24 March 2022
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EMADOC-1700519818-764229
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.

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1. Product and administrative information

Product	
Designated active substance(s)	Avapritinib
Other name(s)	-
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	Jorge Camarero Jiménez / Ingrid Wang
Applicant	Blueprint Medicines (Netherlands) B.V.
Application submission	23 November 2021
Procedure start	13 December 2021
Procedure number	EMA/H/C/005208/X/0004/G
Invented name	Ayvakyt
Proposed therapeutic indication	Advanced systemic mastocytosis (AdvSM) AYVAKYT is indicated 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. Further information on Ayvakyt can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Ayvakyt
CHMP opinion	27 January 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Frauke Naumann-Winter / Tim Leest
Sponsor's report submission	28 September 2021
COMP discussion	18-20 January 2022
COMP opinion (adoption via written procedure)	2 February 2022

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;
- 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.

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. Most adult patients with mastocytosis are diagnosed with systemic mastocytosis (SM). 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 therapeutic indication "AYVAKYT is indicated 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" falls within the scope of the designated orphan condition "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, the treatment paradigm for AdvSM has not changed, and patients with AdvSM have limited treatment options.

Mastocytosis carry substantial morbidity and mortality. Cutaneous Mastocytosis 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, cutaneous mastocytosis 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 prognosis for CM and ISM is excellent, 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, the prognosis is poor for AdvSM, especially in elderly patients: median OS was 41 months for ASM, 24 months for SM-AHN, and 2 months for MCL in the aforementioned study reported by Lim et al.

Number of people affected or at risk

European estimates of incidence and prevalence for mastocytosis that were used by the sponsor were obtained through a systematic search of published literature and relevant EU databases. This search included published literature until 15 November 2020.

The publications on the prevalence are summarised in the following tables:

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

Reference; location; study period	Population	Data Source and study design	Case definition(s)	Outcome measure	Study outcome
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. Data sources were as follows: • Danish medical registries: Danish National Patient Registry (DNPR); • National Pathology Registry (NPR); • Danish National Cancer Registry (DCR); • Civil Registration System (CRS)	SM (all subtypes including urticaria pigmentosa). Cases of SM were classified according to subtypes as defined by the WHO. Subtypes were categorized using combinations of ICD-10 and SNOMED codes. Patients were classified by the most severe disease found in either the pathology registry, cancer registry or NRP. SNOMED codes for mastocytosis had to be supplemented with a biopsy code in order for the patient to be included in the study. Coding differed for the different sources: • *DNPR:* ICD-10 (UP Q82.2; ISM (conf.) D47.0; ISM C96.2; aggressive SM C96.2; SM-AHNMD C96.2 and one of the following – myelod leukemia C92, myelodysplastic syndrome D46, plasma cell myeloma C90, or unclassifiable myelogenous malignancy • *NPR:* SNOMED (mastocytoma M97401; SM, ISM, & aggressive SM M97411; malignant mastocytosis SM-AHNMD M97413, MCL M97423) • *DCR:* Patients with ASM (ICD10: C96.2) or MCL (ICD10: C94.3) Patients with a SNOMED code of M97411 (mastocytosis, not known if benign or	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
			malignant) in the National Pathology Registry but without any mastocytosis diagnoses in the NRP were classified as SM (subtype unknown). UP was considered to be 'probable ISM'. In order to not miss patients in the registries misclassified as mastocytomas that are in fact patients with SM, we included mastocytomas with bone marrow as the recorded site code in our analysis in the SM (subtype unknown) group.		
Kibsgaard et al (2020); Denmark; January 1 1977 – 31 December 2014	Patients of all ages.	Nationwide, retrospective, population-based cohort study. Data sources were as follows: • Danish medical registries: Danish National Patient Registry (DNPR); • National Pathology Registry (NPR); • Civil Registration System (CRS)	ISM Coding differed for the different sources: • DNPR: ICD-10 • NPR: SNOMED Mastocytosis cases were classified according to the corresponding WHO-classification diagnoses. The authors provide a supplement document with an exhaustive list of all relevant ICD-10 and SNOMED codes used (available here).	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.	AdvSM (includes: systemic mastocytosis with associated hematologic neoplasm, aggressive systemic mastocytocis and mast cell leukemia) Classification of patients was based on the 2016 WHO criteria.	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 1) University Medical Center Groningen (UMCG), a national referral center for mastocytosis and a Center of Excellence in the European Competence Network of Mastocytosis,	Indolent and the related smoldering form of SM. Diagnosis of ISM and SSM was established by using the criteria of the World Health Organization Classification of Mastocytosis. If bone marrow data were unavailable or insufficient, ISM was	Prevalence per 10,000	0.13 (42 cases (30 with ISM, 1 SSM, 2 presumed ISM, 9 high-risk ISM (5 with UP))

Table 2. Studies reporting on the incidence of mastocytosis in the EU.

Reference; location; study period	Population	Data Source and study design	Case definition(s)	Outcome measure	Study outcome	Estimated prevalence
Cohen et al (2014); Denmark; January 1 1997-31 December 2010	Adults (> 15 years). SNOMED codes for mastocytosis had to be supplemented with a biopsy code in order for the patient to be included in the study.	Nationwide, retrospective, population-based cohort study. Data sources were as follows: • Danish medical registries: Danish National Patient Registry *(DNPR);* • National Pathology Registry *(NPR);* • Danish National Cancer Registry *(DCR);* • Civil Registration System *(CRS)*	SM (all subtypes including urticarial pigmentosa). Cases of SM were classified according to subtypes as defined by the WHO. Subtypes were categorized using combinations of ICD-10 and SNOMED codes. Patients were classified by the most severe disease found in either the pathology registry, cancer registry or NRP. Coding differed for the different sources : • *DNPR:* ICD-10 • *NPR:* SNOMED • *DCR:* Patients with ASM (ICD10: C96.2) or MCL (ICD10: C94.3) Patients with a SNOMED code of M97411 (mastocytosis, not known if benign or malignant) in the National Pathology Registry but without any mastocytosis diagnoses in the NRP were classified as SM (subtype unknown). UP was considered to be 'probable ISM'. In order to not miss patients in the registries misclassified as mastocytomas that are in fact patients with SM, we included	Incidence rate per 10,000 per year	SM (total) 0.089 (0.082-0.097) [548 cases in a population of 4,500,000] ISM (including UP) 0.073 (0.067-0.080); SM (unk) 0.010 (0.008-0.013); ASM 0.001 (0.0006-0.003); SM-AHNMD 0.004 (0.003-0.006); MCL 0.001 (0.0003-0.002)	SM (total) 7.21 per 10,000* ISM (including UP) 5.91 per 10,000* SM (unk) 0.81 per 10,000* ASM 0.081 per 10,000* SM-AHNMD 0.32 per 10,000* MCL 0.081 per 10,000* [Note: Reported prevalence in article was 7.1-10.3-fold lower than incidence-based estimates; Table 26]
				Cumulative incidence per 10,000	SM (total) 1.246 (1.145-1.354) [548 cases in a population of 4,500,000] ISM (including UP) 1.023 (0.932-1.121); SM (unk) 0.139 (0.107-0.177); ASM 0.018 (0.009-0.034); SM-AHNMD 0.055 (0.036-0.080); MCL 0.011 (0.004-0.025)	

Reference; location; study period	Population	Data Source and study design	Case definition(s)	Outcome measure	Study outcome	Estimated prevalence
			mastocytomas with bone marrow as the recorded site code in our analysis in the SM (subtype unknown) group.			
D'Inca et al (1996); Italy (Reggio Emilia region); 1986-1994	Patients of all ages	Retrospective study Numerator: cases in the Archives of the Division of Internal Medicine and Dermatology and the Service of Pathological Anatomy of the Arcispedale Santa Maria Nuova of Reggio Emilia. Denominator: population data for the entire region.	Cutaneous mastocytosis (CM)	Average incidence	0.03 new cases per 10,000 inhabitants per year [15 cases in a population of 400,000]	2.43 per 10,000*
Kibsgaard et al (2020); Denmark; January 1 1977 – 31 December 2014	Patients of all ages.	Nationwide, retrospective, population-based cohort study. Data sources were as follows: • Danish medical registries: Danish National Patient Registry (DNPR); • National Pathology Registry (NPR); • Civil Registration System (CRS)	ISM Coding differed for the different sources: • DNPR: ICD-10 • NPR: SNOMED Mastocytosis cases were classified according to the corresponding WHO-classification diagnoses. The authors provide a supplement document with an exhaustive list of all relevant ICD-10 and SNOMED codes used (available here).	Incidence rate per 10,000 per year	Mastocytosis overall 0.11 (0.10-0.12) [1275 cases (856 with CM, 393 with ISM, 26 with SM)] CM: 0.075 (0.07-0.09) ISM: 0.04 (0.03-0.05)	Mastocytosis overall 8.91 per 10,000* CM: 6.08 per 10,000* ISM: 3.2 per 10,000* [Note: Reported prevalence in article was 1.8 per 10,000; Table 26]
Marton et al (2016); Hungary (Southern Great Plain region comprising 3 districts); 2001-2013	Adults (≥15 years)	Retrospective study Medical database (outpatient and inpatient) of a haematological clinical centre catering for the	Systemic mastocytosis (SM) ICD-10 code	13-year cumulative incidence	0.27/10,000 (35 cases (14 with ISM, 15 with SM-AHN (SM-AHNMD), and 6 with ASM subtypes) in 1,103,463 inhabitants)	1.68 per 10,000*

Reference; location; study period	Population	Data Source and study design	Case definition(s)	Outcome measure	Study outcome	Estimated prevalence
		population in 3 districts				
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	AdvSM (includes: systemic mastocytosis with associated hematologic neoplasm, aggressive systemic mastocytocis and mast cell leukemia) Classification of patients was based on the 2016 WHO criteria.	Average annual incidence per 10,000 inhabitants.	AdvSM: 0.008 per 10,000 inhabitants.	0.65 per 10,000* [Note: Reported prevalence in article was 0.052 per 10,000; Table 26]

Abbreviations: AdvSM, advanced systemic mastocytosis; ASM, aggressive systemic mastocytosis; CM, cutaneous mastocytosis; CRS, Civil Registration System; DCR, Danish National Cancer Registry; DNPR, Danish National Patient Registry; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision; ISM, indolent systemic mastocytosis, MCL, mast cell leukemia; NPR, National Pathology Registry; SM-AHN, systemic mastocytosis with associated hematologic neoplasm; SM-AHNMD, systemic mastocytosis with 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 Organization.
* The estimate for prevalence was calculated as a function of the full lifespan of the individual. The full life span was estimated to be the EU-28 average life expectancy (males and females combined) at birth for 2014, which is 80.9 years.

Table 3. Studies reporting on the number of cases of mastocytosis in the EU.

Reference; location; study period	Population	Data Source and study design	Case definition(s)	Outcome measure	Study outcome	Estimated prevalence
Broesby-Olsen et al (2016) ; Denmark ; January 1 1997-December 31 2012	Adults (> 15 years). Persons with a prior diagnosis of a solid cancer, VTE, MI, stroke, anaphylaxis, osteoporosis, or fracture more than 3 years before SM diagnosis or index date, were excluded from the study.	Nationwide, population-based cohort study. Data sources were as follows: • Danish medical registries: Danish National Patient Registry *(DNPR);* • National Pathology Registry *(NPR);* • Danish National Cancer Registry *(DCR);* Civil Registration System *(CRS)*	SM SM cases were classified according to the most severe subtype as defined by the WHO. Patients with UP were considered to have probable ISM and were grouped with ISM patients in the analyses. Coding differed for the different sources : • *DNPR:* ICD-10 • *NPR:* Systematized Nomenclature of Medicine-Clinical Terms (SNOMED-CT). • *DCR:* no details given. Patients with a SNOMED code M97411 (mastocytosis, not known if benign or malignant) in the NPR, but no mastocytosis diagnoses in the DNPR or DCR were classified as "SM of unknown subtype," since data did not allow these patients to be further classified into a specific SM subtype. The diagnostic codes did not permit discrimination between ASM and MC sarcoma, an exceedingly rare subtype of SM.	Cases	687 cases in a population of 4,500,000	1.53 per 10,000^

Abbreviations: CRS, Civil Registration System; DCR, Danish National Cancer Registry; DNPR, Danish National Patient Registry; NPR, National Pathology Registry; SM, systemic mastocytosis; SNOMED CT, Systematized Nomenclature of Medicine - Clinical Terms; UMCG, University Medical Center Groningen; UP, urticaria pigmentosa; WHO, World Health Organization.
^Calculated using the population size (4,500,000) of Denmark in 2009.

The sponsor highlights a paucity of data on the prevalence and incidence of mastocytosis in the EU. Only four data sources were identified for prevalence. Cohen et al (2014) estimate the 14-year prevalence of mastocytosis to be 0.959 (0.873-0.105) per 10,000 in Denmark. 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. The four studies differ in terms of the type of SM covered. Cohen covers all types of SM (including Urticaria Pigmentosa:UP), whereas those presented in the Kibsgaard, Van Doormaal and Schwaab studies focus on ISM, ISM and SSM, and AdvSM, respectively. The Cohen and Van Doormaal studies were conducted in subjects aged 15 years and older, while the Kibsgaard and Schwaab studies included patients of all ages. With the exception of UP in Cohen et al, the other studies did not present prevalence for CM.

Additional prevalence estimates were obtained from incidence data. A prevalence of 2.43 cases of CM per 10,000 was estimated based on 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 6.08 per 10,000 and an overall mastocytosis prevalence of 8.91 per 10,000 (Kibsgaard et al, 2020). For Hungary (Marton et al, 2016), the prevalence estimated 1.68 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) and Schwaab et al (2020). The prevalence estimates reported in Cohen et al (2014), Kibsgaard

et al (2020) and Van Doormaal et al (2013) were considered to be the most robust by the sponsor, despite two not including children or the full spectrum of CM. The sponsor states that Brockow (2014) 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.

The COMP accepted the final prevalence estimate of less than 3 in 10,000 proposed by the sponsor.

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).*

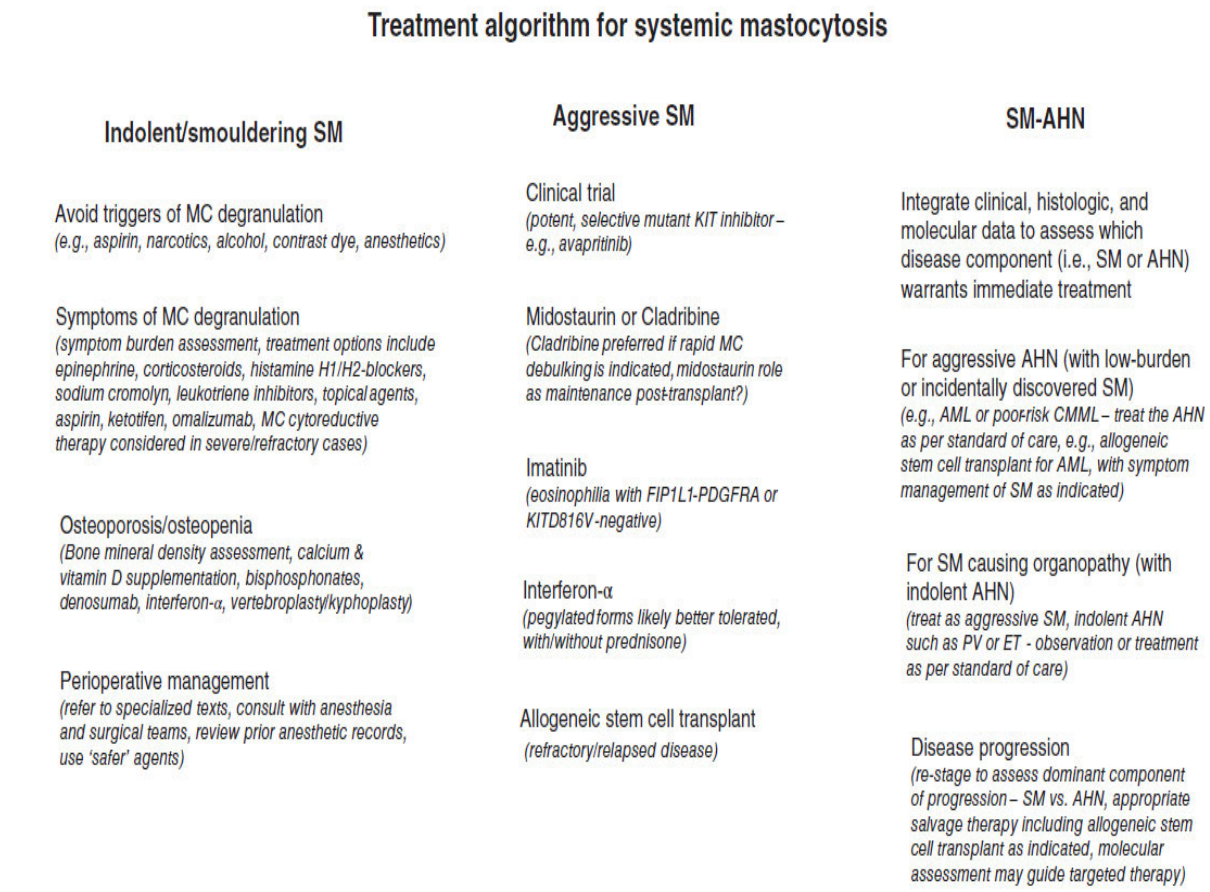
As cimetidine has a therapeutic indication limited to "treatment of upper gastrointestinal bleeding from peptic ulcers or erosions" the indication does not fully overlap with the one for Ayvakyt and therefore cimetidine is not considered a satisfactory method for the target patient population of Ayvakyt and does not have to be considered for the purpose of significant benefit.

Midostaurin is the only product authorized centrally in Europe for mastocytosis and has the following indication: Rydapt is indicated 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).

The therapeutic indication overlaps with the one sought for Ayvakyt and midostaurin can therefore be considered a satisfactory method to treat this target patient population.

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. This is summarized below.

Figure 1.


Treatment algorithm for systemic mastocytosis
Indolent/smouldering SM
Avoid triggers of MC degranulation
(e.g., aspirin, narcotics, alcohol, contrast dye, anesthetics)
Symptoms of MC degranulation
(symptom burden assessment, treatment options include epinephrine, corticosteroids, histamine H1/H2-blockers, sodium cromolyn, leukotriene inhibitors, topical agents, aspirin, ketotifen, omalizumab, MC cytoreductive therapy considered in severe/refractory cases)
Osteoporosis/osteopenia
(Bone mineral density assessment, calcium & vitamin D supplementation, bisphosphonates, denosumab, interferon-α, vertebroplasty/kyphoplasty)
Perioperative management
(refer to specialized texts, consult with anesthesia and surgical teams, review prior anesthetic records, use 'safer' agents)
Aggressive SM
Clinical trial
(potent, selective mutant KIT inhibitor – e.g., avapritinib)
Midostaurin or Cladribine
(Cladribine preferred if rapid MC debulking is indicated, midostaurin role as maintenance post-transplant?)
Imatinib
(eosinophilia with FIP1L1-PDGFRA or KITD816V-negative)
Interferon-α
(pegylated forms likely better tolerated, with/without prednisone)
Allogeneic stem cell transplant
(refractory/relapsed disease)
SM-AHN
Integrate clinical, histologic, and molecular data to assess which disease component (i.e., SM or AHN) warrants immediate treatment
For aggressive AHN (with low-burden or incidentally discovered SM)
(e.g., AML or poor-risk CMML – treat the AHN as per standard of care, e.g., allogeneic stem cell transplant for AML, with symptom management of SM as indicated)
For SM causing organopathy (with indolent AHN)
(treat as aggressive SM, indolent AHN such as PV or ET - observation or treatment as per standard of care)
Disease progression
(re-stage to assess dominant component of progression – SM vs. AHN, appropriate salvage therapy including allogeneic stem cell transplant as indicated, molecular assessment may guide targeted therapy)

Significant benefit

The sponsor's target population is defined by the following indication: *AYVAKYT is indicated 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*.

Initial Scientific Advice from the CHMP regarding the SM program for avapritinib was received on 31 May 2018 (procedure EMEA/H/SA/3738/2/2018/SME/III). Later, Simultaneous National Scientific Advice was obtained from the Spanish Agency of Medicines and Medical Products and the Norwegian Medicines Agency for a planned external-control, observational, retrospective study (BLU-285-2405). But no discussion on the significant benefit with the COMP was held.

The sponsor argues a significant benefit over midostaurin based on a clinically relevant advantage in patients who have already been pretreated with at least one prior systemic therapy (midostaurin). The avapritinib patient population from studies BLU-285-2101 and BLU 285-2202 received at least one prior systemic therapy, in contrast to the midostaurin study population (D2201 FAS), in which more than half of patients received no prior systemic therapy.

The sponsor has provided data from two uncontrolled single arm studies in patients with AdvSM, which are also the basis for the benefit risk assessment: the Phase 1 study BLU-285-2101 in pretreated patients and Phase 2 study BLU-285-2202 in naïve and pretreated patients.

For the purpose of significant benefit the sponsor provided data of a subset of patients who were relapsed or refractory to prior midostaurin treatment. This is summarised below.

<u>Avapritinib in AdvSM patients with prior midostaurin treatment.</u>

The ORR of avapritinib in AdvSM patients who had received prior midostaurin and a starting dose of up to and including 200 mg was 76.0% (19 of 25 patients; 95% confidence interval: 54.9, 90.6), including 2 patients (8.0%) with CR, 4 patients (16.0%) with CRh, and 10 patients (40.0%) with PR (Table 4).

In the Response Adjudication Committee-Response evaluable (RAC-RE) population with prior midostaurin, the median DOR is currently not available. The sponsor however, reports that after a median follow-up of 20.9 months, 3 of the 19 patients had a DOR event (progressive disease/loss of response (LoR) or death due to any cause) at the time of data cut off. The data further demonstrate that avapritinib provides an alternative in patients with AdvSM who no longer respond to midostaurin and for whom there are no other medicinal treatment options.

Table 4. Adjudicated avapritinib best response by mIWG-MRT-ECNM criteria in patients previously treated with midostaurin (Original application population, Pooled BLU-285-2101 + BLU-285-2202, RAC-RE population, starting dose up to and including 200 mg of avapritinib).

Parameter	Patients previously treated with Midostaurin			
	ASM N=1	SM-AHN N=19	MCL N=5	All AdvSM N=25
ORR (CR + CRh + PR + CI), n (%)	1 (100)	14 (73.7)	4 (80.0)	19 (76.0)
95% confidence interval	(2.5, 100)	(48.8, 90.9)	(28.4, 99.5)	(54.9- 90.6)
CR+CRh+PR, n (%)	1 (100)	11 (57.9)	4 (80.0)	16 (64.0)
95% confidence interval	(2.5, 100)	(33.5, 79.7)	(28.4, 99.5)	(42.5, 82.0)
CR+CRh, n (%)	1 (100)	4 (21.1)	1 (20.0)	6 (24.0)
95% confidence interval	(2.5, 100)	(6.1, 45.6)	(0.5, 71.6)	(9.4, 45.1)
Best response, n (%)				
CR	0	1 (5.3)	1 (20.0)	2 (8.0)
CRh	1 (100)	3 (15.8)	0	4 (16.0)
PR	0	7 (36.8)	3 (60.0)	10 (40.0)
CI	0	3 (15.8)	0	3 (12.0)
SD	0	1 (5.3)	1 (20.0)	2 (8.0)
PD	0	0	0	0
NE	0	4 (21.1)	0	4 (16.0)

Abbreviations: CI, clinical improvement; CR, complete remission; CRh, complete remission with partial recovery of peripheral blood counts; mIWG-MRT-ECNM, modified International Working Group-Myeloproliferative Neoplasm Research and Treatment and European Competence Network on Mastocytosis; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial remission; RAC-RE, Response Assessment Committee-response evaluable; SD, stable disease.

As shown in Table 5 below, the ORR of avapritinib in patients previously treated with midostaurin is not significantly different from the ORR seen in patients not previously treated with midostaurin or any other AdvSM population, regardless of prior therapies, support sequential therapies with TKIs in AdvSM, e.g. avapritinib after midostaurin or after at least one other therapy.

Table 5. Adjudicated best response by mIWG-MRT-ECNM criteria in patients by prior therapies (Original application population, Pooled BLU-285-2101 + BLU-285-2202, RAC-RE population, starting dose up to and including 200 mg of avapritinib).

Population	ORR	95% confidence interval
Overall population	42/53 (79.2%)	(65.9, 89.2)
No prior systemic therapy	16/18 (88.9%)	(65.3, 98.6)
No prior midostaurin	23/28 (82.1%)	(63.1, 93.9)
Prior systemic therapy	26/35 (74.3%)	(56.7, 87.5)
Prior midostaurin	19/25 (76.0%)	(54.9, 90.6)

Abbreviations: mIWG-MRT-ECNM, modified International Working Group-Myeloproliferative Neoplasm Research and Treatment and European Competence Network on Mastocytosis; ORR, overall response rate; RAC-RE, Response Assessment Committee-response evaluable.

The efficacy demonstrated in Study BLU-285-2202 in AdvSM patients with at least one prior systemic therapy, including those who have been previously treated with midostaurin, supports a clinically relevant advantage of avapritinib in the AdvSM patient population.

This was accepted as the basis of significant benefit.

4. COMP position adopted on 2 February 2022

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 with 5-year rates of around 60% in patients with systemic mastocytosis;
- although satisfactory methods for the Treatment of the condition have been authorised in the European Union, the assumption that Ayvakyt may be of potential significant benefit in patients who have relapsed or refractory aggressive systemic mastocytosis still holds. Clinically relevant responses were observed in patients who failed one prior systemic therapy. The COMP considered that the product offers a clinically relevant advantage.

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 Avyakyt, avapritinib, for treatment of mastocytosis (EU/3/18/2074) is not removed from the Community Register of Orphan Medicinal Products.