Erleada

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/0036	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/04/2024		SmPC and PL	
IB/0035	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	19/03/2024	n/a		

[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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IB/0034	B.I.b.z - Change in control of the AS - Other variation	23/01/2024	n/a		
PSUSA/10745 /202302	Periodic Safety Update EU Single assessment - apalutamide	12/10/2023	07/12/2023	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10745/202302.
IAIN/0033/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.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	20/11/2023	n/a		
R/0030	Renewal of the marketing authorisation.	20/07/2023	22/09/2023	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Erleada in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0032/G	This was an application for a group of variations. B.II.b.3.b - Change in the manufacturing process of the finished or intermediate product - Substantial changes to a manufacturing process that may have a	21/09/2023	n/a		

	significant impact on the quality, safety and efficacy of the medicinal product B.II.g.1.a - Introduction of a new design space or extension of an approved design space for the finished product - One or more unit operations in the manuf. process of the FP including the resulting IPCs and/or test procedures 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				
X/0028/G	This was an application for a group of variations. Extension application to add a new strength (240 mg) film-coated tablets grouped with the IB variation (C.I.z). The RMP (version 6.1) has also been submitted. C.I.z (IB): to align the SmPC/PL for Erleada 60 mg with the SmPC/PL proposed for the registration of the new Erleada film-coated tablet strength, 240 mg. The PL for Erleada 60 mg is proposed to be updated to ensure consistency. Annex I_2.(c) Change or addition of a new strength/potency C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/06/2023	25/08/2023	SmPC, Labelling and PL	Please refer to Scientific Discussion Erleada-H-C-4452-X-0028/G.
IB/0029/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a	12/07/2023	n/a		

	starting material/reagent/intermediate for AS - Other variation 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.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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 B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.c.2.a - Change in the specification parameters and/or limits of the immediate packaging of the AS - Tightening of specification limits 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.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				
PSUSA/10745	Periodic Safety Update EU Single assessment -	13/10/2022	09/12/2022	SmPC and PL	Refer to Scientific conclusions and grounds recommending

/202202	apalutamide				the variation to terms of the Marketing Authorisation(s)' for PSUSA/10745/202202.
IA/0027/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.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS 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 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	08/11/2022	n/a		
IB/0026	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	09/06/2022	n/a		
IB/0024	B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation	06/05/2022	n/a		

IB/0022/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.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	19/04/2022	n/a		
IA/0023/G	This was an application for a group of variations. B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition) B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition) B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the	06/04/2022	n/a		

	finished product - Tightening of specification limits B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process				
PSUSA/10745 /202108	Periodic Safety Update EU Single assessment - apalutamide	10/03/2022	n/a		PRAC Recommendation - maintenance
II/0017	Update of sections 5.3 of the SmPC in order to update non-clinical information based on final results from study TOX11338. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/02/2022	09/12/2022	SmPC	In a 2 year carcinogenicity study in male Sprague Dawley rats (study TOX11338), apalutamide was administered by oral gavage at doses of 5, 15 and 50 mg/kg/day (0.2, 0.7, and 2.5 times the AUC in patients (human exposure at recommended dose of 240 mg), respectively). Neoplastic findings were noted including an increased incidence of testicular Leydig cell adenoma and carcinoma at doses greater than or equal to 5 mg/kg/day, mammary adenocarcinoma and fibroadenoma at 15 mg/kg/day or 50 mg/kg/day, and thyroid follicular cell adenoma at 50 mg/kg/day. These findings were considered rat specific and therefore of limited relevance to humans.
IB/0018/G	This was an application for a group of variations. 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.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	19/11/2021	n/a		

	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
IB/0019	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)	18/11/2021	09/12/2022	SmPC	
II/0016	Update of sections 4.4 and 4.8 of the SmPC in order to add Stevens-Johnson Syndrome (SJS) to the list of adverse drug reactions (ADRs) with frequency not known. Cases of SJS were observed in post-marketing data. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/11/2021	09/12/2022	SmPC and PL	Cases of Stevens-Johnson Syndrome (SJS) were observed in association with Erleada treatment in post-marketing data and has been added to the list of adverse drug reactions (ADRs) with frequency not known.
II/0015	Update of section 5.1 of the SmPC in order to update the efficacy, safety information based on final results from study 56021927PCR3002 (TITAN) listed as Letter of Recommendations (11 December 2019, EMEA/H/C/004452/II/0001); this is a double-blind, placebo-controlled, multinational, multicenter Phase 3 study in metastatic castration-sensitive prostate cancer (mCSPC) patients. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	07/10/2021	09/12/2021	SmPC	An updated OS analysis was conducted at the time of final study analysis when 405 deaths were observed with a median follow-up of 44 months. Results from this updated analysis were consistent with those from the pre specified interim analysis. The improvement in OS was demonstrated even though 39% of patients in the placebo arm crossed over to receive Erleada, with a median treatment of 15 months on Erleada crossover. Consistent improvement in OS was observed across patient subgroups including high- or low-volume disease, metastasis stage at diagnosis (M0 or M1), and Gleason score at diagnosis (≤7 vs. >7).

PSUSA/10745 /202102	Periodic Safety Update EU Single assessment - apalutamide	30/09/2021	n/a		PRAC Recommendation - maintenance
II/0013	Update of sections 4.6 and 5.3 of the SmPC in order to update information on pregnancy and update non-clinical information following results of a developmental toxicity study in rats. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/06/2021	09/12/2021	SmPC	Erleada is contraindicated in women who are or may become pregnant (see section 4.3). Based on an animal reproductive study and its mechanism of action, Erleada may cause foetal harm and loss of pregnancy when administered during pregnancy to a pregnant woman. There are no data available from the use of Erleada in pregnant women. Apalutamide caused developmental toxicity when administered at oral doses of 25, 50 or 100 mg/kg/day throughout the period of organogenesis (gestational days 6-20) in a preliminary embryofetal developmental toxicity study in rats. These doses resulted in systemic exposures approximately 2, 4 and 6 times, respectively the exposure in humans at the dose of 240 mg/day. Findings included non-pregnant females at 100 mg/kg/day and embryofetal lethality (resorptions) at doses ≥50 mg/kg/day, decreased fetal anogenital distance and a misshapen pituitary gland (more rounded shape) at ≥25 mg/kg/day. Skeletal variations (unossified phalanges, supernumerary short thoracolumbar rib(s) and/or abnormalities of the hyoid) were also noted at doses ≥25 mg/kg/day, without resulting in an effect on mean fetal weight.
PSUSA/10745 /202008	Periodic Safety Update EU Single assessment - apalutamide	11/03/2021	n/a		PRAC Recommendation - maintenance
IB/0012/G	This was an application for a group of variations.	03/03/2021	n/a		

	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
II/0009	Update of section 5.3 of the SmPC in order to include non-clinical information based on final results from a 26-week carcinogenicity study (TOX13540) listed as a category 3 study in the RMP. The RMP version 3.2 is approved C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/02/2021	09/12/2021	SmPC, Annex II, Labelling and PL	Apalutamide was not carcinogenic in a 6-month study in the male transgenic (Tg.rasH2) mouse at doses up to 30 mg/kg per day, which is 1.2 and 0.5 times for apalutamide and N desmethyl apalutamide respectively, the clinical exposure (AUC) at the recommended clinical dose of 240 mg/day.
II/0008	Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to update efficacy and safety information based on final results from study ARN-509-003 (SPARTAN) listed as a PAES in Annex II; this is a multicenter, randomised, double-blind, placebo-controlled, phase III study of ARN-509 in men with non-metastatic (M0) castration-resistant prostate cancer; the package leaflet and Annex II are updated accordingly. The RMP version 3.1 is approved. In addition, the MAH took the opportunity to update the list of local representatives in the Package leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	18/02/2021	09/12/2021	SmPC, Annex II and PL	With median follow-up time of 52.0 months, results from study ARN-509-003 (SPARTAN) showed that treatment with Erleada significantly decreased the risk of death by 22% compared with placebo (HR = 0.784; 95% CI: 0.643, 0.956; 2-sided p = 0.0161). The median OS was 73.9 months for the Erleada arm and 59.9 months for the placebo arm. The pre-specified alpha boundary ($p \leq 0.046$) was crossed and statistical significance was achieved. This improvement was demonstrated even though 19% of patients in the placebo arm received Erleada as subsequent therapy. Ischaemic cerebrovascular disorders and alopecia have been added to the list of adverse drug reactions (ADRs) with frequency common. The existing warning on ischaemic

	data				heart disease has been amended to include information about ischaemic cerebrovascular disorders. Patients should be monitored for signs and symptoms of ischaemic heart disease and ischaemic cerebrovascular disorders. Management of risk factors, such as hypertension, diabetes, or dyslipidaemia should be optimised as per standard of care.
IA/0011/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.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure 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	14/01/2021	n/a		
II/0007/G	This was an application for a group of variations. Update of section 4.8 of the SmPC in order to add toxic epidermal necrolysis and decreased appetite to the list of adverse drug reactions (ADRs) with frequency 'not known' and 'very common' respectively based on cumulative safety reviews. In addition, the MAH took the opportunity to make minor corrections in the SmPC, to update the list of local representatives in the Package Leaflet, and to	12/11/2020	09/12/2021	SmPC, Annex II and PL	

	bring the PI in line with the latest QRD template version 10.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10745 /202001	Periodic Safety Update EU Single assessment - apalutamide	03/09/2020	n/a		PRAC Recommendation - maintenance
IB/0003/G	This was an application for a group of variations. B.I.z - Quality change - Active substance - Other variation B.II.z - Quality change - Finished product - Other variation	09/03/2020	n/a		
PSUSA/10745 /201907	Periodic Safety Update EU Single assessment - apalutamide	13/02/2020	n/a		PRAC Recommendation - maintenance
II/0001	Extension of Indication to include the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT) for Erleada based on the results of study 56021927PCR3002 (TITAN study), a randomised, double-blind, placebo-controlled phase 3 study comparing apalutamide plus ADT versus ADT in patients with mHSPC; as a consequence, sections	12/12/2019	27/01/2020	SmPC, Labelling and PL	Please refer to Scientific Discussion Erleada-H-C-4452-II-01.

	4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated in order to reflect the new indication, to add a warning on ischaemic cardiovascular events and to reflect new safety and efficacy information. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and to make editorial update to the SmPC and Labelling. The RMP version 2.3 is approved. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IA/0004/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.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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	17/12/2019	n/a		