Orladeyo

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
IA/0020	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	19/11/2024	n/a		
PSUSA/10930 /202312	Periodic Safety Update EU Single assessment - berotralstat	25/07/2024	19/09/2024	SmPC and PL	Please refer to Orladeyo-EMEA/H/C/PSUSA/00010930/202312 EPAR:

[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).

					Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
II/0017/G	This was an application for a group of variations. A grouped application comprised of two type II variations, as follows: C.I.4: Update of section 4.4 and 4.5 of the SmPC in order to add a warning on QT prolongation and remove the recommendation for close monitoring for adverse events with concomitant use of P-gp and BCRP inhibitors based on final safety results from the drug-drug interaction study BCX7353-119, as well as to update the effects of cyclosporine on berotralstat. Study BCX7353-119 is a phase 1 drug-drug interaction study to evaluate the effect of cyclosporine on the pharmacokinetics of berotralstat in healthy subjects. C.I.13: Submission of the final reports from parts 2 and 3 of study BCX7353-301; this is a phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of two dose levels of BCX7353 as an oral treatment for the suppression of events in subjects with hereditary angioedema. In addition, the MAH took the opportunity to add additional wording for patients with severely reduced kidney function in the Package Leaflet and to introduce minor editorial changes to the PI, as per	27/06/2024	26/07/2024	SmPC and PL	The MAH has submitted the results from Study BCX7353-119 (Study 119), "A Phase 1 drug-drug interaction study to evaluate the effect of cyclosporine on the pharmacokinetics of berotralstat in healthy subjects" with consequent request for update to the product information for Orladeyo. Based on the results of this drug-drug interaction study BCX7353-119, the MAH has requested to remove the recommendation for close monitoring for adverse events with concomitant use of P-gp and BCRP inhibitors from Section 4.5 of the SmPC, as well as to update the effects of cyclosporine on berotralstat. A a statement has added in section 4.4 of the SmPC regarding the potential for QT prolongation with increased berotralstat concentration. Within this grouped variation, the MAH also submitted clinical study reports for Parts 2 and 3 of Study BCX7353-301 (Study 301), "A Phase 3, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of two dose levels of BCX7353 as an oral treatment for the suppression of events in subjects with hereditary angioedema." The first interim CSR covering Part 1 and some of Part 2 of Study 301 was already submitted and assessed at time of the initial MAA approval. Study 301 was conducted in Japan only and considered the smaller of the two pivotal studies supporting berotralstat approval. As the study was ongoing at the time of initial MAA submission and has since concluded, the final CSRs for Parts 2 and 3 are now submitted for review. The updated data provided within 2nd Interim CSR and addendum and Final CSR, relevant to Part 2 and 3 of Study

	previous guidance. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				BCX7353-301, is generally consistent with that from the initial MAA in terms of efficacy and safety. No updates to the SmPC are proposed by the MAH based on the final results of Study BCX7353-301, which is agreed. SmPC new text
IB/0019	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	20/03/2024	n/a		
IB/0015/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	09/11/2023	n/a		
IA/0016	B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	08/11/2023	n/a		
IB/0014	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	20/10/2023	n/a		
IB/0013/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters	07/08/2023	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits 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				
PSUSA/10930 /202212	Periodic Safety Update EU Single assessment - berotralstat	06/07/2023	n/a		PRAC Recommendation - maintenance
PSUSA/10930 /202206	Periodic Safety Update EU Single assessment - berotralstat	12/01/2023	n/a		PRAC Recommendation - maintenance
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)	13/12/2022	09/10/2023	SmPC	
II/0006	Update of sections 4.4 and 4.5 of the SmPC in order to remove the warning for women of childbearing potential and amend drug-drug interaction information with desogestrel based on final results from study BCX7353-111; this is a phase 1 drug interaction study to evaluate the effects of berotralstat on the pharmacokinetics of a combination oral contraceptive, desogestrel with ethinyl estradiol; the Package Leaflet is updated accordingly.	01/09/2022	09/10/2023	SmPC and PL	SmPC new text Section 4.4 Section 4.5 CYP2C9 substrates Berotralstat is a weak inhibitor of CYP2C9 increasing the Cmax and AUC of tolbutamide by 19% and 73%, respectively. No dose adjustment is recommended for concomitant use of medicines that are predominantly metabolised by CYP2C9 (e.g. tolbutamide) (see section 5.2).

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				The effect of berotralstat on the CYP2C9 conversion of desogestrel to etonogestrel (active metabolite) was negligible. No dose adjustment is recommended for concomitant use of desogestrel. For more information, please refer to the Summary of Product Characteristics and PL changes. Package leaflet change Section 2 Other medicines and Orladeyo The following changes were made Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Particularly, tell your doctor before taking Orladeyo if you are using: • oral contraceptives, medicines used for birth control
IB/0009	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	08/08/2022	n/a		
IB/0008	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	26/07/2022	n/a		
PSUSA/10930 /202112	Periodic Safety Update EU Single assessment - berotralstat	07/07/2022	n/a		PRAC Recommendation - maintenance
IA/0007	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	31/03/2022	n/a		

IB/0005	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	22/02/2022	n/a		
PSUSA/10930 /202106	Periodic Safety Update EU Single assessment - berotralstat	13/01/2022	n/a		PRAC Recommendation - maintenance
IAIN/0002	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	03/08/2021	n/a		
IAIN/0001	A.1 - Administrative change - Change in the name and/or address of the MAH	08/06/2021	01/07/2022	SmPC and PL	