AYVAKYT

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
IB/0033	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)	17/04/2024		SmPC	
IB/0032/G	This was an application for a group of variations.	04/04/2024	n/a		

[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).

	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.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.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				
PSUSA/10878 /202307	Periodic Safety Update EU Single assessment - avapritinib	08/02/2024	n/a		PRAC Recommendation - maintenance
IA/0031	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	07/02/2024	n/a		
II/0023	Extension of indication to include for avapritinib treatment of adult patients with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment based on results from the pivotal part of study BLU-285-2203 (PIONEER), this is a 3-part, randomized, double-blind, placebo-controlled, Phase 2 study to evaluate safety and efficacy of avapritinib (BLU-285) in indolent and smoldering systemic mastocytosis with symptoms inadequately controlled with standard therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1, 5.2 and 5.3 of	09/11/2023	11/12/2023	SmPC and PL	Please refer to Scientific Discussion 'Ayvakyt-H-C-5208-II-0023'

	the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.4 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IAIN/0030/G	This was an application for a group of variations. B.II.a.3.b.1 - Changes in the composition (excipients) of the finished product - Other excipients - Any minor adjustment of the quantitative composition of the finished product with respect to excipients 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) B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	05/12/2023	n/a		
IB/0029/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.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation	27/11/2023	n/a		

	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				
PSUSA/10878 /202301	Periodic Safety Update EU Single assessment - avapritinib	31/08/2023	n/a		PRAC Recommendation - maintenance
R/0025	Renewal of the marketing authorisation.	25/05/2023	24/07/2023		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 AYVAKYT, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
II/0022	Update of sections 4.2 and 5.2 of the SmPC in order to change posology recommendations and to update pharmacokinetic information for use in patients with severe hepatic impairment based on the final results from study BLU-285-0107 listed as a category 3 study in the RMP; this is a phase 1, open-label, single-dose study to investigate the influence of severe hepatic impairment on the pharmacokinetics of avapritinib. The package leaflet is updated accordingly. The RMP version 3.1 has also been submitted. 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	26/04/2023	26/05/2023	SmPC, Annex II and PL	SmPC new text In a clinical study investigating the effect of severe hepatic impairment on the pharmacokinetics of avapritinib following administration of a single oral dose of 100 mg avapritinib, the mean unbound AUC was 61% higher in subjects with severe hepatic impairment (Child-Pugh Class C) as compared to matched healthy subjects with normal hepatic function. The starting dose of avapritinib should be reduced in patients with severe hepatic impairment from 300 mg to 200 mg orally once daily for patients with GIST, and from 200 mg to 100 mg orally once daily for patients with AdvSM.

	new quality, preclinical, clinical or pharmacovigilance data				
IA/0027/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.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure 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.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	24/05/2023	n/a		
IB/0024	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)	13/03/2023		SmPC	Product information section 6.3 is updated to reflect the shelf-life extension of the finished product AYVAKYT 100 mg, 200 mg and 300 mg film-coated tablets (EU/1/20/1473/001-003) as packaged for sale from 3 years to 4 years.
PSUSA/10878 /202207	Periodic Safety Update EU Single assessment - avapritinib	09/02/2023	n/a		PRAC Recommendation - maintenance

IB/0020/G	This was an application for a group of variations. B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation 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) A.7 - Administrative change - Deletion of manufacturing sites	04/10/2022		SmPC	
PSUSA/10878 /202201	Periodic Safety Update EU Single assessment - avapritinib	01/09/2022	n/a		PRAC Recommendation - maintenance
R/0017	Renewal of the marketing authorisation.	19/05/2022	15/07/2022		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 AYVAKYT, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion.
II/0014	C.I.11.b 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	12/05/2022	15/07/2022	Annex II	

	is required Submission of the final report from study BLU-285-1101 listed as a Specific Obligation in the Annex II of the Product Information. This is an interventional Phase 1 study, designed to evaluate the safety, tolerability, PK, pharmacodynamics, and preliminary antineoplastic activity of avapritinib administered orally in patients with unresectable GIST or other relapsed or refractory solid tumours. The Annex II is updated accordingly. 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				
X/0004/G	This was an application for a group of variations. Annex I_2.(c) Change or addition of a new strength/potency C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	27/01/2022	24/03/2022	SmPC, Labelling and PL	
IA/0018	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	16/03/2022	n/a		

PSUSA/10878 /202107	Periodic Safety Update EU Single assessment - avapritinib	10/02/2022	n/a		PRAC Recommendation - maintenance
IB/0016/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.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	04/02/2022	n/a		
IB/0013	B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method	30/12/2021	n/a		
IA/0015/G	This was an application for a group of variations. B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test	09/12/2021	n/a		

IB/0010/G	This was an application for a group of variations. B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	07/10/2021	n/a		
IA/0011/G	This was an application for a group of variations. 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.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.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 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 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.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	06/10/2021	n/a		

	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.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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/10878 /202101	Periodic Safety Update EU Single assessment - avapritinib	02/09/2021	n/a		PRAC Recommendation - maintenance
R/0007	Renewal of the marketing authorisation.	20/05/2021	23/07/2021	Annex II	
IB/0006	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	12/04/2021	n/a		
II/0003/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) B.II.d.1.e - Change in the specification parameters	25/03/2021	23/07/2021	SmPC	

	and/or limits of the finished product - Change outside the approved specifications limits range				
IA/0008	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	12/03/2021	n/a		
II/0002	B.I.a.1.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant update to the relevant AS section in the dossier	04/03/2021	n/a		
IAIN/0005/G	This was an application for a group of variations. 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	17/02/2021	n/a		
IAIN/0001/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	15/10/2020	23/07/2021	Annex II and PL	

	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				