NUBEQA

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
R/0021	Renewal of the marketing authorisation.	19/09/2024	24/10/2024	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of NUBEQA in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.

[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).

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PSUSA/10843 /202401	Periodic Safety Update EU Single assessment - darolutamide	05/09/2024	n/a		PRAC Recommendation - maintenance
N/0022	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/07/2024	24/10/2024	PL	
PSUSA/10843 /202307	Periodic Safety Update EU Single assessment - darolutamide	21/03/2024	16/05/2024	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10843/202307.
IA/0018/G	This was an application for a group of variations. 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.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size	15/09/2023	n/a		
PSUSA/10843 /202301	Periodic Safety Update EU Single assessment - darolutamide	31/08/2023	n/a		PRAC Recommendation - maintenance
IB/0017	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	23/08/2023	n/a		
IB/0016/G	This was an application for a group of variations. 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-	06/07/2023	n/a		

	release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process				
PSUSA/10843 /202207	Periodic Safety Update EU Single assessment - darolutamide	16/03/2023	n/a		PRAC Recommendation - maintenance
II/0009	Extension of indication to include treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel and androgen deprivation therapy, based on final results from Study 17777 (ARASENS); this is a randomized, double-blind, placebo-controlled Phase 3 study designed to demonstrate the superiority of darolutamide in combination with docetaxel over placebo in combination with docetaxel in OS in patients with mHSPC. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated. The Package Leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	26/01/2023	27/02/2023	SmPC and PL	Please refer to Scientific Discussion 'EMEA/H/C/004790/II/0009'

II/0012	Update of section 5.3 of the SmPC based on the final report of carcinogenicity study T104877-7 listed as a category 3 study in the RMP. This is a non-clinical study to assess the carcinogenic potential in mice. The study evaluates the effects of daily oral administration of darolutamide for a period of 6 months in tg-rasH2 transgenic mouse model. The updated RMP version 3.2 is approved. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	12/01/2023	27/02/2023	SmPC	Oral administration of darolutamide to male rasH2 transgenic mice for 6 months did not show carcinogenic potential at doses up to 1000 mg/kg/day, which is 0.9 1.3 times for darolutamide and 2.1 2.3 times for keto darolutamide the clinical exposure (AUC) at the recommended clinical daily dose of 1200 mg/day. Based on this study carcinogenic risk of darolutamide cannot be completely excluded.
PSUSA/10843 /202201	Periodic Safety Update EU Single assessment - darolutamide	01/09/2022	n/a		PRAC Recommendation - maintenance
IB/0013	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	28/07/2022	n/a		
IA/0011	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	24/05/2022	n/a		
PSUSA/10843 /202107	Periodic Safety Update EU Single assessment - darolutamide	10/03/2022	n/a		PRAC Recommendation - maintenance
N/0008	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/12/2021	27/02/2023	PL	

PSUSA/10843 /202101	Periodic Safety Update EU Single assessment - darolutamide	02/09/2021	n/a		PRAC Recommendation - maintenance
IB/0005	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/04/2021	n/a		
IA/0004	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	16/03/2021	n/a		
PSUSA/10843 /202007	Periodic Safety Update EU Single assessment - darolutamide	11/02/2021	n/a		PRAC Recommendation - maintenance
II/0002	Update of section 5.1 of the SmPC in order to update efficacy information based on the final CSR from study 17772 (ARAMIS) listed as a PAES in the Annex II; this is a multinational, randomised, double-blind, placebo-controlled, phase III efficacy and safety study of darolutamide in men with high-risk non-metastatic castration-resistant prostate cancer; the Annex II is updated accordingly. The RMP version 1.1 is accepted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	08/10/2020	21/04/2021	SmPC and Annex II	After the primary analysis of MFS, once the study was unblinded, patients receiving placebo were offered treatment with open label darolutamide (cross over option). Among the 554 patients randomised to placebo, 170 (31%) crossed over to receive darolutamide treatment. The OS analysis was not adjusted for confounding effects of cross over. At the time of the final analysis, treatment with darolutamide resulted in a statistically significant improvement in overall survival compared to placebo (median was not reached in either arm, HR of 0.685 (95% CI: [0.533; 0.881]; p=0.003048)).
IB/0001	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	12/05/2020	21/04/2021	SmPC, Labelling and PL	