Medicinal product no longer authorised

GAVRETO

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
T/0021	Transfer of Marketing Authorisation	21/06/2024	17/07/2024	SmPC, Labelling and PL	
PSUSA/10961 /202309	Periodic Safety Update EU Single assessment - pralsetinib	11/04/2024	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).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

An agency of the European Union

II/0012	Update of sections 4.2, 4.4 and 4.5 of the SmPC in order to amend posology recommendations, warnings and drug-drug interaction information regarding the co-administration with CYP3A4 inhibitors, P-gp inhibitors and CYP3A4 inducers based on final results from the DDI study GP43162, listed as a category 3 study in the RMP, as well as results from the physiologically based pharmacokinetic (PBPK) analyses summarised in the PBPK Report 1120689. Study GP43162 is a phase 1, open-label, fixed-sequence study to evaluate the effect of a single dose of cyclosporine on the single dose pharmacokinetics of pralsetinib in healthy subjects. The package leaflet has been updated accordingly. The RMP version 1.8 is agreed. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/02/2024	25/03/2024	SmPC and PL	Section 4.2 is updated with specific dose modifications when co-administered with CYP3A4 inhibitors and/or p-gp inhibitors. The recommended dose modifications for co-administration with CYP3A4 inducers have been deleted. Sections 4.4 and 4.5 are updated to describe in further details on the warnings that concomitant use with CYP3A4 and/or p-gp inhibitors and CYP3A4 inducers should be avoided. For more information, please refer to the Summary of Product Characteristics.
II/0017	Update of sections 4.2 and 5.2 of the SmPC in order to include information regarding moderate and severe hepatic impairment based on final results from study GP43163 listed as a category 3 study in the RMP; this is a Phase I, open-label, single-dose study to evaluate the pharmacokinetics and safety of pralsetinib in subjects with moderate or severe hepatic impairment compared to healthy subjects. The RMP version 1.8 is agreed. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to update the marketing authorisation renewal date in Annex I.	22/02/2024	25/03/2024	SmPC and PL	Following the results from a Phase I, open-label, single-dose study to evaluate the pharmacokinetics and safety of pralsetinib in subjects with moderate or severe hepatic impairment compared to healthy subjects, sections 4.2 and 5.2 of the SmPC have been updated in order to mention that no dose adjustment is necessary for patients wild mild, moderate or strong hepatic impairment. For more information, please refer to the Summary of Product Characteristics.

Medicinal product no longer authorised

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0016/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation 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.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.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.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold	30/11/2023	n/a		

Medicinal product no longer authorised

	increase compared to the originally approved batch size B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
PSUSA/10961 /202303	Periodic Safety Update EU Single assessment - pralsetinib	28/09/2023	n/a		PRAC Recommendation - maintenance
R/0014	Renewal of the marketing authorisation.	20/07/2023	15/09/2023		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 GAVRETO, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
II/0013	Update of sections 4.4, 4.6 and 5.3 of the SmPC in order to update information on fertility based on final results from study 00571044 (21-0310), this is a 9-week fertility and toxicokinetic study of pralsetinib administered via oral gavage in male Sprague Dawley rats. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce a minor change to the PI and 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	20/07/2023	15/09/2023	SmPC and PL	SmPC new text It was specified in sections 4.4 and 4.6 of the SmPC that effective contraception, which must be used by males with females partners of childbearing potential, includes a barrier method. Section 5.3 of the SmPC was updated to reflect the results of a fertility and early embryonic development study in which male rats administered pralsetinib were mated with untreated female rats and the fact that both intrauterine survival of the embryos and male reproductive performance were unaffected by pralsetinib administration to males at the 20 mg/kg dose level. For more information, please refer to the Summary of

Medicinal product no longer authorised

	data				Product Characteristics.
PSUSA/10961 /202209	Periodic Safety Update EU Single assessment - pralsetinib	26/04/2023	07/07/2023	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10961/202209.
II/0010	Update of sections 4.8, 5.1 and 5.2 of the SmPC in order to update PK/PD, efficacy and safety information in the treatment of adult patients with RET fusion-positive advanced NSCLC based on final results (NSCLC indication) from study ARROW/BO42863 (also known as BLU-667-1101), a Phase 1/2 Study of the Highly-selective RET Inhibitor in Patients With Thyroid Cancer, Non-Small Cell Lung Cancer (NSCLC), and Other Advanced Solid Tumours listed as a specific obligation in the Annex II. The specific obligation is considered fulfilled and deleted from the Annex II. The RMP version 1.5 is agreed. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/06/2023	15/09/2023	SmPC and Annex II	SmPC new text Based on the final result of a Phase 1/2 Study of the Highly-selective RET Inhibitor, in Patients With Thyroid Cancer, Non-Small Cell Lung Cancer (NSCLC), and Other Advanced Solid Tumours, safety, efficacy and PK data have been updated in sections 4.8, 5.1 and 5.2 of the SmPC. The final results of this study are overall consistent with previous data. For more information, please refer to the Summary of Product Characteristics.
IB/0011/G	This was an application for a group of variations. 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.II.b.3.a - Change in the manufacturing process of	10/01/2023	n/a		

Medicinal product no longer authorised

	the finished or intermediate product - Minor change in the manufacturing process 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.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits 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.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 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				
PSUSA/10961 /202203	Periodic Safety Update EU Single assessment - pralsetinib	29/09/2022	n/a		PRAC Recommendation - maintenance
R/0006	Renewal of the marketing authorisation.	21/07/2022	13/09/2022		
IB/0008	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)	09/06/2022	13/09/2022	SmPC	

Medicinal product no longer authorised

IB/0004/G	This was an application for a group of variations. 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.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) B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	22/03/2022	13/09/2022	SmPC and PL	PI was update to relfect extension of the shelf life of the finished product from 24 to 30 months for Pralseltinib 100 mg capsules.
IB/0005	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	28/02/2022	n/a		
IB/0003/G	This was an application for a group of variations. B.I.b.z - Change in control of the AS - Other variation B.I.b.z - Change in control of the AS - Other variation	09/02/2022	n/a		
IAIN/0001/G	This was an application for a group of variations. B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	10/12/2021	13/09/2022	Annex II and PL	

Medicinal product no longer authorised

	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 A.7 - Administrative change - Deletion of manufacturing sites				

Medicinal product no longer authorised