Cyramza

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/0053	Update of sections 4.8 and 5.1 of the SmPC in order to update efficacy and safety data on paediatric patients following the outcome of Article 46 procedure EMEA/H/C/002829/P46/009 and based on results from study J1S-MC-JV02 (JV02). This is a randomized, open-label, phase 1/2 study evaluating	21/03/2024		SmPC, Labelling and PL	SmPC new text No new safety concerns were reported in the limited number of paediatric patients treated with ramucirumab in combination therapy in study J1S-MC-JV02. The efficacy and safety of ramucirumab in combination with gemcitabine and docetaxel compared to gemcitabine 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).

	ramucirumab in paediatric patients and young adults with relapsed, recurrent, or refractory synovial sarcoma. In addition, the MAH took the opportunity to implement editorial updates to the SmPC and the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				docetaxel alone was evaluated in J1S-MC-JV02 (JV02), a randomised, multicentre, global, Phase 2 study in 23 paediatric patients and young adults aged 36 months to 29 years with relapsed, recurrent, or progressive synovial sarcoma (SS). Randomization (2:1) was stratified by staging at relapse (metastatic disease versus locally advanced). The study was terminated without formal evaluation of the primary PFS endpoint since at the interim futility analysis, JV02 did not meet the pre-specified 60 % confidence in treatment superiority (PFS HR of less than 1 for SS). There was one partial response and no complete response in the experimental arm. No responses, complete or partial, were observed in the control arm.
IA/0052	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	16/06/2023	n/a		
II/0051	B.II.b.4.d - Change in the batch size (including batch size ranges) of the finished product - The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes	23/02/2023	n/a		
IA/0050	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	12/12/2022	26/01/2024	SmPC	
PSUSA/10323 /202204	Periodic Safety Update EU Single assessment - ramucirumab	01/12/2022	n/a		PRAC Recommendation - maintenance
IB/0049/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of	29/08/2022	n/a		

	the AS - Minor change in the manufacturing process of the AS 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				
II/0043	Update of section 4.4 and 4.8 of the SmPC in order to add a new warning on heart failure following a detailed cumulative review of post-marketing data. The Package Leaflet and Labelling are updated accordingly. In addition, the MAH took the opportunity to update the package leaflet to include hypothyroidism as a common side effect. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/06/2022	25/07/2022	SmPC, Labelling and PL	SmPC new text In pooled data from ramucirumab clinical trials, cardiac failure was reported at a numerically higher incidence in patients receiving ramucirumab in combination with a variety of chemotherapy regimens, or erlotinib, compared to chemotherapy or erlotinib alone. This increased incidence was not observed in patients receiving ramucirumab compared to placebo from single agent clinical trials. In the post-marketing setting, cardiac failure was observed for ramucirumab, mostly in combination with paclitaxel. Patients should be monitored for clinical signs and symptoms of cardiac failure during treatment, and suspension of treatment should be considered if clinical signs and symptoms of cardiac failure develop. See section 4.8. For more information, please refer to the Summary of Product Characteristics.
II/0047	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	10/03/2022	n/a		

IB/0046	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	22/02/2022	n/a		
II/0044	B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method	16/12/2021	n/a		
IA/0045	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	18/10/2021	n/a		
II/0041	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	02/09/2021	n/a		
IB/0042	C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation	21/08/2021	18/07/2022	SmPC and PL	
IA/0040	A.7 - Administrative change - Deletion of manufacturing sites	18/02/2021	n/a		
II/0039	Update of section 4.8 of the SmPC in order to add hypothyroidism to the list of adverse reactions with a	04/02/2021	18/07/2022	SmPC, Labelling and	

	frequency of common based on the updated reference safety information for ramucirumab. The Package Leaflet is also updated. In addition, minor updates are included to the list of local representatives in the product information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data			PL	
II/0038	Update of sections 4.4 and 4.8 of the SmPC in order to add posterior reversible encephalopathy syndrome (PRES) and dysphonia as a warning and as undesirable effect, respectively. The Labelling and Package Leaflet are updated accordingly. The RMP version 9.3 has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and to bring the PI in line with the latest QRD template. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/05/2020	18/07/2022	SmPC, Labelling and PL	Cases of posterior reversible encephalopathy syndrome (PRES), including fatal cases, have been rarely reported in patients receiving ramucirumab. PRES symptoms may include seizure, headache, nausea/vomiting, blindness, or altered consciousness, with or without associated hypertension. A diagnosis of PRES can be confirmed by brain imaging (e.g., magnetic resonance imaging). Discontinue ramucirumab in patients who experience PRES. The safety of reinitiating ramucirumab in patients who develop PRES and recover is not known. For more information, please refer to the Summary of Product Characteristics.
II/0033	Extension of indication for Cyramza to include in combination with erlotinib, the first-line treatment of adult patients with metastatic non-small cell lung cancer with activating epidermal growth factor receptor (EGFR) mutations; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the	12/12/2019	23/01/2020	SmPC and PL	Please refer to the Scientific Discussion Cyramza-H-C-2829-II-0033

	SmPC are updated. The package leaflet is updated accordingly. The RMP version 9.1 has also been agreed. The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
PSUSA/10323 /201904	Periodic Safety Update EU Single assessment - ramucirumab	31/10/2019	n/a		PRAC Recommendation - maintenance
IAIN/0037	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	30/10/2019	23/01/2020	SmPC and PL	
IA/0036	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	11/10/2019	n/a		
R/0031	Renewal of the marketing authorisation.	25/07/2019	26/09/2019	SmPC, Labelling and PL	
IB/0035	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	05/08/2019	n/a		

II/0027	Extension of indication to include Cyramza as monotherapy for the treatment of adult patients with hepatocellular carcinoma who have an alpha fetoprotein (AFP) of ≥ 400 ng/mL, after prior sorafenib therapy; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in accordance. The Package Leaflet is updated in accordance. RMP version 8.3 has been agreed. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	27/06/2019	01/08/2019	SmPC and PL	Please refer to the Scientific Discussion EMEA/H/C/002829/II/0027
IB/0034/G	This was an application for a group of variations. 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.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	16/07/2019	n/a		
II/0030	Update of section 4.8 of the SmPC in order to add haemangioma and thrombotic microangiopathy (TMA) as new adverse drug reactions as common and rare, respectively based on review of clinical trials, post-marketing cases and the published scientific literature. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation	04/04/2019	01/08/2019	SmPC and PL	ADRs of haemangioma and thrombotic microangiopathy were reported in ramucirumab clinical trials at a frequency of common (1.5%) and rare (0.03%), respectively, and through post-marketing reporting.

	holder (MAH) took the opportunity to update the list of local representatives for Estonia, Latvia and Lithuania in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0029	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	14/03/2019	01/08/2019	Annex II	
IB/0028	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	03/01/2019	n/a		
II/0023/G	This was an application for a group of variations. Submission of the final report from study Study I4T-MC-JVCZ (Randomized Phase 2 Trial Evaluating Alternative Ramucirumab Doses in Combination with Paclitaxel in Second-Line Metastatic or Locally Advanced, Unresectable Gastric or Gastroesophageal Junction Adenocarcinoma) and Study I4T-MC-JVDB (Randomized Phase 2 Trial Evaluating Pharmacokinetics and Safety of Four Ramucirumab Dosing Regimens in Second Line Gastric or Gastroesophageal Junction Adenocarcinoma); Annex	13/12/2018	01/08/2019	Annex II	

	II of the product information has been updated to remove study I4T-MC-JVDB. 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 C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
PSUSA/10323 /201804	Periodic Safety Update EU Single assessment - ramucirumab	31/10/2018	n/a		PRAC Recommendation - maintenance
II/0024/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.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.2.c.3 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing for a biol/immunol	20/09/2018	01/08/2019	Annex II and PL	

	product and any of the test methods is a biol/immunol/immunochemical method				
II/0025	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	13/09/2018	n/a		
II/0022	B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product	03/05/2018	n/a		
IG/0898	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	12/02/2018	20/09/2018	Annex II	
PSUSA/10323 /201704	Periodic Safety Update EU Single assessment - ramucirumab	30/11/2017	n/a		PRAC Recommendation - maintenance
IB/0020	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	27/09/2017	20/09/2018	Annex II	
N/0018	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/05/2017	20/09/2018	Labelling	
PSUSA/10323 /201610	Periodic Safety Update EU Single assessment - ramucirumab	05/05/2017	n/a		PRAC Recommendation - maintenance

PSUSA/10323 /201604	Periodic Safety Update EU Single assessment - ramucirumab	01/12/2016	n/a		PRAC Recommendation - maintenance
IB/0016	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	28/10/2016	n/a		
II/0015/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.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 B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	15/09/2016	n/a		
IA/0013/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.7 - Administrative change - Deletion of	01/06/2016	n/a		

	manufacturing sites				
II/0012/G	This was an application for a group of variations. 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) B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS	26/05/2016	n/a		
PSUSA/10323 /201510	Periodic Safety Update EU Single assessment - ramucirumab	13/05/2016	n/a		PRAC Recommendation - maintenance
IG/0662	A.1 - Administrative change - Change in the name and/or address of the MAH	23/02/2016	17/02/2017	SmPC, Labelling and PL	
II/0004	Extension of Indication to include a new indication for Cyramza, in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil), for the treatment of adult patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin and a fluoropyrimidine; as a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in	17/12/2015	25/01/2016	SmPC, Annex II and PL	Please refer to the published Assessment Report Cyramza H-2829-II-04-AR.

	accordance. Furthermore, Annex II has been updated to include an obligation for the MAH to conduct a Post Authorisation Efficacy Study (PAES). In addition, the Marketing authorisation holder (MAH) took the opportunity to correct minor editorial mistakes and to align Annex II to the QRD version 9.1. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0003	Extension of Indication to include a new indication for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer with progression after platinum-based chemotherapy for CYRAMZA; as a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, one minor typographical error was corrected in section 4.2 of the SmPC. Version 6 of the Risk Management Plan was agreed. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	17/12/2015	25/01/2016	SmPC and PL	Please refer to the published Assessment Report Cyramza H-2829-II-03-AR.
PSUSA/10323 /201504	Periodic Safety Update EU Single assessment - ramucirumab	06/11/2015	n/a		PRAC Recommendation - maintenance
IB/0009/G	This was an application for a group of variations.	06/10/2015	n/a		

	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.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				
II/0002/G	This was an application for a group of variations. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.a.3.c - Change in batch size (including batch size ranges) of AS or intermediate - The change requires assessment of the comparability of a biological/immunological AS B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method	24/09/2015	25/01/2016	Annex II	

IA/0008	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	16/09/2015	25/01/2016	SmPC	
IB/0006/G	This was an application for a group of variations. 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.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method	13/07/2015	n/a		
IB/0005/G	This was an application for a group of variations. B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	29/05/2015	n/a		
IAIN/0001	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 -	19/01/2015	25/01/2016	Annex II and PL	

	Not including batch control/testing				