Inlyta

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
PSUSA/10022 /202201	Periodic Safety Update EU Single assessment - axitinib	29/09/2022	n/a		PRAC Recommendation - maintenance
IA/0032	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	20/08/2021	21/09/2022	SmPC and PL	

[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).

IA/0031	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	05/05/2021	n/a		
IA/0030	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	20/11/2020	n/a		
IB/0029	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	29/10/2020		SmPC and PL	
PSUSA/10022 /201901	Periodic Safety Update EU Single assessment - axitinib	19/09/2019	11/11/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10022/201901.
IAIN/0028	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	31/10/2019	09/12/2020	SmPC, Annex II, Labelling and PL	
IG/1124	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	11/09/2019	n/a		
IB/0025	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	22/05/2019	n/a		

PSUSA/10022 /201801	Periodic Safety Update EU Single assessment - axitinib	20/09/2018	22/11/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10022/201801.
T/0024	Transfer of Marketing Authorisation	11/07/2018	03/08/2018	SmPC, Labelling and PL	
PSUSA/10022 /201701	Periodic Safety Update EU Single assessment - axitinib	01/09/2017	n/a		PRAC Recommendation - maintenance
R/0021	Renewal of the marketing authorisation.	23/03/2017	22/05/2017	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 Inlyta in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10022 /201601	Periodic Safety Update EU Single assessment - axitinib	02/09/2016	n/a		PRAC Recommendation - maintenance
IAIN/0020	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	09/06/2016	22/05/2017	SmPC and PL	
IA/0018	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	20/04/2016	n/a		
IB/0017/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	04/04/2016	n/a		

	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.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.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.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
PSUSA/10022 /201501	Periodic Safety Update EU Single assessment - axitinib	10/09/2015	n/a		PRAC Recommendation - maintenance

N/0014	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/06/2015	11/05/2016	PL	
II/0013	Update of sections 4.4 and 4.8 of the SmPC and relevant section of the Package Leaflet following a safety update of the Core Data Sheet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/05/2015	11/05/2016	SmPC and PL	
IB/0012/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.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	27/03/2015	n/a		
II/0011	Submission of an update of the proposed research plan with an extensive summary of ongoing research for predictive anti-angiogenic biomarkers in advanced RCC published in the scientific literature in order to provide information on this matter. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/02/2015	n/a		

PSUSA/10022 /201407	Periodic Safety Update EU Single assessment - axitinib	12/02/2015	n/a		PRAC Recommendation - maintenance
PSUV/0009	Periodic Safety Update	11/09/2014	n/a		PRAC Recommendation - maintenance
II/0006	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/06/2014	n/a		
II/0008	Update of section 4.5 of the SmPC to delete the information on CYP1A2 induction by smoking further results of a population pharmacokinetic modelling analysis of the evaluation of the effect of smoking on axitinib pharmacokinetics. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/05/2014	07/11/2014	SmPC	An analysis on pooled pharmacokinetic data from a total 210 subject was performed. Among these, there were 83 (39.5 %) current smokers and 56 (26.7 %) ex-smokers. The analysis did not indicate any clinically significant effect of smoking on the pharmacokinetics of axitinib. Thus, based on the currently available evidence, the CHMP agreed that it is not justified to recommend any dose modifications for axinitib in patients who are smokers.
II/0007	Update of sections 4.4 and 4.8 of the SmPC in order to add "cardiac failure events" as a new adverse drug reaction reported with a frequency “common” following a routine review of the MAH's safety database. The Package Leaflet is proposed to be updated accordingly. The MAH also took the opportunity to make minor editorial changes to the SmPC and Package leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/05/2014	07/11/2014	SmPC and PL	In a controlled clinical study with axitinib (N = 359) for the treatment of patients with RCC, cardiac failure events were reported in 1.7 % patients receiving axitinib, including cardiac failure (0.6%), cardiopulmonary failure (0.6%), left ventricular dysfunction (0.3%), and right ventricular failure (0.3%). Grade 4 cardiac failure adverse reactions were reported in 0.6 % of patients receiving axitinib. Fatal cardiac failure was reported in 0.6 % of patients receiving axitinib. In monotherapy studies with axitinib (N = 672) for the treatment of patients with RCC, cardiac failure events (including cardiac failure, cardiac failure congestive,

					cardiopulmonary failure, left ventricular dysfunction, ejection fraction decreased, and right ventricular failure) were reported in 1.8% patients receiving axitinib. Grade 3/4 cardiac failure events were reported in 1.0% patients and fatal cardiac failure events were reported in 0.3% patients receiving axitinib. Signs or symptoms of cardiac failure should periodically be monitored throughout treatment with axitinib. Management of cardiac failure events may require temporary interruption or permanent discontinuation and/or dose reduction of axitinib therapy.
PSUV/0005	Periodic Safety Update	06/03/2014	n/a		PRAC Recommendation - maintenance
II/0003/G	This was an application for a group of variations. Update of section 4.8 of the SmPC in order to include glossodynia as an adverse reaction. In addition section 4.8 of the SmPC has been updated with the frequencies of the adverse drug reactions as it was requested by the CHMP further to the assessment of the PSUR 1. The MAH took also the opportunity to make minor changes in section 4.8 based on the post marketing experience. Finally the MAH made one minor change in section 4.2 of the SmPC. The Package Leaflet was updated accordingly. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the	24/10/2013	07/11/2014	SmPC and PL	Based on the post-marketing data and the known association of glossodynia to other VEGFR inhibitors, a causal relationship to axitinib is at least a reasonable possibility, and therefore section 4.8 of the SmPC was updated to include it. Following the CHMP recommendation further to the assessment of the PSUR 1, the frequencies of the adverse drug reactions (ADRs) in the section of 4.8 of the SmPC were updated to reflect the new safety data cut-off date (1 June 2012) and reported according to treatment emergent, all-causality frequency. The MAH took also the opportunity to consolidate the ADRs included under "Gastrointestinal perforation and fistula" in section 4.8 of the SmPC in order to improve the readability of the adverse drug reactions table and to align adverse drug reaction terms used in the Core Data Sheet (CDS) and SmPC, to add the ADR "hyperbilirubinaemina" and to delete the ADR "blood bilirubin increased".

	MAH C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				Finally, the MAH made a minor change in section 4.2 of the SmPC in order to provide a more balanced phrasing and clarify the optional nature of the dose titration.
X/0001	Annex I_2.(c) Change or addition of a new strength/potency	27/06/2013	26/08/2013	SmPC, Annex II, Labelling and PL	This line extension introduces two additional tablet strengths 3mg and 7 mg of axitinib in addition to the currently approved 1mg and 5 mg tablets. The proposed maximum clinical dose is 10 mg twice daily. The two additional strengths are intended to simplify dosing for patients who need dose modification up or down from the starting dose of 5 mg twice daily.
N/0004	The MAH applied to include the contact details for Croatia to the list of local representatives. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/07/2013	22/05/2017	PL	
IG/0235/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV	06/12/2012	n/a		C.I.z - To replace the Detailed Description of the Pharmacovigilance System (DDPS) with the Pharmacovigilance System Master File (PSMF).