Rozlytrek

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/10874 /202406	Periodic Safety Update EU Single assessment - entrectinib	30/01/2025	24/03/2025	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10874/202406.
PSUSA/10874 /202312	Periodic Safety Update EU Single assessment - entrectinib	11/07/2024	n/a		PRAC Recommendation - maintenance

[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).

X/0017/G	This was an application for a group of variations. - C.I.6.a - Extension of the currently approved indication of Rozlytrek in solid tumours with NTRK gene fusion to patients from 1 month to 12 years of age (both for the coated granules and already approved hard capsules presentations). Based on final results from studies CO40778 (STARTRK-NG), GO40782 (STARTRK-2) and BO41932 (TAPISTRY). Study CO40778 is a Phase I/II open-label, dose-escalation and expansion study of entrectinib in paediatrics with locally advanced or metastatic solid or primary CNS tumours and/or who have no satisfactory treatment options; Study GO40782 is an open-label, multicenter, global Phase II basket study of entrectinib for the treatment of patients with solid tumours that harbour an NTRK1/2/3, ROS1, or ALK gene rearrangement (fusion), and Study BO41932 is a Phase II, global, multicenter, open-label, multi-cohort study designed to evaluate the safety and efficacy of targeted therapies or immunotherapy as single agents or in rational, specified combinations in participants with unresectable, locally advanced or metastatic solid tumours determined to harbour specific oncogenic genomic alterations or who are tumour mutational burden (TMB)-high as identified by a validated next-generation sequencing (NGS) assay. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 of the SmPC are updated. - C.I.4. - Addition of wording regarding the possibility to prepare a suspension in water of the	25/04/2024	27/06/2024	SmPC, Annex II, Labelling and PL	Please refer to Scientific Discussion: EMEA/H/C/004936/X/0017/G.

	content of the capsules to be used orally or via the e.g., gastric or nasogastric tube. As a consequence, sections 4.2, 5.2, 6.3, 6.4 and 6.6 of the SmPC are updated. The Package Leaflet and Labelling are updated in accordance. The RMP (version 5.2) is updated in accordance. The MAH took the opportunity to introduce minor editorial changes to the PI and to update Annex II of the SmPC. Annex I_2.(d) Change or addition of a new pharmaceutical form Annex I_2.(e) Change or addition of a new route of administration C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one Annex I_2.(c) Change or addition of a new strength/potency				
IA/0023	A.7 - Administrative change - Deletion of manufacturing sites	13/06/2024	n/a		
R/0020	Renewal of the marketing authorisation.	21/03/2024	16/05/2024	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 Rozlytrek, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion. Sections 4.4, 4.8 and 5.1 of the SmPC are updated to reflect the new safety and efficacy data. The Package Leaflet is updated accordingly.
IB/0022/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation	22/04/2024	n/a		
PSUSA/10874 /202306	Periodic Safety Update EU Single assessment - entrectinib	11/01/2024	n/a		PRAC Recommendation - maintenance
R/0015	Renewal of the marketing authorisation.	26/04/2023	07/07/2023	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 Rozlytrek, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
PSUSA/10874 /202212	Periodic Safety Update EU Single assessment - entrectinib	06/07/2023	n/a		PRAC Recommendation - maintenance
IA/0018	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)	29/06/2023	n/a		
II/0014	Update of sections 4.2 and 5.2 of the SmPC in order to update the pharmacokinetic information based on final results from study GP411174 listed as an additional pharmacovigilance activity in the RMP; this is a Phase I, non-randomized, single-dose, open-label study to investigate the effect of impaired hepatic function on the pharmacokinetics of entrectinib in volunteers with different levels of hepatic function. The RMP version 4.1 has also been agreed. In addition, the MAH took the opportunity to update in Annex II section C and to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/01/2023	09/03/2023	SmPC, Annex II and PL	The pharmacokinetics of entrectinib were studied in subjects with mild (Child-Pugh A), moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment, relative to subjects with normal hepatic function. Following administration of a single oral dose of 100 mg entrectinib, the combined AUClast of entrectinib and M5 showed no relevant change in the hepatic impaired groups compared to the normal function group. The AUClast geometric mean ratio (90% CI) was 1.30 (0.889, 1.89) for the mild, 1.24 (0.886, 1.73) for the moderate, and 1.39 (0.988, 1.95) for the severe hepatic impaired groups compared to the normal hepatic function group. For the unbound entrectinib and M5, the AUClast (fu) geometric mean ratio (90% CI) was 1.91 (1.21, 3.02) for the mild, 1.57 (1.06, 2.31) for the moderate, and 2.34 (1.57, 3.48) for the severe hepatic impaired groups compared to the normal hepatic function group. Although the effect of hepatic impairment on unbound PK parameters generally followed a similar

					direction as total PK parameters, due to the high non-specific binding in buffer and high variability, results should be interpreted with caution. No dose adjustment is recommended for patients with mild, moderate or severe hepatic impairment. Patients with severe hepatic impairment should be carefully monitored for hepatic function and adverse reactions. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10874 /202206	Periodic Safety Update EU Single assessment - entrectinib	12/01/2023	n/a		PRAC Recommendation - maintenance
II/0012	Submission of the final integrated analysis report for cardiac risks, listed as a category 3 study in the RMP, in order to fulfil MEA/003. This is an integrated safety analysis report to assess cardiac risks based on GO40782 [STARTRK-2], CO40778 [STARTRK-NG], and BO41932 [TAPISTRY] studies (PAESs). Section 4.4 of the SmPC has been updated to better reflect the cardiac safety findings. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	08/09/2022	09/03/2023	SmPC	Congestive heart failure (CHF) has been reported in less than 5% of patients across clinical trials with Rozlytrek. These reactions were observed in patients with or without a history of cardiac disease and resolved in 70% of those patients upon institution of appropriate clinical management and/or Rozlytrek dose reduction/interruption. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10874 /202112	Periodic Safety Update EU Single assessment - entrectinib	07/07/2022	n/a		PRAC Recommendation - maintenance
IB/0011/G	This was an application for a group of variations. B.II.f.1.d - Stability of FP - Change in storage	27/06/2022	09/03/2023	SmPC, Labelling and PL	

	conditions of the finished product or the diluted/reconstituted product 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)				
II/0010	Submission of the final report from study (RO7102122) to address the non-clinical recommendation issued within the initial MAA. This is an in-vitro study for the evaluation of entrectinib against novel clinically-relevant NTRK fusions using the Ba/F3 cell line. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	02/06/2022	n/a		
R/0007	Renewal of the marketing authorisation.	24/03/2022	30/05/2022	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 Rozlytrek, 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.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch	05/04/2022	n/a		

	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				
PSUSA/10874 /202106	Periodic Safety Update EU Single assessment - entrectinib	13/01/2022	n/a		PRAC Recommendation - maintenance
IB/0005/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)	10/08/2021	30/05/2022	SmPC and PL	
PSUSA/10874 /202012	Periodic Safety Update EU Single assessment - entrectinib	08/07/2021	n/a		PRAC Recommendation - maintenance
R/0002	Renewal of the marketing authorisation.	22/04/2021	21/06/2021		
IB/0004/G	This was an application for a group of variations. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation 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.I.b.2.c - Change in test procedure for AS or	31/05/2021	n/a		

	starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits 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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				

	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 B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
IB/0001	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)	15/10/2020	21/06/2021	SmPC, Labelling and PL	