Lorviqua

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/10760 /202309	Periodic Safety Update EU Single assessment - lorlatinib	11/04/2024	n/a		PRAC Recommendation - maintenance
R/0031	Renewal of the marketing authorisation.	25/01/2024	05/04/2024	SmPC and Annex II	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the

[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).

					opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Lorviqua, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
PSUSA/10760 /202303	Periodic Safety Update EU Single assessment - lorlatinib	09/11/2023	09/01/2024	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10760/202303.
IA/0032/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 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	08/11/2023	n/a		
IA/0030	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	08/11/2023	n/a		
IA/0029/G	This was an application for a group of variations.	16/08/2023	n/a		

	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				
IA/0028	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	24/07/2023	n/a		
PSUSA/10760 /202209	Periodic Safety Update EU Single assessment - lorlatinib	14/04/2023	n/a		PRAC Recommendation - maintenance
R/0025	Renewal of the marketing authorisation.	26/01/2023	04/04/2023	SmPC and Annex II	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Lorviqua, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.

PSUSA/10760 /202203	Periodic Safety Update EU Single assessment - lorlatinib	27/10/2022	n/a		PRAC Recommendation - maintenance
IA/0024	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	21/09/2022	n/a		
II/0022	Submission of an updated RMP version 5.0 to revise plans for conduct of hepatic impairment studies. The RMP is updated to reflect the hepatic impairment study B7461009 "A Phase 1 Study to Evaluate the Effect of Hepatic Impairment on the Pharmacokinetics and Safety of Lorlatinib in Advanced Cancer Patients" termination and to include new hepatic impairment study B7461040 "A Phase 1, Open-label, Single-dose, Parallel-group Study to Evaluate The Plasma Pharmacokinetics and Safety of Lorlatinib in Participants with Moderate and Severe Hepatic Impairment Relative to Participants with Normal Hepatic Function". 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	15/09/2022	n/a		
IB/0021	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	17/05/2022	n/a		

	data				
PSUSA/10760 /202109	Periodic Safety Update EU Single assessment - lorlatinib	07/04/2022	n/a		PRAC Recommendation - maintenance
R/0019	Renewal of the marketing authorisation.	27/01/2022	04/04/2022	SmPC, Labelling and PL	The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Lorviqua, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion. The MAH did not request the renewal of the following presentations for Lorviqua within this renewal procedure: EU/1/19/1355/001 (25 mg film-coated tablet; 120 tablets).
II/0015	Extension of indication to include the treatment of adult patients with anaplastic lymphoma kinase (ALK)-positive advanced non-small cell lung cancer (NSCLC) previously not treated with an ALK inhibitor based on results from the phase III randomised CROWN (1006) study listed as a specific obligation (SOB) in the Annex II; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package leaflet is updated accordingly. Version 4.1 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to include minor editorial changes in the PI.	16/12/2021	27/01/2022	SmPC, Annex II and PL	Please refer to Scientific Discussion 'Lorviqua-H-C-004646-II-0015'.

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
PSUSA/10760 /202103	Periodic Safety Update EU Single assessment - lorlatinib	28/10/2021	n/a		PRAC Recommendation - maintenance
N/0018	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/10/2021	27/01/2022	PL	
II/0013	Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to include hypertension and hyperglycaemia as new adverse drug reactions (ADRs) with frequency common and very common respectively together with recommended dose modifications and warnings, based on data from Phase 3 study B7461006, comparing lorlatinib versus crizotinib for the first line treatment of advanced ALK-positive NSCLC. The Package Leaflet is updated accordingly. The RMP version 2.1 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/06/2021	28/07/2021	SmPC and PL	Section 4.4 of the SmPC was amended to include the following two new warnings on hypertension and hyperglycaemia. Hypertension has been reported in patients receiving lorlatinib. Blood pressure should be controlled prior to initiation of lorlatinib. Blood pressure should be monitored after 2 weeks and at least monthly thereafter during treatment with lorlatinib. Lorlatinib should be withheld and resumed at a reduced dose or permanently discontinued based on severity. Hyperglycaemia has occurred in patients receiving lorlatinib. Fasting serum glucose should be assessed prior to initiation of lorlatinib and monitored periodically thereafter according to national guidelines. Lorlatinib should be withheld and resumed at a reduced dose or permanently discontinued based on severity. Section 4.2 and 4.8 of the SmPC were also updated to reflect the information regarding hypertension and hyperglycaemia in the recommended lorlatinib dose modifications and adverse reactions, respectively. For more information, please refer to the Summary of

					Product Characteristics.
IB/0016	B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)	07/06/2021	n/a		
PSUSA/10760 /202009	Periodic Safety Update EU Single assessment - lorlatinib	09/04/2021	n/a		PRAC Recommendation - maintenance
R/0011	Renewal of the marketing authorisation.	28/01/2021	31/03/2021		
II/0009/G	This was an application for a group of variations. Update of sections 4.2 and 5.2 of the SmPC in order to change the posology recommendations in patients with severe renal impairment based on the results from Study B7461010 (a phase 1, single dose open-label study to evaluate the pharmacokinetics of lorlatinib in subjects with impaired renal function). The package leaflet has been updated accordingly. Update of sections 4.4 and 4.5 of the SmPC in order to include information regarding drug drug interaction with moderate CYP3A4/5 inducers based on study B7461026 (Phase 1, open-label, fixed sequence, 2-period study to investigate the effect of multiple doses of modafinil on the pharmacokinetics of single dose lorlatinib in healthy participants). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/01/2021	09/03/2021	SmPC and PL	The results of study B7461010 investigating the effect of renal impairment on the standard pharmacokinetics (PK) of a single oral dose of lorlatinib 100 mg in participants with normal renal function and varying degrees of renal impairment showed that the exposure (AUCinf) to lorlatinib increased approximately 4%, 19% and 41% for the mild, moderate and severe renal impairment groups, respectively. No starting dose adjustments are recommended for patients with mild or moderate renal impairment. A reduced dose of lorlatinib is recommended in patients with severe renal impairment (absolute eGFR < 30 mL/min), e.g. a once daily starting dose of 75 mg taken orally. The results of study B7461026 showed a decrease in lorlatinib exposure in healthy adult participants under fasting conditions when administered following multiple doses of modafinil, a moderate CYP3A4 inducer compared with lorlatinib given alone. The adjusted geometric mean for AUCinf and Cmax values of lorlatinib decreased approximately by 23% and 22%, respectively, in the presence of modafinil however no clinically meaningful

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				changes in liver function tests were seen. Concomitant use of modafinil did not have a clinically meaningful effect on lorlatinib pharmacokinetics. For more information, please refer to the Summary of Product Characteristics.
II/0008	Update of sections 4.2, 4.4 and 4.8 of the SmPC to replace the term "Hallucinations" with the new term "Psychotic effects" and to include the new term of "mental status changes" as adverse drug reactions (ADRs) further to the cumulative review of the data available through Clinical Databases and Safety Database. The package leaflet has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/11/2020	17/12/2020	SmPC and PL	Further to a review of the MAH clinical and safety databases for all reported cases including psychotic effects and changes in cognitive function, mood, mental status or speech, the term "Psychotic effects" was selected to be the cluster term for these AEs to be consistent with other CNS effects (cluster terms: Cognitive effects, Mood effects, and Speech effects). In addition, the cluster term "Psychotic effects" includes all AEs that are components of the cluster term "Hallucinations." Therefore, the cluster term "Hallucinations" is replaced with the cluster term "Psychotic effects" in the SmPC. In addition, a new ADR of "mental status changes" have been added to the SmPC section 4.8 with a "common" frequency. For more information, please refer to the Summary of Product Characteristics.
IA/0014	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	09/12/2020	n/a		
N/0010	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/11/2020	09/03/2021	PL	
PSUSA/10760 /202003	Periodic Safety Update EU Single assessment - lorlatinib	29/10/2020	n/a		PRAC Recommendation - maintenance

PSUSA/10760 /201909	Periodic Safety Update EU Single assessment - lorlatinib	17/04/2020	n/a		PRAC Recommendation - maintenance
R/0004	Renewal of the marketing authorisation.	30/01/2020	03/04/2020		
II/0002	Update of sections 4.5 and 5.2 of the SmPC in order to further reflect the induction potential of lorlatinib on CYP2C9, P-gp, CYP2B6 and UGT1A1 substrates based on the results from the drug-drug interaction sub-study of B7461001. Furthermore, the Marketing authorisation holder (MAH) corrected information regarding ADRs in section 4.8 of the SmPC and added clarification regarding linearity/non-linearity of lorlatinib PK in section 5.2 of the SmPC. In addition, the MAH took the opportunity to 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	02/04/2020	17/12/2020	SmPC, Annex II and PL	As part of a sub-study of Study B7461001, single oral doses of different probes (100 mg bupropion for CYP2B6, 500 mg tolbutamide for CYP2C9, 500 mg acetaminophen for UGT, and 60 mg fexofenadine for P-gp) were administered alone and then in combination with repeated dosing of lorlatinib (100 mg once daily). On the basis of the results of this study, lorlatinib can be considered as a weak inducer of CYP2B6, CYP2C9 and UGT. However, patients should be monitored in case of concomitant treatment with medicinal products with narrow therapeutic indices metabolised by CYP2C9 or UGT. In addition, lorlatinib has been shown to be a moderate inducer of P-gp and medicinal products that are P- gp substrates with narrow therapeutic indices should be used with caution in combination with lorlatinib.
IB/0003	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)	04/12/2019	03/04/2020	SmPC	
IB/0001	B.II.e.5.z - Change in pack size of the finished product - Other variation	01/08/2019	03/04/2020	SmPC, Labelling and PL	