LUMYKRAS

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
R/0018	Renewal of the marketing authorisation.	19/09/2024	14/11/2024		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

[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).

					renewal of the conditional MA for LUMYKRAS, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
II/0010/G	This was an application for a group of variations. Update of sections 4.2, 4.4, 4.5, 4.8 and 5.2 of the SmPC in order to update safety and efficacy information based on results from study 20190009 (CodeBreaK 200) listed as a specific obligation in the Annex II, and on results from study 20170543 (CodeBreak 100) Phase 2 Part B. Study 20190009 is a Phase 3 Multicenter, Randomized, Open Label, Active-controlled, Study of sotorasib Versus Docetaxel for the Treatment of Previously Treated Locally Advanced and Unresectable or Metastatic NSCLC Subjects With Mutated KRAS p.G12C; while study 20170543 is a Phase 1/2, Open-label Study Evaluating the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of sotorasib monotherapy in Subjects With Advanced Solid Tumors With KRAS p.G12C Mutation and sotorasib Combination Therapy in Subjects With Advanced NSCLC With KRAS p.G12C Mutation. The Package Leaflet is updated accordingly. The RMP version 3.0 is agreed. In addition, Annex II of the SmPC has been updated to reflect the replacement of the existing SOB (Codebreak 200) by the newly agreed SOB (Codebreak 202). C.I.4 - Change(s) in the SPC, Labelling or PL due to	19/09/2024	21/10/2024	SmPC, Annex II and PL	SmPC new text: Results of the Codebreak 200 trial, a Phase 3 multicenter, randomized, open Label, active-controlled study comapring sotorasib versus docetaxel for the treatment of previously treated locally advanced and unresectable or metastatic NSCLC subjects with mutated KRAS p.G12C have been reflected in section 4.2, 4.4, 4.5 and 4.8 of the SmPC. In particular, further information on the existing warnings for hepatotoxicity and interstitial lung disease/pneumonitis have been included in section 4.4. Frequencies of adverse reactions (ADRs) have been adjusted, and hepatitis, renal impairment, renal failure, chronic kidney disease, acute kidney injury, decrease appetite and hypokalameia have been included as new ADR in section 4.8. Finally, section 4.5 has been updated to add amlodipine and manidipine to the list of CYP3A4 substrates with narrow therapeutic indices. For more information, please refer to the Summary of Product Characteristics.

	new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10970 /202311	Periodic Safety Update EU Single assessment - sotorasib	13/06/2024	n/a		PRAC Recommendation - maintenance
X/0009	Annex I_2.(c) Change or addition of a new strength/potency	21/03/2024	16/05/2024	SmPC, Labelling and PL	
IB/0015/G	This was an application for a group of variations. B.I.e.5.b - Implementation of changes foreseen in an approved change management protocol - Requires further supportive data B.I.e.5.b - Implementation of changes foreseen in an approved change management protocol - Requires further supportive data B.I.e.5.b - Implementation of changes foreseen in an approved change management protocol - Requires further supportive data B.I.e.5.b - Implementation of changes foreseen in an approved change management protocol - Requires further supportive data B.I.e.5.b - Implementation of changes foreseen in an approved change management protocol - Requires further supportive data	18/03/2024	n/a		
IB/0016	B.II.f.1.b.1 - Stability of FP - Extension of the shelf	12/02/2024	16/05/2024	SmPC	

	life of the finished product - As packaged for sale (supported by real time data)				
PSUSA/10970 /202305	Periodic Safety Update EU Single assessment - sotorasib	11/01/2024	n/a		PRAC Recommendation - maintenance
II/0007	Update of sections 4.2, 4.4 and 5.2 of the SmPC in order to update recommendations for patients with moderate to severe hepatic impairment following final results from study 20200362 listed as a category 3 PASS study in the EU RMP; this is a Phase I clinical study to evaluate the pharmacokinetics (PK) of a single oral dose of sotorasib administered in subjects with moderate or severe hepatic impairment compared with subjects who have normal hepatic function. The EU RMP version 1.3 has also been agreed. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.3. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	11/01/2024	16/05/2024	SmPC	SmPC new text Further to the results of study 20200362, it is concluded in section 4.2 and 4.4 that Lumykras is not recommended for use in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment and that there is currently no data on the clinical safety and efficacy of multiple doses of sotorasib when administered to patients with moderate and severe hepatic impairment. Furthermore, it was clarified in section 5.2 that compared to subjects with normal hepatic function after a single oral dose is administered (960 mg), the mean systemic exposure AUCinf of Lumykras decreased by 25.4% in subjects with moderate impairment and increased by 3.6% in subjects with severe hepatic impairment. The unbound AUCinf of Lumykras increased by 1.8-fold in subjects with moderate hepatic impairment and by 6-fold in patients with severe hepatic impairment.
R/0012	Renewal of the marketing authorisation.	14/09/2023	20/11/2023		
II/0011	Update of sections 4.2 and 4.5 of the SmPC in order to update information regarding the co-administration of sotorasib with acid reducing agents, based on the results from study 20220024; this is a phase 1, single-center, open-label drug-drug interaction study to evaluate the impact of	14/09/2023	19/10/2023	SmPC and PL	Further to the results of a drug-drug interaction study, the recommendations on co-administering sotorasib with acid-reducing agents, such as PPIs or H2 receptor antagonists, in the SmPC (sections 4.2 and 4.5) have changed. Under fasted conditions, co administration of repeat doses of omeprazole with a single dose of 960 mg sotorasib and

	omeprazole, a proton pump inhibitor, on the pharmacokinetics of sotorasib co-administered with an acidic beverage in healthy volunteers. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				240 mL of an acidic beverage (non-diet cola) decreased sotorasib Cmax by 32% and AUC by 23%. The clinical relevance of the decreased sotorasib exposure when co-administered with omeprazole and cola is unclear and efficacy might be reduced. If co-administration of LUMYKRAS with an acid-reducing agent (such as a PPI or an H2 receptor antagonist) is required, LUMYKRAS should be taken with an acidic beverage (such as cola). Alternatively, LUMYKRAS should be taken 4 hours before or 10 hours after administration of a local antacid. For more information, please refer to the Summary of Product Characteristics.
IA/0014	B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised	20/09/2023	n/a		
PSUSA/10970 /202211	Periodic Safety Update EU Single assessment - sotorasib	06/07/2023	n/a		PRAC Recommendation - maintenance
PSUSA/10970 /202205	Periodic Safety Update EU Single assessment - sotorasib	12/01/2023	n/a		PRAC Recommendation - maintenance
IAIN/0006	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	22/11/2022	n/a		

R/0002	Renewal of the marketing authorisation.	15/09/2022	21/11/2022		
II/0004	Update of section 4.5 of the SmPC based on the results of Study 2020042, a phase 1 clinical drug interaction study undertaken to assess the effect of concomitant sotorasib administration on the systemic exposure of breast cancer resistance protein (BCRP) transporter substrates. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in 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	15/09/2022	21/11/2022	SmPC and PL	Further to the results of study 20200426, it is concluded that Lumykras is a weak BCRP inhibitor. Co-administration of Lumykras with a BCRP substrate led to an increase in the plasma concentrations of the BCRP substrate, which may increase the effect of the substrate. Co-administration of Lumykras with rosuvastatin (a BCRP substrate) increased the rosuvastatin Cmax by 70% and AUC by 34%. When Lumykras is co-administered with a BCRP substrate, including but not limited to lapatinib, methotrexate, mitoxantrone, rosuvastatin and topotecan, patients should be monitored for adverse reactions of the BCRP substrate and reduce the BCRP substrate dose in accordance with its current summary of product characteristics. For more information, please refer to the Summary of Product Characteristics.
II/0003	Update of section 4.2 of the SmPC based on results from the enteral feeding tube in vitro study (RPT-574024), undertaken to assess the feasibility of administration of sotorasib 120 mg film-coated tablets through an enteral feeding tube. The Package Leaflet was updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/09/2022	21/11/2022	SmPC and PL	The SmPC section 4.2 has been updated as follows: In patients who have difficulty swallowing solids and if administration through a nasogastric (NG) tube or percutaneous endoscopic gastrostomy (PEG) tube is required, patients should disperse the 120 mg tablets. The dispersed suspension and rinse should be administered as per the NG or PEG tube manufacturer's instructions with appropriate water flushes within 2 hours of preparation, stored at room temperature. The PL has been updated accordingly
IA/0001	B.I.a.1.i - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS -	16/03/2022	n/a		

	Introduction of a new site of micronisation				