24 September 2020
EMADOC-1700519818-499131
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Ayvakyt (avapritinib)

Treatment of gastrointestinal stromal tumours

EU/3/17/1889

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)	(S)-1-(4-fluorophenyl)-1-(2-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-4-yl)piperazin-yl)pyrimidin-5-yl)ethan-1-amine
Other name(s)	(S)-1-(4-fluorophenyl)-1-(2-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-4-yl)piperazin-yl)pyrimidin-5-yl)ethan-1-amine,
International Non-Proprietary Name	Avapritinib
Tradename	Ayvakyt
Orphan condition	Treatment of gastrointestinal stromal tumours –
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 date	15 June 2017
EC decision date	17 July 2017
EC registration number	EU/3/17/1889
Post-designation procedural history	
Transfer of sponsorship	Transfer from PhaRA bvba to Blueprint Medicines (Netherlands) B.V. – EC decision of 20 May 2019
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Maria Concepcion Prieto Yerro / Ingrid Wang
Applicant	Blueprint Medicines (Netherlands) B.V.
Application submission date	01 July 2019
Procedure start date	18 July 2019
Procedure number	EMEA/H/C/005208
Invented name	Ayvakyt
Proposed therapeutic indication	Ayvakyt is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation. 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 date	23 July 2020
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Frauke Naumann-Winter/ Maria Elisabeth Kalland
Sponsor's report submission	2 March 2020

COMP discussion	16-18 June 2020
COMP opinion (adoption via written procedure)	29 July 2020

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2017 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 clinical data demonstrating that patients affected by the condition respond to treatment;
- the condition is chronically debilitating and life-threatening, in particular due to the high rate of relapse and development of metastatic disease resulting in a poor survival;
- the condition was estimated to be affecting approximately 2 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 have been authorised in the European Union (EU), 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 that demonstrated clinical responses in patients, who have relapsed or were refractory after treatment with best standard of care including authorised products. The Committee considered that this constitutes a clinically relevant advantage.

3. Review of criteria for orphan designation at the time of marketing authorisation

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

Gastrointestinal stromal tumours (GIST) are non-epithelial tumours of mesenchymal origin that arise predominantly in the gastrointestinal tract (GIT).

GIST is thought to develop from the interstitial cells of Cajal or their stem cell precursors that are located in the myenteric plexus of the GI tract. In 85% cases of GIST, tumour behaviour is driven by KIT mutations. C-kit receptor tyrosine kinase gene encodes for a transmembrane receptor. GIST is most common in the stomach (60-70%), followed by the small intestine (20-30%), and then the colon and rectum (5%). GIST is associated with several gene mutations.

The median age of diagnosis of GIST is 60-65 years and is most commonly diagnosed between the ages of 50 and 80 years. GIST rarely occurs in the paediatric population (<1%) and in this age group, tumours may have a different pathogenesis than adult GIST as neither KIT nor PDGFRα mutations seem to be present.

The most common symptom at presentation is bleeding. Patients with GIST may also have various other symptoms, such as abdominal pain or discomfort, early satiety, bloating, obstructive jaundice, dysphagia, fever and anaemia-related symptoms such as fatigue and palpitations, or they may present with an abdominal tumour with no symptoms. Between 10% and 25% of patients present with metastatic disease. GIST often remains clinically silent until tumours reach a large size, when mass effects, bleeding, or rupture may ensue.

The COMP continues to designate this condition.

The proposed therapeutic indication "*Ayvakyt® is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation"* falls within the scope of the designated orphan condition "Treatment of gastrointestinal stromal tumours".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed on the 23 July 2020 by a CHMP positive benefit/risk assessment.

Chronically debilitating and/or life-threatening nature

The condition is known to be life threatening with a median overall survival of < 5 years in locally advanced or metastatic GIST. Survival has, however, improved with the authorisation of imatinib: in the pre-imatinib period 1990-1998, the 12 months and 5-year survival rates for GIST patients were respectively 81.5% and 48%; in the period 1999-2005, the 12 months and 5-year survival rates increased to 86.4% and 63.1%, respectively, and further improved in the period 2006-2011 being 89.7% and 69%, respectively.

The COMP continues to consider the condition to be chronically debilitating and life-threatening, in particular due to the high rate of relapse and development of metastatic disease resulting in a poor survival.

Number of people affected or at risk

It was noted by the COMP that most of the cancer registries searched classified cancers by site and do not mention GIST in their reports or public information.

To overcome this, two approaches to the prevalence calculation have been provided.

- The first is a literature search to establish the reported prevalence in different Member States.
- The second considers the incidence reported in the literature and offers a calculation based on the overall survival of the patients using the equation of incidence X duration (years) = prevalence.

Overall, 16 data sources were found reporting GIST incidence and 2 data sources reported GIST prevalence (Norway and the UK). From these 2 data sources, the estimates ranged from 0.8 per 10,000 in Norway to 1.5 per 10,000 population in the UK, with the upper 95% CI limits at 1.2 and 2 per 10,000 population in Norway and the UK, respectively.

Among the studies reporting incidence, most had a regional or country level focus, with only one study including data from several European countries (Stiller et al, 2013). The sponsor states that only data sources that provided European age-adjusted estimates for comparability purposes were selected. In order to estimate prevalence from incidence, the sponsor used survival data for GIST with localized disease at diagnosis (median OS of 14.5 years). Following this logic, the estimated prevalence could be considered as the maximum prevalence possible for the disease. This was accepted by the COMP.

From the data submitted by the sponsor it can be seen that in general the reported prevalence and incidence of the condition are highly variable and in a range of 0.1 to 2.8 in 10,000.

In the current ESMO Guideline a publication from Sweden in 2005 indicated that the incidence was 0.1 in 10,000. (Nilsson B, Bumming P, Meis-Kindblom JM et al. Gastrointestinal stromal tumours: the incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era–a population-based study in western Sweden. Cancer 2005; 103: 821–829.).

In conclusion the incidence is reported from 0.1 to 2.1 in 100.000, with the most recent publications providing estimates of approx. 1.5 in 100.000. The sponsor initially introduced age-standardisation into the calculation which lowers the estimate for the incidence, to which the COMP did not agree. In a written procedure the sponsor submitted a revised non-age-standardised prevalence calculation which estimated that the prevalence was 3.1 in 10,000. The COMP rounded this off to 3 in 10,000 and accepted this final figure for the purpose of maintaining the orphan designation.

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

The sponsor indicated that no new products have been authorised since the original designation in 2017. The following products have an approval in the EU:

Table 1.

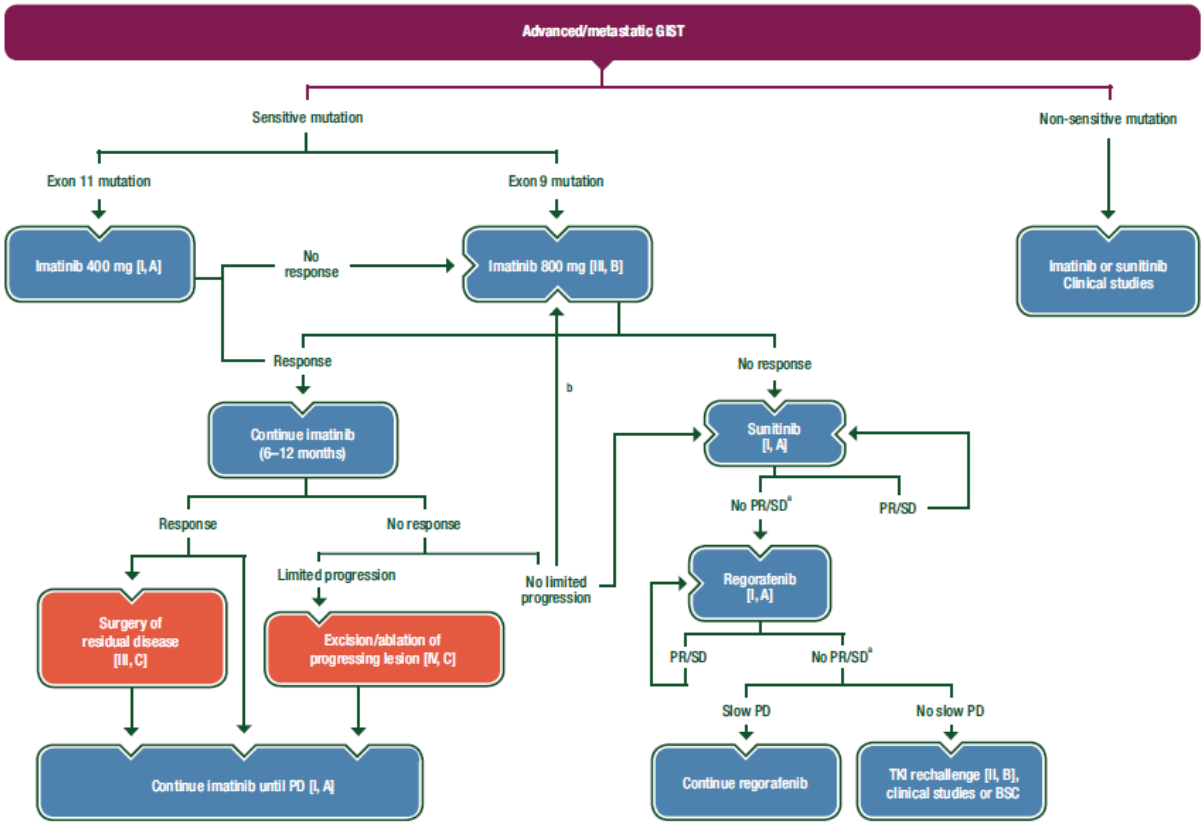
Tradename (INN)	**Member State(s) Approved**	**Marketing Authorization Holder (MAH)**	**Authorized Indication (GIST-Related)**
Glivec (imatinib)	EU/EEA (centralized procedure)	Novartis Europharm Ltd	- Treatment of adult patients with Kit (CD117)-positive unresectable and / or metastatic malignant GIST - Adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment
Sutent (sunitinib)	EU/EEA (centralized procedure)	Pfizer Limited	Treatment of unresectable and/or metastatic malignant GIST in adults after failure of imatinib treatment due to resistance or intolerance.
Stivarga (regorafenib)	EU/EEA (centralized procedure)	Bayer Pharma AG	Treatment of unresectable or metastatic GIST who progressed on or are intolerant to prior treatment with imatinib and sunitinib

Current ESMO Guidelines on this condition were released in 2018 (Casali, Ann of Oncol. 2018; 29 (S4): iv68–78.

The standard treatment of localised GIST is complete surgical excision of the lesion, with no dissection of clinically negative lymph nodes.

For advanced forms the following algorithm is recommended.

Figure 1. Management of advanced/metastatic GIST. A Surgery of limited progression may be considered if previously treated with 400 mg imatinib. BSC, best supportive care; GIST, gastrointestinal stromal tumour; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.



Imatinib is the standard treatment for locally advanced inoperable and metastatic disease, as well as for patients previously treated with adjuvant imatinib who did not relapse while receiving it. Imatinib is also the standard treatment for patients with metastatic disease who have had all lesions removed surgically, although surgery is not recommended as a primary approach in the metastatic setting. Sunitinib and regorafenib are authorised in the setting of metastatic or unresectable disease after failure of previous treatment(s) (see table above). No product is specifically authorised for a molecularly defined subgroup of patients.

Significant benefit

The therapeutic indication of avapritinib is: "*Ayvakyt is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) harbouring the platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation*." The sponsor is therefore targeting a patient population with a specific mutation which has been resistant to current authorised medicines.

The sponsor claims that PDGFRA D842V-mutant GIST patients show a very low response rate and short PFS following treatment with the medicinal products currently authorized for treatment of GIST in the EU.

The clinical development programme supporting the efficacy of avapritinib in GIST includes one single pivotal study called the NAVIGATOR study. It is an on-going Phase 1, first-in-human, dose-

escalation, expansion, open-label study to evaluate the safety, tolerability, PK, PD and efficacy of avapritinib in adults with unresectable GIST. At the time of the MAA submission, efficacy data have been provided with a data cut-off date of 16 November 2018. An additional 14 months of follow-up (data cut-off date: 17 January 2020) was provided during the MA assessment.

The study design consisted of two parts: a dose escalation part (Part 1, completed), and a dose expansion part (Part 2, ongoing). The open-label, uncontrolled design of the NAVIGATOR study, along with the reduced sample size, pose relevant limitations to the interpretation of the results.

The most recently updated data in the PDGFRA D842V mutated GIST population (DCO: 17-Apr-2020) was consistent with the efficacy results previously submitted, and confirmed a high and durable response to avapritinib: ORR of 95% (95% CI: 82.3, 99.4), median PFS of 24 months (95% CI: 18.4, NE), and a DOR of 22.1 months (95% CI: 14.1, NE). The median OS was not yet reached (36-months OS rate is 70.6% (95% CI: 55.2, 86.0). Among the PDGFRA-D842V mutated GIST patients from an ongoing, controlled, phase 3 study (BLU-285-1303; VOYAGER; DCO: 09-Mar-2020), ORR in the avapritinib group was 42.9% (all partial responses), while none of the patients in the regorafenib group responded (0% ORR). Regarding median PFS, there was a statistically significant difference, with a non-estimable median PFS in GIST patients with PDGFRA D842V mutations who were randomized to avapritinib (95% CI: 9.7, not NE) compared to 4.5 months in patients receiving regorafenib (95% CI: 1.7, NE). These data were considered supportive to the data from the NAVIGATOR study.

The result in term of durable responses compared favourably with that reported from the literature to other TKIs in the target GIST population. Overall, the reported results in the mutated population were considered relevant in the context of a patient population with limited treatment options and poor responses to approved TKI agents. This benefit was considered to be clinically meaningful.

The COMP accepted that a clinically relevant advantage in the proposed target population exists and considered significant benefit holds for the purpose of the maintenance of orphan status.

4. COMP position adopted on 29 July 2020

The Committee for Orphan Medicinal Product (COMP) considered that the designated orphan condition "Treatment of gastrointestinal stromal tumours" is acceptable.

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 gastrointestinal stromal tumours (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 and life-threatening, in particular due to the high rate of relapse and development of metastatic disease resulting in a poor survival;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that avapritinib may be of significant benefit in the treatment of adult patients with unresectable or metastatic GIST harbouring the PDGFRA D842V mutation, a population for which no effective treatments are available, still holds;

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, (S)-1-(4-fluorophenyl)-1-(2-(4-(6-(1-methyl-1H-pyrazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-4-yl)piperazin-yl)pyrimidin-5-yl)ethan-1-amine, avapritinib, for treatment of gastrointestinal stromal tumours (EU/3/17/1889) is not removed from the Community Register of Orphan Medicinal Products.