18 November 2021
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Qinlock (ripretinib)
Treatment of gastrointestinal stromal tumours
EU/3/17/1936

Sponsor: Deciphera Pharmaceuticals (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	1-[4-bromo-5-[1-ethyl-7-(methylamino)-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl]-3-phenylurea
Other names	--
International Non-Proprietary Name	Ripretinib
Tradename	Qinlock
Orphan condition	Treatment of gastrointestinal stromal tumours
Sponsor's details:	Deciphera Pharmaceuticals (Netherlands) B.V. Atrium Building Floor 4th Strawinskylaan 3051 Amsterdam Noord-Holland 1077 ZX Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Worldwide Clinical Trials Limited
COMP opinion	12 October 2017
EC decision	07 November 2017
EC registration number	EU/3/17/1936
Post-designation procedural history	
Transfer of sponsorship	Transfer from Worldwide Clinical Trials Limited to Pharma Gateway AB – EC decision of 18 May 2018 Transfer from Pharma Gateway AB to Deciphera Pharmaceuticals (Netherlands) B.V. – EC decision of 07 July 2020
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Filip Josephson / Blanca Garcia-Ochoa
Applicant	Deciphera Pharmaceuticals (Netherlands) B.V.
Application submission	12 September 2020
Procedure start	01 October 2020
Procedure number	EMA/H/C/005614/0000
Invented name	QINLOCK
Proposed therapeutic indication	Treatment of adult patients with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib. Further information on Qinlock can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Qinlock
CHMP opinion	16 September 2021
COMP review of orphan medicinal product designation procedural history	
COMP rapporteurs	Maria Elisabeth Kalland / Frauke Naumann-Winter

Sponsor's report submission	29 April 2021
COMP discussion and adoption of list of questions	07-09 September 2021
COMP opinion	07 October 2021

2. Grounds for the COMP opinion

The sponsor Worldwide Clinical Trials Limited submitted on 26 June 2017 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing 1-[4-bromo-5-[1-ethyl-7-(methylamino)-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl]-3-phenylurea for treatment of gastrointestinal stromal tumours (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

Having examined the application, the COMP considered that the sponsor has established the following:

• the intention to treat the condition with the medicinal product containing 1-[4-bromo-5-[1-ethyl-7-(methylamino)-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl]-3-phenylurea was considered justified based on clinical data in patients with relapsed or refractory gastrointestinal stromal tumours showing achievement of partial responses or stable disease;

• the condition is chronically debilitating and life-threatening, in particular due to the high rate of relapse and development of metastatic disease resulting in poor survival;

• the condition was estimated to be affecting approximately 1.6 in 10,000 persons in the European Union, at the time the application was made.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

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 1-[4-bromo-5-[1-ethyl-7-(methylamino)-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl]-3-phenylurea will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrated durable 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.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing 1-[4-bromo-5-[1-ethyl-7-(methylamino)-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl]-3-phenylurea as an orphan medicinal product for the orphan indication: treatment of gastrointestinal stromal tumours.

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 (GISTs) are a common form of soft tissue sarcoma, a relatively rare subset of cancers arising from mesenchymal cells in the body. The most frequent location for GISTs is the stomach or small intestine, and they have the following approximate distributions: stomach (60-70%); small intestine (20-30%); rectum (3%); colon (1–2%); esophagus (<1%); omentum/ mesentery (rare). The majority of the tumours arise from activating mutations in the proto-oncogene receptor tyrosine kinase (KIT; 80-85%) and the related platelet-derived growth factor receptor alpha (PDGFRA; 5-10%) genes, whereas a small percentage (10-15%) are wildtype in either KIT or PDGFRA.

Symptoms of GIST vary depending on the location, size, and aggressiveness of the tumour. The most common symptom at presentation is bleeding. The condition is also often manifested by fatigue and palpitations, abdominal pain or discomfort, and gastrointestinal (GI) obstruction. The median age at diagnosis of GIST is 60-65 years. The condition is often diagnosed between the ages of 50 to 80 years. GIST rarely occurs in the paediatric population (<1%) and in this age group, tumours may have a different pathogenesis than adult GISTs as neither KIT nor PDGFRα mutations seem to be present.

The understanding of gastrointestinal stromal tumours and their classification has not changed since the initial orphan designation. The approved therapeutic indication "Qinlock is indicated for the treatment of adult patients with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib" 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 by the positive benefit/risk assessment of the CHMP on the basis of the submitted evidence including data from the pivotal study DCC-2618-03-001 (INVICTUS).

Chronically debilitating and/or life-threatening nature

The prognosis of GIST varies based on tumour size, mitotic rate, location, and mutation status. In general, small tumours of less than 2 cm are considered low risk for metastasis, whereas larger tumours carry more risk, particularly if they are of a higher mitotic rate. GIST located in the stomach is typically of a lower risk compared to intestinal GIST. Mutation status has some correlation with prognosis but is not commonly included in prognostic classification tools (Casali et al., 2018).

The sponsor provided the example of Sweden, where 44% of symptomatic, clinically detected GISTs were categorized as high risk (29%) or overtly malignant (15%), with tumour-related deaths occurring in 63% of patients and 83% of patients, respectively (estimated median survival of 40 months and 16 months, respectively). Symptoms of GIST include acute abdomen caused by tumour rupture, GI obstruction, appendicitis-like pain, fatigue and palpitations, dysphagia, fever, and early satiety. Between 10-25% of the patients present with metastatic disease.

The condition therefore is chronically debilitating and life-threatening in nature.

Number of people affected or at risk

The prevalence was presented to the COMP to remain below the established orphan designation threshold of 5 per 10,000 people in the EU. Based on a prevalence calculation from incidence data, the prevalence proposed by the sponsor ranges from 1.3 to 1.6 per 10,000 people.

In 2017, Hompland and colleagues calculated the median overall survival (OS) of patients diagnosed with metastatic GIST from 1995 to 2013. Survival data for 115 patients with metastatic GIST from the sarcoma database at Oslo University Hospital were included in this study report. The median OS from diagnosis of those patients was 6.9 years with a 95% CI of 5.6 to 8.3 years (Hompland et al., 2017). The incidence data used for the prevalence estimate was based on a study using pooled data from the national German cancer registry (ZfKD), which reported the highest crude incidence for GIST of approximately 0.19 per 10,000 inhabitants (Ressing et al., 2018). This study described a German-wide population-based incidence of GIST over a period of 10 years from 2004 to 2013.

With a median OS of 6.9 years and an incidence of 0.19 per 10,000 inhabitants (Ressing et al., 2018), the prevalence of GIST was calculated to be 1.3 per 10,000 inhabitants (P=0.19*6.9). For a conservative estimate, the upper bound of the 95% CI reported for the OS of the Norwegian study cohort was used in the prevalence calculation giving a prevalence estimate of 1.6 per 10,000 inhabitants (P=0.19*8.3).

The COMP questioned this figure since it only refers to metastatic patients. The sponsor provided an updated prevalence calculation on request and suggested the value of 2.6 in 10,000 based on a review of data from several studies considered relevant to the whole GIST population. This was based on a calculation of the OS in a large, open cohort of patients (N=1215) diagnosed with GIST (Call et al., 2012). The cohort consisted of patients with advanced or metastatic disease and non-metastatic disease at diagnosis. The median OS for the entire cohort was calculated to be 11.7 years, which is consistent with the median OS reported by Nilsson and colleagues in 2005 (Nilsson et al., 2005). Based on the status of the disease at time of diagnosis, the median OS was calculated to be 6.9 years for patients reporting metastatic or advance disease at diagnosis and 14.5 years for patients without metastatic or advanced disease at diagnosis. Because GIST in children is rare and the paediatric population only accounts for 1-2% of all GIST cases, the authors excluded this paediatric population from the cohort. The median OS calculated for the adult population group was 13.6 years. For a conservative calculation, the median OS for the adult population was used in the prevalence calculation giving an estimate of 2.6 per 10,000 inhabitants (P=0.19*13.6).

The COMP accepted this calculation and phrased the final accepted value as 'less than 3 in 10,000' for consistency with recent assessments.

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

Metastatic or unresectable GIST is present in approximately half of the patients at diagnosis, and radiotherapy and traditional chemotherapy are not effective (Aubin et al., 2011; Eisenberg et al.,

2011). Surgical resection is the only potentially curative treatment for GIST but there is a 50% recurrence (Kee et al., 2012). Medicinal products for the treatment of GIST are available, with imatinib being the standard of care in high-risk patients with advanced/metastatic disease. There is no established standard of care after first-line therapy with imatinib. The sponsor refers to the European Society for Medical Oncology (ESMO) and EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up of GIST which provides an overview of clinical treatment options (Casali et al., 2018). According to the guidelines, the current treatment scheme involves sequential administration of the tyrosine kinase inhibitors (TKIs) imatinib (Glivec), sunitinib (Sutent), and regorafenib (Stivarga). Once patients experience progressive disease while on regorafenib, the options in the fourth-line setting are either TKI re-challenge, best supportive palliative care, or recruitment into clinical trials.

The sponsor provided a list of authorized products in the EU for the treatment of GIST, which includes: imatinib mesylate (first line), avapritinib (first line), sunitinib malate (second line), and regorafenib monohydrate (third line treatment):

Table 1. Approved medicinal products for the treatment of GIST in the EU

EU Centralised number	**Product name (INN)**	**Indication**	**Significant benefit**
EMEA/H/C/000406	Glivec (imatinib)	Glivec is indicated for the treatment of adult patients with Kit (CD 117)-positive unresectable and/or metastatic malignant gastrointestinal stromal tumours (GIST)	No, earlier line
EMEA/H/C/000687	Sutent (sunitinib)	Sutent is indicated for the treatment of unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) in adults after failure of imatinib mesilate treatment due to resistance or intolerance	No, earlier line
EMEA/H/C/002573	Stivarga (regorafenib)	Stivarga is indicated as monotherapy for the treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib	No, earlier line
EMEA/H/C/005208	Ayvakyt (avapritinib)	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.	No, covers only specific mutation

The approved therapeutic indication "Qinlock is indicated for the treatment of adult patients with advanced gastrointestinal stromal tumour (GIST) who have received prior treatment with three or more kinase inhibitors, including imatinib" needs to be considered in relation to the other approved products for the treatment of the condition.

Qinlock is intended for use in the fourth- and later lines setting and there are no approved targeted therapies that broadly inhibit secondary drug-resistant mutations in GIST that occur upon failure with the authorised therapeutic options.

Considering the approved indications as noted above, the COMP concluded that no authorised products exist for the adult patients with advanced GIST who have received prior treatment with three or more kinase inhibitors, including imatinib. The authorised indication of Qinlock targets a different patient population than the indication of the authorised products, as it includes additional patient populations for whom the above products are not authorised.

The COMP concluded that there is no approved treatment that qualifies as a satisfactory treatment for the purpose of the examination of the significant benefit vis-à-vis Qinlock, as the authorised treatment options do not cover the entire patient population for which Qinlock is intended.

Significant benefit

Qinlock is intended for a patient population for whom no other satisfactory method is available (see above). No justification for significant benefit is therefore required.

4. COMP position adopted on 07 October 2021

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 poor survival;
- at present no satisfactory method has been authorised in the European Union for the treatment of the entirety of patients covered by the therapeutic indication of Qinlock.

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 Qinlock, 1-[4-bromo-5-[1-ethyl-7-(methylamino)-2-oxo-1,2-dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl]-3-phenylurea, ripretinib for treatment of gastrointestinal stromal tumours (EU/3/17/1936) is not removed from the Community Register of Orphan Medicinal Products.