Retsevmo

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/0021	Extension of indication to include the treatment of adults and adolescents 12 years and older with advanced RET fusion-positive thyroid cancer in the first-line setting for RETSEVMO based on interim data from studies LIBRETTO-001 (LOXO-RET-17001) and LIBRETTO-121; LIBRETTO-001 is an open-label,	25/01/2024	29/02/2024	SmPC and PL	Please refer to Scientific Discussion Retsevmo-H-C-005357-II-0021

[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).

	multicentre, global Phase 1/2 study of selpercatinib in patients with RET-altered advanced solid tumors. LIBRETTO-121 is a Phase 1/2 study of selpercatinib in paediatric patients with advanced RET-altered solid or primary central nervous system tumours. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 5.3 of the RMP 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				
R/0026	Renewal of the marketing authorisation.	12/10/2023	05/01/2024	SmPC, Annex II 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 Retsevmo, 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.
PSUSA/10917 /202305	Periodic Safety Update EU Single assessment - selpercatinib	30/11/2023	n/a		PRAC Recommendation - maintenance
IA/0027/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new/updated or	06/10/2023	n/a		

	deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting				

	material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer				
PSUSA/10917 /202211	Periodic Safety Update EU Single assessment - selpercatinib	22/06/2023	16/08/2023	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10917/202211.
II/0016	Update of section 4.8 of the SmPC in order to add chylothorax and chylous ascites to the list of adverse drug reactions (ADRs) with a "common" frequency based on a review of adverse events. In addition, the MAH took the opportunity of this variation to update the dose modification guidance for "haemorrhagic events" and 'other adverse reactions' in section 4.2 of the SmPC to reflect the available data. 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	25/05/2023	26/06/2023	SmPC and PL	For more information, please refer to the Summary of Product Characteristics.
II/0023	Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to introduce a new dose modification regimen in the event of 'interstitial lung disease (ILD)/pneumonitis' and to introduce it as a new warning and add it to the list of adverse drug reactions (ADRs) with frequency common, based on	23/02/2023	24/03/2023	SmPC and PL	Severe, life-threatening, or fatal cases of ILD/pneumonitis have been reported in patients treated with selpercatinib. Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis. In any patient who presents with acute or worsening of respiratory symptoms which may be indicative of ILD (e.g., dyspnoea, cough, and

	an internal safety review. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce minor formatting changes to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				fever), selpercatinib should be withheld and ILD promptly investigated and treated as medically appropriate. Based on the severity of ILD/pneumonitis, the dose of selpercatinib should be interrupted, reduced, or permanently discontinued. For more information, please refer to the Summary of Product Characteristics.
R/0018	Renewal of the marketing authorisation.	13/10/2022	09/12/2022		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 Retsevmo, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
PSUSA/10917 /202205	Periodic Safety Update EU Single assessment - selpercatinib	01/12/2022	n/a		PRAC Recommendation - maintenance
II/0017	Update of section 4.5 and 5.2 of the SmPC in order to reflect the final results from the drug-drug interaction (DDI) study J2G-MC-JZJV; this is a phase 1, single-center, open-label, DDI study to investigate the effect of selpercatinib on the pharmacokinetic profiles of dabigatran, a P-glycoprotein (P-gp) substrate, in healthy volunteers. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to	10/11/2022	24/03/2023	SmPC and PL	The results of study J2G-MC-JZJV have shown a significant increase in Cmax (43%) and AUC0-∞ (38%) of dabigatran (single dose at D1 and D8) after a single dose of selpercatinib (single dose at D8) in healthy volunteers. Selpercatinib is therefore a mild inhibitor of P-gp and caution should be used when taking a sensitive P-gp substrate (e.g., fexofenadine, dabigatran etexilate, colchicine, saxagliptin), and particularly those with a narrow therapeutic index (e.g., digoxin).

	new quality, preclinical, clinical or pharmacovigilance data				
IA/0020	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	03/10/2022	n/a		
II/0014/G	This was an application for a group of variations. Extension of indication to include first-line treatment of advanced RET-mutant medullary thyroid cancer (MTC) in adults and adolescents 12 years and older based on interim results from Study LIBRETTO-001 (LOXO-RET-17001) on the clinical safety and efficacy of selpercatinib in patients with RET-mutant MTC who are cabozantinib and vandetanib treatment-naïve (MTC:-Cab/-Van). LIBRETTO-001 is a global, multicohort, open-label, Phase 1/2 study in adult and adolescent patients with advanced RET-altered tumours. As a consequence, sections 4.1 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 3.0 of the RMP has also been submitted. As part of the application the MAH is requesting a 1-year extension of the market protection. The application also includes an updated Phase II Environmental Risk Assessment in order to reflect the patient population as per the approved indication. C.I.6.a - Change(s) to therapeutic indication(s) -	21/07/2022	02/09/2022	SmPC and PL	Please refer to Scientific Discussion 'Retsevmo-H-C-005357-II-0014'

	Addition of a new therapeutic indication or modification of an approved one C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
IA/0019	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	25/08/2022	n/a		
II/0011	Extension of indication to include the first-line treatment of RET fusion-positive NSCLC for Retsevmo based on results from study LIBRETTO-001, an open-label, multicentre, global Phase 1/2 study of selpercatinib in patients with RET-altered advanced solid tumours; as a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. In addition, section 5.1 of the SmPC is revised to reflect updated efficacy data in previously treated RET-fusion positive NSCLC based on a data cut-off of 15 June 2021. The Package Leaflet is updated in accordance. Version 1.3 of the RMP has also been submitted. 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	22/04/2022	21/06/2022	SmPC and PL	Please refer to Scientific Discussion 'Retsevmo-H-C-005357-II-0011'

II/0010	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/04/2022	21/06/2022	SmPC and PL	
PSUSA/10917 /202111	Periodic Safety Update EU Single assessment - selpercatinib	10/06/2022	n/a		PRAC Recommendation - maintenance
PSUSA/10917 /202105	Periodic Safety Update EU Single assessment - selpercatinib	16/12/2021	28/02/2022	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10917/202105.
IA/0013	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	21/02/2022	n/a		
R/0008	Renewal of the marketing authorisation.	14/10/2021	16/12/2021	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 RETSEVMO, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
IB/0009/G	This was an application for a group of variations. B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new	24/09/2021	n/a		

	specification parameter to the specification with its corresponding test method 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 B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process 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				
IB/0003/G	This was an application for a group of variations. B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g.	22/06/2021	16/12/2021	SmPC, Labelling and PL	

	tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes 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.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) 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.e.1.b.1 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Solid, semi-solid and non-sterile liquid pharmaceutical forms B.II.b.1.b - Replacement or addition of a				

	manufacturing site for the FP - Primary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site A.7 - Administrative change - Deletion of manufacturing sites				
IA/0005/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	15/06/2021	n/a		
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/04/2021	16/12/2021	PL	
IA/0002	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	12/03/2021	n/a		