Xtandi

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
X/0029	Annex I_2.(c) Change or addition of a new strength/potency Annex I_2.(d) Change or addition of a new pharmaceutical form	20/07/2017	21/09/2017	SmPC, Labelling and PL	
II/0035	Update of sections 4.4 and 4.8 of the SmPC to reflect the final results of the post authorisation safety study (PASS) CL-9785-0403 which evaluated the risk of seizure among subjects with mCRPC treated with	09/06/2017	21/09/2017	SmPC	Section 4.8 of the SmPC reflects that 8 of 366 (2.2%) patients treated with enzalutamide in study 9785-CL-0403 experienced a seizure. The duration of treatment was 9.3 months. Section 4.4 warns and advises prescribing

[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).

	enzalutamide who were at potential increased risk of seizure (UPWARD) and was listed as a category 3 in the RMP. The RMP version 11.0 has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to make a correction in section 5.1 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				physicians, that in case of seizures the decision for treatment continuation should be taken on a case by case basis. The updated RMP version 11.0 is accepted.
II/0034	Update of section 5.1 of the SmPC in order to reflect relevant information for physicians namely on the observed differences in treatment effect based on prior chemotherapy treatment history. In addition, the MAH took this opportunity to reflect the ATC code for enzalutamide. The RMP version 11.0 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/05/2017	21/09/2017	SmPC	Section 5.1 of the SmPC reflects comprehensive data on observed differences in treatment effect based on prior chemotherapy treatment history. Results of the PREVAIL and TERRAIN trials in prior chemo-naïve patients and results of study 9785-CL-0410 in patients previously treated with at least 24 weeks of abiraterone (plus prednisone) are included in the SmPC.The updated RMP version 11.00 is accepted.
II/0036	Update of sections 4.6 and 5.3 of the SmPC to reflect the final results of study AE-7592-G, “Transfer of Radioactivity into Fetuses and Breast Milk in Rats after a Single Oral Administration of [14C] MDV3100- ISN: 9785-ME-0046”. The Package Leaflet is updated accordingly. The RMP version 11.0 has also been submitted.	09/03/2017	21/09/2017	SmPC and PL	Results of a non-clinical study in pregnant rats have shown that enzalutamide and/or its metabolites are transferred to fetuses. Therefore enzalutamide may cause harm to the unborn child or potential loss of pregnancy if taken by women who are pregnant. This study also showed that enzalutamide and/or its metabolites are secreted in rat milk. It is not known if enzalutamide is present in human milk but its use has always been contraindicated in women

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				who are or may become pregnant.
PSUSA/10095 /201608	Periodic Safety Update EU Single assessment - enzalutamide	09/03/2017	n/a		PRAC Recommendation - maintenance
IB/0032	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	16/08/2016	n/a		
IB/0030/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for 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	07/07/2016	n/a		
IAIN/0031	B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	09/06/2016	n/a		
II/0028/G	This was an application for a group of variations. Update of sections 4.8 and 5.1 of the SmPC based on the results of study 9785-CL-0222 (TERRAIN); an active-controlled study, which evaluated the safety and efficacy of enzalutamide vs bicalutamide in men with metastatic CRPC. The Package Leaflet has been updated accordingly. Further, the MAH provides supportive data from study MDV3100-09 (STRIVE), a	01/04/2016	12/12/2016	SmPC and PL	The TERRAIN study enrolled 375 chemo- and antiandrogen-therapy naïve patients who were randomized to receive either enzalutamide at a dose of 160 mg once daily (N = 184) or bicalutamide at a dose of 50 mg once daily (N = 191). Median PFS was 15.7 months for patients on enzalutamide versus 5.8 months for patients on bicalutamide [HR = 0.44 (95% CI: 0.34, 0.57), p < 0.0001]. Progression-free survival was defined as objective evidence of radiographic disease progression by

	second phase 2 study of enzalutamide vs bicalutamide. 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				independent central review, skeletal related events, initiation of new antineoplastic therapy or death by any cause, whichever occurred first. Consistent PFS benefit was observed across all pre-specified patient subgroups. Safety data presented are within the known safety profile of enzalutamide.
PSUSA/10095 /201508	Periodic Safety Update EU Single assessment - enzalutamide	17/03/2016	n/a		PRAC Recommendation - maintenance
II/0026	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	17/12/2015	12/12/2016	Annex II	
PSUSA/10095 /201502	Periodic Safety Update EU Single assessment - enzalutamide	24/09/2015	27/11/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10095/201502.
IB/0025	B.I.a.z - Change in manufacture of the AS - Other variation	12/10/2015	n/a		
II/0020/G	This was an application for a group of variations. Update of section 4.5 of the SmPC in order to update information on drug-drug interactions after analysis of studies 9785-CL-0405 and 9785-CL-0406. The	17/09/2015	27/11/2015	SmPC and PL	Following oral administration of the moderate CYP2C8 and strong CYP3A4 inducer rifampin (600 mg once daily) to healthy male subjects, the AUC of enzalutamide plus the active metabolite decreased by 37% while Cmax remained unchanged. No dose adjustment is necessary when Xtandi

	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 C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				is co-administered with inducers of CYP2C8 or CYP3A4. Enzalutamide (160 mg once daily) did not cause a clinically relevant change in the AUC or Cmax of caffeine (CYP1A2 substrate) or pioglitazone (CYP2C8 substrate). The AUC of pioglitazone increased by 20% while Cmax decreased by 18%. The AUC and Cmax of caffeine decreased by 11% and 4%, respectively. No dose adjustment is indicated when a CYP1A2 or CYP2C8 substrate is co-administered with Xtandi.
IB/0023	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/08/2015	n/a		
IA/0024/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	23/07/2015	n/a		
IA/0022/G	This was an application for a group of variations. 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.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to 10-fold	26/06/2015	n/a		

IB/0019/G	This was an application for a group of variations. 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.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.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	24/06/2015	n/a		
II/0015	Update of sections 4.2, 4.4 and 5.2 of the SmPC in order to update the safety and pharmacokinetic information in hepatic impairment after finalisation of the study 9785-CL-0404.	21/05/2015	22/06/2015	SmPC	No dose adjustment is necessary for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C, respectively). An increased drug half-life has however been observed in patients with severe hepatic

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				impairment.
PSUSA/10095 /201408	Periodic Safety Update EU Single assessment - enzalutamide	26/03/2015	27/05/2015		Please refer to Xtandi-EMEA/H/C/PSUSA/10095/201408 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation.
II/0018	Update of section 5.1 of the SmPC in order to update the Pharmacodynamic properties information regarding Overall Survival (OS) after analysis of data from the PREVAIL (MDV3100-03) study satisfying part of the Obligation to conduct post-authorisation measures as reported in the annex II. The annex II is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/04/2015	22/06/2015	SmPC and Annex II	At the pre-specified interim analysis for overall survival when 540 deaths were observed, treatment with enzalutamide demonstrated a statistically significant improvement in overall survival compared to treatment with placebo with a 29.4% reduction in risk of death [HR=0.706, (95% CI: 0.596; 0.837), p < 0.0001]. An updated survival analysis was conducted when 784 deaths were observed. Results from this analysis were consistent with those from the interim analysis (Table 2, Figure 1). At the updated analysis 52% of enzalutamide-treated and 81% of placebo-treated patients had received subsequent therapies for metastatic CRPC that may prolong overall survival.
II/0016	Update of sections 4.4 and 4.8 of the SmPC in order to add a warning and update the safety information on posterior reversible encephalopathy syndrome (PRES) following analysis of post-marketing case reports. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to correct typographical and formatting errors in the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	26/03/2015	27/05/2015	SmPC and PL	There have been rare reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving Xtandi. PRES is a rare, reversible, neurological disorder which can present with rapidly evolving symptoms including seizure, headache, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinuation of Xtandi in patients who develop PRES is recommended.

	data				
IB/0017	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	03/02/2015	n/a		
IB/0014	To introduce the changes requested by PRAC and CHMP in September 2014, to add the signals of QT interval prolongation due to long term use for medicinal products for androgen deprivation therapy. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	16/01/2015	27/05/2015	SmPC and PL	
IB/0012/G	This was an application for a group of variations. 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) B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	09/12/2014	27/05/2015	SmPC	
II/0008	Extension of indication for the treatment of adult men with metastatic castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated. As a consequence, section 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and the package leaflet have been updated accordingly. Annex II has also been updated	23/10/2014	28/11/2014	SmPC, Annex II and PL	Please refer to Scientific Discussion Xtandi-H-2639-II-08 AR.

	to include an obligation to conduct a post-authorisation measure. The MAH also propose to update the contact details of local representatives in the package leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IB/0011	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	25/09/2014	n/a		
II/0007/G	This was an application for a group of variations. Update of sections 4.4 and 4.5 of the SmPC further to the results of a study investigating the interaction with docetaxel. Section 4.5 of the SmPC is also updated further to results of a study of enzymes induced by Xtandi. Section 5.2 is updated further to the results of a study investigating the transport of the metabolite M2 by BCRP, of a study to assess protein binding displacement between Xtandi and other medicinal products, of two studies investigating the in vitro metabolism of 14C-M2, and of a pharmacokinetic study in Japanese patients. 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	25/09/2014	28/11/2014	SmPC	In a clinical study in patients with metastatic CRPC, Xtandi (160 mg once daily) had no clinically relevant effect on the pharmacokinetics of intravenously administered docetaxel (75 mg/m2 by infusion every 3 weeks). The AUC of docetaxel decreased by 12% [geometric mean ratio (GMR) =0.882 (90% CI: 0.767, 1.02)] while Cmax decreased by 4% [GMR = 0.963 (90% CI: 0.834, 1.11)]. Co-administration of enzalutamide has no clinically relevant effect on the pharmacokinetics of intravenous docetaxel; however, an increase in the occurrence of docetaxel-induced neutropenia cannot be excluded. Enzymes that may be induced by enzalutamide include CYP2B6 but not CYP1A2 and patients taking medicinal products that are substrates of CYP2B6 should be evaluated for possible loss of pharmacological effects (or increase in effects in cases where active metabolites are formed) during the first month of enzalutamide treatment, and dose adjustment should be considered as appropriate. Enzalutamide is 97% to 98% bound to plasma proteins,

	data 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 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				primarily albumin. The active metabolite is 95% bound to plasma proteins. There was no protein binding displacement between enzalutamide and other highly bound drugs (warfarin, ibuprofen and salicylic acid) in vitro. Enzalutamide is extensively metabolized. There are two major metabolites in human plasma: N desmethyl enzalutamide (active) and a carboxylic acid derivative (inactive). In vitro, N-desmethyl enzalutamide is metabolized to the carboxylic acid metabolite by carboxylesterase 1, which also plays a minor role in the metabolism of enzalutamide to the carboxylic acid metabolite. N desmethyl enzalutamide was not metabolized by CYPs in vitro. In vitro data indicate that N-desmethyl enzalutamide is not a substrate for P-gp or BCRP. Based on pharmacokinetic data from a study in Japanese patients with prostate cancer, there were no clinically relevant differences in exposure between Japanese and Caucasians. There are insufficient data to evaluate potential differences in the pharmacokinetics of enzalutamide in other races.
II/0006/G	This was an application for a group of variations. Update of section 5.3 of the Summary of Product Characteristics further to the results of embryo-foetal development studies in mice and rabbits and repeat dose toxicity studies in dogs. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/09/2014	28/11/2014	SmPC	Enzalutamide treatment of pregnant mice resulted in an increased incidence of embryo-fetal deaths and external and skeletal changes. Consistent with the pharmacological activity of enzalutamide, atrophy, aspermia/hypospermia and hypertrophy/hyperplasia in the reproductive system were note in dogs (39 weeks). In studies in mice (4 weeks) and dogs (39 weeks), changes in the reproductive organs associated with enzalutamide were decreases in organ weight with atrophy of the prostate and epididymis. Leydig cell hypertrophy and/or hyperplasia were observed in mice

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				(4 weeks) and (dogs 39 weeks).
IB/0010	To update section 4.8 with undesirable effects with unknown frequency in the section on musculoskeletal and connective tissue disorders of the SmPC and package leaflet following a recommendation by PRAC. In addition the presentation of the side effects in this section have been updated to the latest QRD template. Furthermore minor corrections to the FR annexes were implemented to bring it in line with the EN annexes. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/09/2014	28/11/2014	SmPC and PL	
PSUV/0009	Periodic Safety Update	10/07/2014	n/a		PRAC Recommendation - maintenance
IAIN/0005	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	10/03/2014	n/a		
IA/0004/G	This was an application for a group of variations. 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	18/12/2013	n/a		

	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 B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				
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 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	16/12/2013	n/a		
IAIN/0002/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV and/or QPPV contact details and/or back-up procedure C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of	20/09/2013	n/a		

	the PhV system				
IAIN/0001	C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	06/08/2013	n/a		