EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

VITRAKVI

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/10799 /202405	Periodic Safety Update EU Single assessment - larotrectinib	16/01/2025	n/a		PRAC Recommendation - maintenance
N/0038	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/08/2024	18/07/2025	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/0037	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	23/07/2024	n/a		
R/0035	Renewal of the marketing authorisation.	30/05/2024	22/07/2024	SmPC	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 VITRAKVI, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion. Sections 4.8 and 5.1 of the SmPC are updated to reflect the new safety and efficacy data.
II/0036	Submission of an updated RMP version 2.1 in order to adjust the sample size for the non-interventional PASS ON-TRK as well as to update epidemiological, clinical trial and post-marketing data. 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	11/07/2024	n/a		
PSUSA/10799/202311	Periodic Safety Update EU Single assessment - larotrectinib	13/06/2024	n/a		PRAC Recommendation - maintenance
PSUSA/10799/202305	Periodic Safety Update EU Single assessment - larotrectinib	11/01/2024	n/a		PRAC Recommendation - maintenance

II/0030	Update of sections 4.2, 4.4, 4.5, 4.8, and 5.1 of the SmPC in order to update the efficacy data and the list of adverse drug reactions (ADRs) based on interim results from studies 20289 and 20290. In addition, the MAH revised the posology recommendations in patients with liver function abnormalities and amended an existing warning on hepatotoxicity, updated information on drug-drug interaction regarding the effects of CYP3A inhibitors and inducers and P-gp inducers. The 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	20/07/2023	16/08/2023	SmPC, Annex II and PL	Based on an extended follow-up and inclusion of additional patients in the pivotal trials (20289 and 20290) for Vitrakvi, the efficacy and safety data has been updated in its SmPC (new data cut off 20 July 2022). In the updated efficacy analysis, the overall rate response (ORR) of larotrectinib in solid tumours (N=313) is 61%, consistent with what was previously reported (N=225; ORR 65%). The subset of patients with primary CNS tumours now consists of 41 patients. Section 4.8 of the SmPC has been updated based on data from the new data cut off. Among patients exposed to larotrectinib (N=418), eight patients fulfilled the criteria for drug-induced liver injury (DILI). As a consequence, the term ‘liver injury’ has been added as an ADR in section 4.8 of the SmPC. The warning on ‘transaminase elevations’ in section 4.4 of the SmPC was revised to use the term ‘hepatotoxicity’ in order to reflect more precisely the nature of the reported cases. In addition, section 4.2 of the SmPC has been updated to remind physicians to frequently monitor liver function of patients after observing abnormalities in liver function tests, and provide them with guidance on the management of dose reductions and dose interruptions.
R/0031	Renewal of the marketing authorisation.	25/05/2023	07/07/2023	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 VITRAKVI, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.

PSUSA/10799 /202211	Periodic Safety Update EU Single assessment - larotrectinib	06/07/2023	n/a		PRAC Recommendation - maintenance
IB/0032	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	06/06/2023	n/a		
IA/0029	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	07/03/2023	n/a		
PSUSA/10799 /202205	Periodic Safety Update EU Single assessment - larotrectinib	12/01/2023	n/a		PRAC Recommendation - maintenance
IB/0027/G	This was an application for a group of variations. B.II.e.1.z - Change in immediate packaging of the finished product - Other variation B.II.a.3.z - Changes in the composition (excipients) of the finished product - Other variation B.II.e.1.z - Change in immediate packaging of the finished product - Other variation B.II.a.3.z - Changes in the composition (excipients) of the finished product - Other variation B.II.a.3.z - Changes in the composition (excipients) of the finished product - Other variation	20/09/2022	07/07/2023	SmPC and PL	
R/0024	Renewal of the marketing authorisation.	23/06/2022	25/08/2022		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 VITRAKVI, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion
IB/0025	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	14/07/2022	n/a		
PSUSA/10799/202111	Periodic Safety Update EU Single assessment - larotrectinib	10/06/2022	n/a		PRAC Recommendation - maintenance
II/0021	Update of section 5.2 of the SmPC in order to reflect the outcome of an updated analysis of the population pharmacokinetic (PopPk) model based on additional PK sampling in patients aged 1 month to 6 years from study LOXO-TRK-15003 (SCOUT) imposed as a specific obligation (SOB). The MAH is also proposing to delete this SOB from Annex II. The MAH took the opportunity of this variation to introduce corrections to section 4.8 of the SmPC and to Annex II. In addition the MAH corrected the name of a local representative in the PL. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/06/2022	25/08/2022	SmPC and Annex II	The SmPC was updated to reflect the fact that adverse reactions of Grade 3 or 4 in severity were observed more frequently in patients < 6 years of age. They were reported in 67% of patients from birth to < 3 months and in 44% of patients ≥ 3 months to < 6 years. Also decreased neutrophil count has been reported to have led to study drug discontinuation, dose modification and dose interruption (see section 4.8 of the SmPC). In addition, the section 5.2 of the SmPC was updated to provide further information reflecting that exposure (Cmax and AUC on day 1) in paediatric patients at the recommended dose of 100 mg/m2 with a maximum of 100 mg BID was higher that in adults given the recommended dose of 100 mg BID. For more information, please refer to the Summary of Product Characteristics.
IB/0022/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)	08/02/2022	25/08/2022	SmPC	

	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)				
PSUSA/10799 /202105	Periodic Safety Update EU Single assessment - larotrectinib	13/01/2022	n/a		PRAC Recommendation - maintenance
II/0017	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	11/11/2021	25/08/2022	SmPC and PL	
IA/0020/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.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	09/09/2021	n/a		
IB/0019	B.I.e.5.b - Implementation of changes foreseen in an approved change management protocol - Requires further supportive data	31/08/2021	n/a		
R/0014	Renewal of the marketing authorisation.	24/06/2021	18/08/2021	SmPC	
IB/0016	B.I.e.5.b - Implementation of changes foreseen in an approved change management protocol - Requires further supportive data	29/06/2021	n/a		

PSUSA/10799/202011	Periodic Safety Update EU Single assessment - larotrectinib	10/06/2021	n/a		PRAC Recommendation - maintenance
IB/0015/G	This was an application for a group of variations. A.6 - Administrative change - Change in ATC Code/ATC Vet Code 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)	16/04/2021	18/08/2021	SmPC and Annex II	
IA/0013	A.7 - Administrative change - Deletion of manufacturing sites	05/03/2021	n/a		
II/0010/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites B.II.a.3.b.2 - Changes in the composition (excipients) of the finished product - Other excipients - Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the product 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.3.b - Change in the manufacturing process of the finished or intermediate product - Substantial	28/01/2021	18/08/2021	SmPC, Labelling and PL	

	changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range				
PSUSA/10799/202005	Periodic Safety Update EU Single assessment - larotrectinib	14/01/2021	n/a		PRAC Recommendation - maintenance
IB/0011/G	This was an application for a group of variations. B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion	17/12/2020	n/a		

	of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information 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.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products				
R/0006	Renewal of the marketing authorisation.	25/06/2020	25/08/2020	SmPC 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 VITRAKVI, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion. Sections 4.8 and 5.1 of the SmPC have been updated to reflect the new pooled efficacy and safety data from the 188 patients with solid tumours (including primary CNS tumours) representing the pivotal population at the cut-off date of 15 July 2019.
IAIN/0008	B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in imprints, bossing or other markings	21/08/2020	18/08/2021	SmPC and PL	
II/0001	Update of section 4.5 of the SmPC in order to reflect the results of study PH-40955 investigating the inductive potential of Larotrectinib on the expression of cytochrome P450 (CYP) enzymes showing that larotrectinib is a weak inducer of PXR regulated enzymes. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/06/2020	25/08/2020	SmPC and PL	The SmPC section 4.5 of the SmPC has been updated to reflect that larotrectinib is a weak inducer of PXR regulated enzymes based on the results of study PH-40955 investigating the inductive potential of Larotrectinib on the expression of cytochrome P450 (CYP) enzymes
IB/0007	B.I.e.4.b - Changes to an approved change management protocol - Minor changes that do not change the strategy defined in the protocol	15/06/2020	n/a		
PSUSA/10799	Periodic Safety Update EU Single assessment -	11/06/2020	n/a		PRAC Recommendation - maintenance

/201911	larotrectinib				
IB/0004	B.I.e.4.b - Changes to an approved change management protocol - Minor changes that do not change the strategy defined in the protocol	20/03/2020	n/a		
IA/0005/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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	18/03/2020	n/a		
IB/0002	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	16/01/2020	n/a		