II/0029	Update of sections 4.2 and 5.2 of the Summary of Product Characteristics (SmPC) in order to clarify information on posology recommendations in renally	11/11/2021	12/01/2022	SmPC	Study 474-120 (a Phase I, Open-Label Study to Investigate the Effect of Renal Impairment on the Single-Dose Pharmacokinetics using 25 mg of Obeticholic Acid) revealed

	impaired patients and add information on pharmacokinetic properties following the results from Study 474-120 (a Phase I, Open-Label Study to Investigate the Effect of Renal Impairment on the Single-Dose Pharmacokinetics of Obeticholic Acid). Editorial changes have also been made to the Section 4.5. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				results in plasma exposures to the active substance and its conjugates increased by approximately 1.4 to 1.6 fold in subjects with mild (modification of diet in renal disease [MDRD] eGFR ≥ 60 and < 90 mL/min/1.73 m2), moderate (MDRD eGFR ≥ 30 and < 60 mL/min/1.73 m2) and severe (MDRD eGFR ≥ 15 and < 30 mL/min/1.73 m2) renal impairment compared to subjects with normal renal function. This modest increase is not considered to be clinically meaningful. Therefore, information on posology recommendation in section 4.2 of the Summary of product Characteristics is proposed to confirm current recommendation that no dose adjustment is required in renally impaired patients. Furthermore, section 5.2 is updated to add information on pharmacokinetic properties following the study's results. Editorial changes have also been made to Section 4.5. For more information, please refer to the Summary of Product Characteristics.
II/0026	Update of the RMP to version 1.3 (dated of 11 June 2021) in order to update the format in accordance with template to EMA/164014/2018 Rev.2.0.1 and to add Specific Obligation clinical studies 747-302 and 747-401 to part IV. Plans for post-authorisation efficacy studies of the RMP. This change has been agreed by the CHMP in the outcome Ocaliva 2020 Annual Renewal (EMEA/H/C/004093/R/0023). Other changes also include an update to the exposure data from clinical studies and addition of data on post-marketing experience up to the DLP (26 May 2020) and addition of some specific relevant SmPC wording in the risk minimisation measures.	30/09/2021	n/a		The RMP update (version 1.3, dated 11 June 2021) was approved and reflects the implementation of the following changes: • Update RMP in accordance with template EMA/164014/2018 Rev.2.0.1. • Specific Obligation clinical studies 747-302 and 747-401 have been added to part IV. Plans for post-authorisation efficacy studies of the RMP and the due dates of Studies 747-302 and 747-401 updated to Dec 2023. • Data on post-marketing experience up to the DLP of PBRER #6 (26 May 2020) have been added. • Exposure data from clinical studies up to DLP of 26 Oct

	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				2018 have been added. • Specific relevant SmPC wording have been included where applicable in the Risk Minimisation Measure. • Change to EU Qualified Person for Pharmacovigilance (QPPV). • The important identified risk of pruritus was removed. • The missing information of 'Use in elderly and very elderly patients (≥65 years)' and 'Use during pregnancy and breast-feedingwas removed.
IB/0031	B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test	20/08/2021	n/a		
PSUSA/10555 /202005	Periodic Safety Update EU Single assessment - obeticholic acid	14/01/2021	n/a		PRAC Recommendation - maintenance
R/0023	Renewal of the marketing authorisation.	12/11/2020	11/01/2021	SmPC, Annex II, Labelling and PL	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Ocaliva, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion. Despite additional measures implemented and aimed at increasing recruitment, the submission due date of the CSR of Study 747-401 is postponed to 2023 due to COVID related patient enrolment difficulties. In addition, the MAH took the opportunity to bring the PI in line with the last

					QRD template (version 10.1).
IAIN/0025/G	This was an application for a group of variations. B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	16/11/2020	18/11/2021	SmPC, Annex II and PL	
R/0018	Renewal of the marketing authorisation.	27/02/2020	28/04/2020		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for OCALIVA, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
IA/0022	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	30/01/2020	n/a		
IB/0021	B.II.c.z - Change in control of excipients in the Finished Product - Other variation	24/01/2020	n/a		

PSUSA/10555 /201905	Periodic Safety Update EU Single assessment - obeticholic acid	16/01/2020	n/a		PRAC Recommendation - maintenance
IA/0020/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	19/12/2019	n/a		
II/0016/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for	12/09/2019	n/a		

	the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant update to the relevant AS section in the dossier B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
PSUSA/10555 /201811	Periodic Safety Update EU Single assessment - obeticholic acid	14/06/2019	n/a		PRAC Recommendation - maintenance
N/0017	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/06/2019	11/02/2020	PL	

IAIN/0015	A.1 - Administrative change - Change in the name and/or address of the MAH	22/03/2019	11/02/2020	SmPC, Labelling and PL	
IAIN/0013/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	08/02/2019	11/02/2020	Annex II and PL	
T/0012	Transfer of Marketing Authorisation	11/12/2018	23/01/2019	SmPC, Labelling and PL	
PSUSA/10555 /201805	Periodic Safety Update EU Single assessment - obeticholic acid	17/01/2019	n/a		PRAC Recommendation - maintenance
R/0009	Renewal of the marketing authorisation.	18/10/2018	12/12/2018		
IB/0011	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	17/10/2018	12/12/2018	SmPC	

PSUSA/10555 /201712	Periodic Safety Update EU Single assessment - obeticholic acid	12/07/2018	n/a		PRAC Recommendation - maintenance
PSUSA/10555 /201706	Periodic Safety Update EU Single assessment - obeticholic acid	25/01/2018	21/03/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10555/201706.
IB/0007/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold	15/03/2018	n/a		

	increase compared to the originally approved batch size B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				
IB/0006/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	09/01/2018	n/a		
R/0002	Renewal of the marketing authorisation.	12/10/2017	01/12/2017		The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for OCALIVA, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion.
IA/0005	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch	24/10/2017	n/a		

	control/testing takes place				
IA/0003/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	01/08/2017	n/a		
IB/0001/G	This was an application for a group of variations. B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	21/04/2017	01/12/2017	SmPC, Labelling and PL	