11 December 2023
EMA/OD/0000127063
EMADOC-360526170-1642825
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Ayvakyt (Avapritinib)

Treatment of mastocytosis

EU/3/18/2074

Sponsor: Blueprint Medicines (Netherlands) B.V.

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted

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 Un on

Table of contents

1. Product and administrative information

Product	
Designated active substance(s)	Avapritinib
Other name(s)	Ayvakyt, Avapritinib,
International Non-Proprietary Name	Avapritinib
Tradename	Ayvakyt
Orphan condition	Treatment of mastocytosis
Sponsor's details:	Blueprint Medicines (Netherlands) B.V. Gustav Mahlerplein 2 1082 MA Amsterdam Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	PhaRA bvba
COMP opinion	13 September 2018
EC decision	26 October 2018
EC registration number	EU/3/18/2074
Post-designation procedural history	
Transfer of sponsorship	Transfer from PhaRA bvba to Blueprint Medicines (Netherlands) B.V – EC decision of 20 May 2019
Type II variation procedural history	
Rapporteur / Co-rapporteur	Carolina Prieto Fernandez / Ingrid Wang
Applicant	Blueprint Medicines (Netherlands) B.V.
Application submission	15 December 2022
Procedure start	27 January 2023
Procedure number	EMA/H/C/005208/II/0023
Invented name	Ayvakyt
Proposed therapeutic indication	AYVAKYT is indicated for the treatment of adult patients with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment. Further information on Ayvakyt can be found in the European public assessment report (EPAR) on the Agency's website: http://www.ema.europa.eu/en/medicines/human/EPAR/Ayvakyt
CHMP opinion	09 November 2023
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Karri Penttila / Elisabeth Johanne Rook
Sponsor's report submission	19 January 2023
COMP discussion	07-09 November 2023
Oral explanation	N/A
COMP opinion	09 November 2023

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2018 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing avapritinib was considered justified based on preliminary non-clinical data showing improved survival as well as preliminary clinical data showing an improvement in overall response rate;
- the condition is chronically debilitating due to symptoms such as flushing, tachycardia, pruritus, abdominal cramping, peptic ulcers and diarrhoea, and life-threatening due to bone marrow failure, hepatomegaly, splenomegaly , and poor survival with 5-year rates of around 60% in patients with systemic mastocytosis;
- the condition was estimated to be affecting approximately 3 in 10,000 persons in the European Union, at the time the application was made.
- In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing avapritinib will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data which demonstrate an improved overall response rate compared to the current approved medicine. The Committee considered that this constitutes a clinically relevant advantage.

The COMP therefore recommends the designation of this medicinal product, containing avapritinib as an orphan medicinal product for the orphan indication: treatment of mastocytosis.

3. Review of criteria for orphan designation at the time of type II variation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Mastocytosis is a rare disease characterized by abnormal expansion and accumulation of tissue mast cells (MC) in one or multiple organs, which is frequently associated with somatic gain-of-function point mutations within the tyrosine kinase receptor KIT (CD117). Manifestations may be limited to the skin (cutaneous mastocytosis, CM), as commonly in paediatric cases with spontaneous regression at puberty. Or it may be extended to multiple organs (systemic mastocytosis, SM) that may be associated with multiorgan dysfunction and shortened survival, as generally seen in adult patients (Pardanani 2021 Am J Hematol 96: 508– 525).

Based on histopathological findings and organ damage, SM is divided into indolent SM (ISM), smoldering SM (SSM), SM with an associated hematologic non-MC-lineage disease (SM-AHNMD), aggressive SM (ASM), and MC leukaemia (MCL). The clinical course and prognosis vary greatly among these groups of patients. In all variants of SM and most patients, neoplastic cells display the KIT mutation D816V. This suggests that additional KIT-independent molecular defects cause progression.

Indeed, additional oncogenic lesions, including RAS- and TET2 mutations, have recently been identified in advanced SM. In patients with SM-AHNMD, such additional lesions are often detectable in the 'AHNMD component' of the disease. Clinically relevant symptoms of SM result from i) malignant MC infiltration and the subsequent organ damage seen in advanced SM and/or ii) the release of pro-inflammatory and vasoactive mediators from MC, found in all disease-variants. (Am J Cancer Res 2013;3(2):159-172).

This condition continues to be acceptable for orphan regulatory purposes.

The approved extension of the therapeutic indication "*AYVAKYT is indicated for the treatment of adult patients with indolent systemic mastocytosis (ISM) with moderate to severe symptoms inadequately controlled on symptomatic treatment*" falls entirely within the orphan indication "treatment of mastocytosis".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

The sponsor claims that since the application for orphan designation of avapritinib for the treatment of mastocytosis in 2018, the treatment paradigm for indolent systemic mastocytosis has not changed, and patients have limited treatment options.

Mastocytosis carry substantial morbidity and mortality. Cutaneous mastocytosis (CM) has a good prognosis in most cases (Valent 2005). It occurs mainly in children, often regresses during puberty, and rarely progresses to SM. In adults however, CM is persistent and often progresses to SM, or it can have an associated haematologic disorder, such as hypereosinophilic syndrome that may become aggressive (Pottier 2003, Valent 2005).

Mediator-release symptoms of flushing, tachycardia, pruritus, abdominal cramping, peptic ulcer disease, and diarrhoea can be difficult to control, can seriously impact the quality of life of patients experiencing these symptoms, and can be life-threatening (Castells 2002, Valent 2005). Infiltration of various organs by malignant cells in aggressive forms SM cause the "C-findings" of cytopenias, osteoporosis, pathologic fractures, hepatomegaly with ascites and impaired liver function, splenomegaly with hypersplenism, malabsorption, hypoalbuminemia, weight loss, or life-threatening organopathy in other organ systems (O'Brien 2004).

The disease course of CM and ISM is in general benign, as reported by Lim et al. in 2009. Indeed, patients with ISM in the USA have much the same life expectancy as the general population. However, in rare cases ISM may develop into more aggressive forms. The prognosis is poor for advanced SM, especially in elderly patients: median OS was 41 months for ASM, 24 months for SM-AHNMD, and 2 months for MCL in the aforementioned study reported by Lim et al.

However, although not life-threatening, both CM and ISM, being life-long conditions, are characterized by fluctuations of symptoms making mastocytosis a burdensome condition. This is illustrated by a recent study where 50-70% of patients with ISM and SSM report being impacted regarding their work or daily activities, or social activities (Jennings et al, 2018). Recently published results of the TouchStone SM Patient Survey revealed that nearly two-thirds of patients reported avoiding leaving their home due to SM symptoms and 66% experienced pain from symptoms that interfered with their ability to work, with 30% filing for medical disability due to their disease (Mesa et al, 2022).

A separate 2011 study of patients with ISM found that 64% of patients had depression. The majority (56%) had moderate depression and 8% had severe depression (Moura et al, 2011). The analysis found that depression in patients with ISM did not seem to be related to physical symptoms and should be considered an independent symptom of disease. In addition, indolent SM is associated with a high rate of anaphylaxis that is often coupled with hypotension and has the potential to be fatal.

The COMP has previously determined that the proposed condition mastocytosis is chronically debilitating due to symptoms such as flushing, tachycardia, pruritus, abdominal cramping, peptic ulcers and diarrhoea, and life-threatening due to bone marrow failure, hepatomegaly, splenomegaly, and poor survival with 5-year rates of around 60% in patients. This view is retained for this type II variation, extension of indication procedure after the initial marketing authorisation.

Number of people affected or at risk

The sponsor proposes a less than 3 in 10,000 prevalence estimate on the basis of literature and databases searches. This is in line with the COMP's previous conclusion for orphan designation in 2022, and at the time of maintenance of the orphan designation in the context of the initial marketing authorisation application in 2018.

Six data sources were identified for prevalence (Table 1): Cohen et al (2014) estimate the 14-year prevalence of mastocytosis to be 0.959 (0.873-0.105) per 10,000 in Denmark. A more recent study by Kibsgaard et al (2020) estimated ISM prevalence in Denmark to be at 1.8 cases per 10,000. In the Netherlands, Van Doormaal et al (2013) estimate SM prevalence to be 1.3 per 10,000. Schwaab et al (2020) estimated the prevalence of AdvSM to be 0.053 per 10,000 in Germany. Zanotti et al. (2021) estimate the prevalence of SM to be 1.22 per 10,000 in the Veneto region, and 1.72 per 10,000 in the Verona region of Italy. In Sweden, Ungerstedt et al (2022) estimate the prevalence of SM to be 1.06 per 10,000 in the Stockholm region. The six studies differ in terms of the type of SM covered.

Additional prevalence estimates were obtained from incidence data. A prevalence of 2.41 cases of CM per 10,000 was estimated from incidence data from Italy, including subjects of all ages (D'Inca et al, 1996). Similarly, Danish incidence data for subjects of all ages resulted in an estimated CM prevalence of 6.03 per 10,000 and an overall mastocytosis prevalence of 8.84 per 10,000 (Kibsgaard et al, 2020). For Hungary (Marton et al, 2016), the prevalence estimated 1.67 cases of SM per 10,000. These calculated prevalences may be overestimates given the conservative method used for their calculation, as showcased previously with the examples from Kibsgaard et al (2020), Cohen et al (2014), Schwaab et al (2020) and Ungerstedt et al (2022).

The sponsor argues that prevalence estimates reported in Cohen et al (2014), Kibsgaard et al (2020) and Van Doormaal et al (2013) are the most robust, despite two not including children or the full spectrum of CM. Brockow (2014) has expressed the view that Van Doormaal's finding is comparable to other estimates. He states that at the consensus meeting of mastocytosis experts in Boston in 2010, a general cumulative prevalence of approximately 1 in 10,000 persons was estimated by other centers (Luis Escribano, Patrizia Bonadonna, personal communication in Brockow (2014). Valent (2013) states that the estimated prevalence of mastocytosis in "Middle Europe" is 0.5-1 per 10,000. These estimates are in line with the findings in original studies from the literature.

Prevalence estimates found on EU databases and websites also support these estimates including Orphanet and RARECARENET (Orphanet, 2022; RARECARENET, 2017), and Haenisch et al (2012) report that for SM, data from the French mastocytosis network (Association Française pour les Initiatives de Recherche sur le Mastocyte et Les Mastocytoses), the Spanish mastocytosis network (Red Espanola de Mastocitosis), the Italian Mastocytosis Registry, and the German Competence Network on

Mastocytosis (own unpublished results), suggest a prevalence of at least one in 364,000 in EU, which corresponds to a prevalence of 0.027 in 10,000.

It is concluded that based on the available literature the reported prevalence of mastocytosis (including SM, CM, and their subtypes, and MCS) remains below 3 in 10,000. This is in line with recent (initial MA of 2022) considerations of the committee and may be considered acceptable.

Table 1. Studies reporting on the prevalence of mastocytosis in the EU.

Reference; location; period	**Population**	**Data Source**	**Outcome**	**Study outcome per 10,000**
Cohen et al (2014); Denmark; 1 January 1997 – 31 December 2010; Prevalence calculated as of January 2011.	Adults (≥15 years)	Nationwide, retrospective, population-based cohort study.	14-year limited-duration prevalence per 10,000	SM (total): 0.959 (0.873-0.105) ISM (including UP): 0.824 (0.744-0.910); SM (unk): 0.096 (0.071-0.128); ASM: 0.009 (0.003-0.021); SM-AHN (SM-AHNMD): 0.031 (0.018-0.050); MCL: 0.000
Kibsgaard et al (2020); Denmark; January 1 1977 – 31 December 2014	Patients of all ages	Nationwide, retrospective, population-based cohort study.	Prevalence per 10,000	ISM: 1.8
Schwaab et al (2020); Germany (two referral centres in southwest Germany: Mannheim and Aachen); 2009-2018	Patients of all ages, referred, diagnosed and treated at the mast cell referral centres	Retrospective study, based on mast cell referral centre data.	Prevalence per 10,000	AdvSM: 0.052
Van Doormaal et al (2013); The Netherlands (Groningen region); 1 January 2011	All consecutive adult patients (≥15 years) living in the Groningen region	Retrospective study.	Prevalence per 10,000	ISM & SSM: 0.13 (42 cases: 30 with ISM, 1 SSM, 2 presumed ISM, 9 high-risk ISM [5 with UP])
Zanotti et al (2021); Italy (Veneto Regio and Verona province); January 2006- January 2021. Prevalence calculated as of January 2021.	Adults (≥15 years).	Regionwide, prospective, population-based cohort study.	Prevalence per 100,000 converted to prevalence per 10,000	SM Veneto: 1.22 Verona: 1.72
Ungerstedt et al (2022); Sweden (Stockholm region); January 2006- December 2020.	Adults (≥18 years).	Retrospective study	Prevalence per 100,000 converted to	SM Stockholm: 1.06

Prevalence calculated as of 31 December 2020.			prevalence per 10,000	

Abbreviations: AdvSM = advanced system c mastocytosis; ASM = aggressive systemic mastocytosis; CMD = clonal mast cell disorders; CRS = Civil Registrat on System; DCR = Danish National Cancer Registry; DNPR = Danish Nat onal Patient Registry; EU = European Union; GISM = group for study of mastocytosis; ICD-10 = Internat onal Statistical Classif cation of Diseases and Related Health Problems 10th Revision; ISM = indolent systemic mastocytosis, MCL = mast cell leukemia; NPR = Nat onal Pathology Registry; SM-AHN = systemic mastocytosis with associated hematolog c neoplasm; SM-AHNMD = systemic mastocytosis w th clonal hematologic non-mast cell-lineage disease; SM unk = systemic mastocytosis unknown subtype; SNOMED CT = Systematized Nomenclature of Medicine - Clinical Terms; UMCG, University Medical Center Groningen; UP = urticaria pigmentosa, WHO = World Health Organizat on.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

Cimetidine is authorized for use in systemic mastocytosis in Portugal: profilaxia das úlceras de stress em doentes graves com risco de hemorragia; no tratamento de hipersecreção patológica, nomeadamente síndrome de Zollinger-Ellison, mastocitose sistémica e adenomas endócrinos múltiplos; como medida de suporte, no tratamento da hemorragia digestiva altapor úlcera péptica ou erosões (in English: prophylaxis of stress ulcers in critically ill patients at risk of bleeding; in the treatment of pathological hypersecretion, namely Zollinger-Ellison syndrome, systemic mastocytosis and multiple endocrine adenomas; as a supportive measure in the treatment of upper gastrointestinal bleeding from peptic ulcer or erosions).

Cimetidine has a therapeutic indication that is limited to treatment of gastric signs and symptoms of the disease, and this indication does not overlap with the broader target patient population covered by the therapeutic indication for Ayvakyt.

Midostaurin and avapritinib are authorized centrally in Europe for mastocytosis as reflected in table 2.

There are no specific European Guidelines in the treatment of these patients and many products are used off-label in the treatment of this condition. Some guidance regarding treatment algorithm is proposed in Pardani Am J Hematol 2019;94:363–377.

Per the authorised indications cited above, no products have been identified that cover patients with CM, ISM, and SSM. The sponsor noted that as currently used best supportive care (BSC) therapies are not authorized for the treatment of CM, ISM and SSM patient populations, they cannot be considered as satisfactory methods for the purposes of Article 3(1)(b) Commission Notice 2016/C 424/03.

In conclusion, it has been established that none of the identified products can be considered as satisfactory methods for the treatment of the condition in question as authorized in the European Union.

Table 2. Sourced from the sponsor’s report.

Tradename (INN)	Member States where authorized	MAH	Authorized indication
Rydapt (midostaurin)	EU/EEA	Novartis Europharm Limited	As monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM AHN), or mast cell leukaemia (MCL)
AYVAKYT (avapritinib)	EU/EEA	Blueprint Medicines (Netherlands) B.V.	As monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with an associated haematological neoplasm (SM-AHN) or mast cell leukaemia (MCL), after at least one systemic therapy

Abbreviations: AdvSM = advanced systemic mastocytosis; EEA = European Economic Area; EU = European Union; INN = international non-proprietary name; MAH = marketing authorization holder.

Significant benefit

Not applicable, see section above.

4. COMP position adopted on 09 November 2023

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of mastocytosis (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be less than 3 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to symptoms such as flushing, tachycardia, pruritus, abdominal cramping, peptic ulcers and diarrhoea, and life-threatening due to bone marrow failure, hepatomegaly, splenomegaly, and poor survival in patients with systemic mastocytosis;
- at present, no satisfactory method has been authorised in the European Union for the treatment of the entirety of patients covered by the new therapeutic indication of Ayvakyt.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Ayvakyt, avapritinib for treatment of mastocytosis (EU/3/18/2074) is not removed from the Community Register of Orphan Medicinal Products.