Xofigo

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
N/0054	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/07/2024		PL	
R/0049	Renewal of the marketing authorisation.	20/07/2023	15/09/2023	PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Xofigo in the approved indication remains favourable and

[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).

					therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0052	Submission of the final report from study 20702/DIRECT listed as a category 3 study in the RMP. This is a non-interventional drug utilisation study to investigate the risk of off-label use. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	31/08/2023	n/a		
IB/0051	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	04/05/2023	15/09/2023	Annex II	
IA/0050/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 A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	23/02/2023	n/a		
IB/0048	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	15/02/2023	n/a		

II/0047	B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP	19/01/2023	n/a		
SW/0045	Post Authorisation Safety Study results - EMEA/H/C/PSR/S/0034 – Variation	14/10/2021	13/12/2021	Annex II	The study results do not show an increase in the risk of death or cancer–specific death within the scope of the currently authorised therapeutic indication (third and later lines of therapy or in patients ineligible for any available systemic metastatic castration-resistant prostate cancer treatment). Therefore, in view of available data regarding the PASS final study report, the PRAC considered that removal of the condition of the marketing authorisation and respective changes to the Risk Management Plan were warranted.
PSUSA/10132 /202105	Periodic Safety Update EU Single assessment - radium-223 dichloride	02/12/2021	n/a		PRAC Recommendation - maintenance
II/0042/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.1.f - Change in the specification parameters and/or limits of the finished product - Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product	02/09/2021	n/a		
II/0041	B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting	02/09/2021	n/a		

	material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP				
IB/0043	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	25/05/2021	n/a		
PSUSA/10132 /202005	Periodic Safety Update EU Single assessment - radium-223 dichloride	26/11/2020	n/a		PRAC Recommendation - maintenance
IB/0039	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	24/04/2020	27/10/2020	Annex II and PL	
IA/0038/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 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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP -	04/12/2019	n/a		

	Replacement/addition of a site where batch control/testing takes place B.II.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised				
PSUSA/10132 /201905	Periodic Safety Update EU Single assessment - radium-223 dichloride	28/11/2019	n/a		PRAC Recommendation - maintenance
II/0037	B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products	31/10/2019	27/10/2020	SmPC and PL	
II/0034	B.II.d.1.f - Change in the specification parameters and/or limits of the finished product - Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product	17/01/2019	n/a		
PSUSA/10132 /201805	Periodic Safety Update EU Single assessment - radium-223 dichloride	29/11/2018	n/a		PRAC Recommendation - maintenance
IA/0035	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	01/10/2018	n/a		
A20/0028	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 30 November 2017 the opinion of the European Medicines Agency further to analyses of preliminary data of a clinical trial evaluating Xofigo in a patient	26/07/2018	28/09/2018	SmPC and PL	Please refer to the assessment report: Xofigo EMEA/H/A-20/1459/C/002653/0028

	population with asymptomatic or mildly symptomatic prostate cancer (ERA-223), found that the incidences of treatment emergent fractures and deaths were increased in the treatment arm (radium-223 dichloride plus abiraterone acetate and prednisone/prednisolone) compared to the control arm (placebo plus abiraterone acetate and prednisone/prednisolone). The CHMP was requested to assess the impact thereof on the benefit-risk balance of Xofigo and to give its recommendation whether the marketing authorisation of this product should be maintained, varied, suspended or revoked. As the request results from the evaluation of data resulting from pharmacovigilance activities, the CHMP opinion should be adopted on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee. The notification for the procedure is appended to this recommendation.				
IB/0032	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	19/09/2018	n/a		
R/0030	Renewal of the marketing authorisation.	26/04/2018	21/06/2018	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Xofigo in the approved indication remains favourable, but recommended that one additional five-year renewal be required based on the following pharmacovigilance grounds:

					• Results from an ad-hoc analysis of study 15396 (EudraCT 2013-003438-33) involving the use of Xofigo in combination with abiraterone and prednisone/prednisolone in patients with asymptomatic or mildly symptomatic metastatic CRPC indicated that there may be an increased incidence of fractures and deaths among patients receiving Xofigo in combination with abiraterone acetate and prednisone/prednisolone compared to patients receiving placebo in combination with abiraterone acetate and prednisone/prednisolone. • At its November 2017 plenary, PRAC agreed that a thorough evaluation of the issue should be within a procedure under Article 20 of Regulation (EC) 726/2004. This procedure has not concluded but may result in the introduction of specific risk minimisation measures or an obligation for the MAH to undertake a post-marketing study to gather further safety data that may impact on the benefit risk balance of the product. • At the March plenary meeting PRAC agreed that provisional routine risk minimisation measures in the form of updates to the product information would be necessary to minimise the risks of fractures and death associated with the use of radium-223 dichloride treatment initiated concurrently with abiraterone acetate and prednisone/prednisolone treatment. These changes include amendments to sections 4.3, 4.4, and 5.1 of the SmPC. The PRAC considered that radium-223 dichloride should be contraindicated in combination with abiraterone acetate and prednisone/prednisolone. Further warnings and precautions of use relating to the risks of fracture and death among patients receiving Xofigo in combination with abiraterone acetate and prednisone/prednisolone were also

					included together with important information that the safety and efficacy of combination with second generation androgen receptor antagonists (e.g. enzalutamide) have not been established.
II/0029	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/06/2018	n/a		
II/0031	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	12/04/2018	n/a		
II/0027	B.I.a.1.c - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions	30/11/2017	n/a		
PSUSA/10132 /201705	Periodic Safety Update EU Single assessment - radium-223 dichloride	30/11/2017	n/a		PRAC Recommendation - maintenance
PSUSA/10132 /201611	Periodic Safety Update EU Single assessment - radium-223 dichloride	22/06/2017	14/08/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10132/201611.
II/0025	Update of sections 4.2, 5.1, 5.2, and 11 of the SmPC based on the update of the Xofigo Company Core Data Sheet (CCDS) to version 5.0. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.0 and to introduce non safety related editorial changes to	22/06/2017	14/08/2017	SmPC, Annex II, Labelling and PL	5.1 Pharmacodynamic properties Pharmacodynamic effects Cardiac electrophysiology / QT prolongation No significant QTc prolonging effects were observed after intravenous injection of Xofigo in comparison with placebo in a subgroup of 29 patients in the phase III study (ALSYMPCA). Clinical efficacy and safety

	increase comprehensibility. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				The primary efficacy endpoint was overall survival. Main secondary endpoints included time to symptomatic skeletal events (SSE), time to progression of total alkaline phosphatase (ALP), time to progression of prostate specific antigen (PSA), response to total ALP and normalisation of total ALP. 5.2 Pharmacokinetic properties At 10 minutes post injection, activity was observed in the bone and in the intestine. At 4 hours post injection, the mean percentage of the radioactive dose present in bone and intestine was approximately 61% and 49% respectively.
II/0022/G	This was an application for a group of variations. B.II.b.1.d - Replacement or addition of a manufacturing site for the FP - Site which requires an initial or product specific inspection 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.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	21/04/2017	n/a		
T/0024	Transfer of Marketing Authorisation	10/03/2017	03/04/2017	SmPC, Labelling and PL	

PSUSA/10132 /201605	Periodic Safety Update EU Single assessment - radium-223 dichloride	01/12/2016	n/a		PRAC Recommendation - maintenance
IAIN/0021/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	25/10/2016	n/a		
II/0014/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	21/07/2016	n/a		

N/0019	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/06/2016	03/04/2017	Labelling and PL	
PSUSA/10132 /201511	Periodic Safety Update EU Single assessment - radium-223 dichloride	09/06/2016	n/a		PRAC Recommendation - maintenance
IAIN/0018/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.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	30/05/2016	03/04/2017	Annex II and PL	
II/0015	B.I.b.1.g - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Widening of the approved specs for starting mat./intermediates, which may have a significant effect on the quality of the AS and/or the FP	01/04/2016	n/a		
PSUSA/10132 /201505	Periodic Safety Update EU Single assessment - radium-223 dichloride	03/12/2015	n/a		PRAC Recommendation - maintenance
IB/0013	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	13/10/2015	n/a		

II/0011	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/07/2015	08/09/2015	SmPC, Labelling and PL	
PSUSA/10132 /201411	Periodic Safety Update EU Single assessment - radium-223 dichloride	11/06/2015	n/a		PRAC Recommendation - maintenance
IB/0010/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	29/04/2015	n/a		
IA/0008/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.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor	04/02/2015	n/a		

	changes to an approved test procedure 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.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
II/0007	Replacement of the stopper material of the container closure system of Xofigo solution for injection. B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products	22/01/2015	08/09/2015	SmPC and PL	
PSUV/0005	Periodic Safety Update	04/12/2014	n/a		PRAC Recommendation - maintenance
IAIN/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 A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	19/09/2014	08/09/2015	Annex II and PL	
IB/0004/G	This was an application for a group of variations.	28/08/2014	n/a		

	B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method 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				
PSUV/0002	Periodic Safety Update	13/06/2014	n/a		PRAC Recommendation - maintenance
N/0003	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/04/2014	08/09/2015	PL	
II/0001	To widen the limit for assay in the specification of the active substance. B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS	20/02/2014	n/a		