9 November 2022
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Pyrukynd (mitapivat sulfate)
Treatment of pyruvate kinase deficiency
EU/3/20/2270

Sponsor: Agios 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)	Mitapivat sulfate
Other name(s)	-
International Non-Proprietary Name	Mitapivat
Tradename	Pyrukynd
Orphan condition	Treatment of pyruvate kinase deficiency
Sponsor's details:	Agios Netherlands B.V. Zuidplein 36 1077 XV Amsterdam Noord-Holland Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Agios Netherlands B.V.
COMP opinion	19 March 2020
EC decision	22 April 2020
EC registration number	EU/3/20/2270
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	A. Moreau / A. Genazzani
Applicant	Agios Netherlands B.V.
Application submission	25 June 2021
Procedure start	15 July 2021
Procedure number	EMA/H/C/005540
Invented name	Pyrukynd
Proposed therapeutic indication	Pyrukynd is indicated for the treatment of pyruvate kinase deficiency (PK deficiency) in adult patients (see section 4.4). Further information on Pyrukynd can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Pyrukynd
CHMP opinion	15 September 2022
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	E. Costa / E. J. Rook
Sponsor's report submission	11 August 2021
COMP opinion (adoption via written procedure)	19 September 2022

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2020 designation was based on the following grounds:

"The sponsor Agios Netherlands B.V. submitted on 27 November 2019 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing MITAPIVAT SULFATE for treatment of pyruvate kinase deficiency (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 mitapivat sulfate was considered justified based on clinical data in patients showing improvement in haemoglobin levels and reduction in markers of haemolysis;
- the condition is chronically debilitating and life-threatening due to symptoms of chronic haemolytic anaemia and sequelae of periodic red blood cell transfusions, comprising fatigue, shortness of breath, splenomegaly, cholecystolithiasis, heart failure, as well as compromised immune function and thromboembolic complications after splenectomy. The condition is also life-threatening due to aggravation of haemolytic anaemia during pregnancy and aplastic crisis during viral infections, as well as hydrops fetalis and perinatal death;
- the condition was estimated to be affecting less than 0.5 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.

The sponsor has also established that there exists no satisfactory method of treatment in the European Union for patients affected by the condition.

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 mitapivat sulfate as an orphan medicinal product for the orphan condition: treatment of pyruvate kinase deficiency".

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

Pyruvate kinase deficiency (PK deficiency) is a type of hereditary haemolytic anaemia caused by a deficiency in pyruvate kinase, which leads to destruction of red blood cells (RBCs). It has been estimated that there are about 371 PKLR gene variants associated with the disease.

In normal cells, pyruvate kinase enzymatically catalyses the metabolic conversion of phosphoenolpyruvate (PEP) and adenosine diphosphate (ADP) into pyruvate and adenosine triphosphate (ATP) as the final step in glycolysis, creating 50% of the RBC ATP (Grace et al, 2015). ATP is the main source of energy of the RBC. Pyruvate kinase deficiency leads to insufficient ATP production, resulting in RBC haemolysis due to an impaired ability to maintain cellular membrane homeostasis (van Wijk and van Solinge, 2005). Pyruvate kinase deficiency has been reported to be associated with reduced RBC survival (Aizawa et al, 2003).

For some patients with PK deficiency, the disease manifests itself at birth, and the diagnosis is early. But for many patients, diagnosis may take months or even years, or they remain non-diagnosed. The diagnosis of PK deficiency is multifactorial, based on the exclusion of the most common causes of haemolytic anaemias, and upon the demonstration of decreased enzyme activity and/or the identification of causative mutations in the PKLR gene.

The condition has been previously accepted by the COMP and is appropriate for an orphan designation.

The approved therapeutic indication "Pyrukynd is indicated for the treatment of pyruvate kinase deficiency (PK deficiency) in adult patients (see section 4.4)" falls within the scope of the designated orphan condition "treatment of pyruvate kinase deficiency".

The objective of section 4.4 of the SmPC (Summary of medicinal Product Characteristics) is to provide information on "Special warnings and precautions for use" to healthcare professionals. The cross reference to section 4.4 pertains to the evidence on the use of this medicinal product in patients who were homozygous for the R479H mutation or who had 2 non-missense mutations (without the presence of another missense mutation) in the PKLR gene.

Intention to diagnose, prevent or treat

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

Chronically debilitating and/or life-threatening nature

At the time of initial designation and review at initial marketing authorisation, the COMP agreed that the condition was chronically debilitating and life-threatening.

At the time of this review Pyruvate kinase deficiency is presented to the COMP to remain chronically debilitating and life-threatening disease. However, clinical manifestations are heterogeneous, and severity varies considerably depending on the genotype of the condition. Infections and pregnancy, and other cause of oxidative stress could trigger haemolysis. Common symptoms include fatigue, shortness of breath, tachycardia, jaundice, and bone changes associated with extramedullary erythropoiesis (Grace, Bianchi, et al, 2018; Grace, Cohen, et al, 2018). Patients with PK deficiency suffer from acute and long-term clinical complications associated with chronic nonspherocytic haemolytic anaemia and ineffective erythropoiesis (Grootendorst et al, 2021).

Untreated PK deficiency is characterized by lifelong haemolytic anaemia and subsequent associated comorbidities, including iron overload, need for cholecystectomy, pulmonary hypertension, extramedullary haematopoiesis, liver cirrhosis, endocrinopathy, and bone fracture.

Recent real-world evidence using US veterans health administration data suggests that patients with PK deficiency may have an increased risk for mortality compared with age-matched controls (Zagadailov et al, 2020). PK deficiency patients had a significantly higher risk of mortality, with a hazard ratio for mortality of 2.3 (2-sided P value: 0.0306). The study was limited in both the sample size and generalizability of patients.

The COMP concluded that the condition remains chronically debilitating and life-threatening due to lifelong haemolytic anaemia and subsequent associated comorbidities leading to a reduction in life expectancy.

Number of people affected or at risk

At the time of designation, the prevalence (P) was agreed to be 0.5 per 10,000.

For this review the prevalence was presented to the COMP to remain less than 5 per 10,000 and was estimated to be 0.584 per 10,000.

To update the prevalence calculation, the sponsor conducted a systematic literature review encompassing searches in Medline, Embase, PubMed, Ovid, a single conference year of the Deutsche Gesellschaft fur Hamatologie und Medizinische Onkologie, and other publicly available sources of information. The search yielded prevalence estimates for PK deficiency in the European Union (EU), Norway, Iceland, Liechtenstein, and in populations with relevant European origin (e.g., Canada); however, the estimates provided by Carey, de Medicis, and Beutler are population-based, and thus were deemed to be more robust estimates by the sponsor (Table 1).

Table 1. Publications With PK Deficiency Prevalence Estimates Derived from European/European Origin Populations

First Author (Year)Citation	**Reported Results**	**Prevalence Estimates (per 10,000)**	**Geographic Location or Ethnic Group Analysed**	**Derivation**
Carey PJ et al (2000)[1)]	Period prevalence: 3.2 per million	0.032	From within the former Northern Health Region of the United Kingdom	*
de Medicis E et al (1992)[2)]	Period prevalence: 1 per 117,206	0.085	Canada	†
Mañú-Pereira MM et al (2021)[3.]	PK deficiency patients in follow-up: 0.36 to 4.47 per million (range by country)	0.0036 to 0.0447	Europe (Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Lithuania, Netherlands, Portugal, Spain, Sweden, and United Kingdom)	
Beutler E and Gelbart T (2000)[4.]	Estimated prevalence: 51 per million	0.51	Caucasian Population (geography not reported)	*

Abbreviations: HWE = Hardy-Weinberg equilibrium; CI = confidence interval; MAF = mutant allele frequency; N/A = not applicable; NR = not reported; PK deficiency = pyruvate kinase deficiency; SD = standard deviation.

* Estimate provided by study authors.

† Units converted from authors' estimate.

‡ Estimate derived assuming HWE.

1 Carey PJ, Chandler J, Hendrick A, et al. Prevalence of pyruvate kinase deficiency in northern European population in the north of England. Northern Region Haematologists Group. Blood. 2000;96(12):4005-4006.

2 de Medicis E, Ross P, Friedman R, et al. Hereditary nonspherocytic hemolytic anemia due to pyruvate kinase deficiency: a prevalence study in Quebec (Canada). Hum Hered. 1992;42(3):179-183.

3 Mañú-Pereira MM, Bianchi P, Wijk RV, Glenthoj A. Rare Anaemia Disorders European Epidemiological Platform (RADEEP): Distribution of Patients Affected by Pyruvate Kinase Deficiency in Europe. Conference abstract presented at European Hematology Association; 2021; Virtual.

4 Beutler E, Gelbart T. Estimating the prevalence of pyruvate kinase deficiency from the gene frequency in the general white population. Blood. 2000;95(11):3585-3588.

The estimated prevalence of PK deficiency (Table 2) is derived by applying the selected prevalence estimates to the EU population, which includes the 27 EU member states as well as Liechtenstein, Norway, and Iceland.

Table 2. Calculation of PK Deficiency Prevalence in the European Union.

Country	Source	Final Data Collection Year	Population 1	Number of Cases	Prevalence / 10,000	Type of Prevalence
EU	Carey et al, 2000	1999	453,090,377	1,713	0.0378	Diagnosed
	de Medicis et al, 1992	1989	453,090,377	4,413	0.0974	Diagnosed
	Beutler and Gelbart, 2000	N/S	453,090,377	26,479	0.584	Overall[2]
EU[3]	Mañú-Pereira et al, 2021	N/S	453,090,377	163 to 2,025	0.0036 to 0.0447	Diagnosed

Abbreviations: EU = European Union; N/S = not specified; PK deficiency = pyruvate kinase deficiency.

1. Population size was taken from Eurostat 2020 per the EU guideline on the format and content of orphan designations (ENTR/6283/00 Rev 5), including the 27 EU member states as well as Iceland, Liechtenstein, and Norway https://ec.europa.eu/eurostat/databrowser/view/demo_pjan/default/table?lang=en

2. Overall prevalence includes diagnosed and undiagnosed populations

3. This study directly reported prevalence per one million, based on the lowest and highest prevalence of patients with PK deficiency in clinical follow-up, reported among 14 European countries and the United Kingdom. The highest prevalence was from Denmark; the country with the lowest prevalence was not reported.

Taking into consideration that a significant number of patients with PK deficiency may remain undiagnosed (Secrest et al, 2020), the sponsor is proposing a total estimated prevalence of PK deficiency (diagnosed and undiagnosed cases) in the EU to be 26,479 patients (0.584 people per 10,000) (Beutler and Gelbart, 2000).

The COMP concluded that the previously accepted prevalence estimate of approximately 0.5 per 10,000 persons in the EU is still valid.

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

There is currently no authorised treatment in the EU for this indication.

The current standard clinical care of patients with PK deficiency is mainly supportive and involves the treatment and management of symptoms and complications of PK deficiency (Table 3). This includes red blood cell transfusions, splenectomy, iron chelation, cholecystectomy and jaundice therapies. Haematopoietic stem cell transplant has been pursued in a small number of patients with mixed outcomes.

Red blood cell transfusions are most often used to treat anaemia in infants and younger children with PK deficiency and are effective in stabilizing nadir Hb levels in the approximate range of 6 to 8 g/dL to ensure that a child grows and thrives. In general, the decision to regularly transfuse a patient with PK deficiency is multifactorial and is based on individual basis. With decreasing rates of viral infections/haemolytic triggers, the frequency of transfusions continues to fall through adolescence to adulthood, with 14% of subjects aged 12 to <18 years and 11% of adults with PK deficiency reported as receiving regular transfusions (≥6 transfusions over a 12-month period) (Grace and Barcellini, 2020). Most adults with the disease have undergone splenectomy as children and require only sporadic or ad hoc transfusions, which are usually administered in the context of an acute haemolytic episode triggered by infection, trauma, pregnancy, or stress. While effective at stabilizing Hb levels, repeated transfusions, even in low numbers, can worsen iron overload, a serious complication requiring further intervention to remove excess iron. As a result of the risks associated with iron overload, monitoring for iron overload is essential and includes evaluation of liver iron concentration by MRI, a procedure requiring general anaesthesia in children.

Splenectomy is recommended in guidelines for patients with PKD who receive regular transfusions or are severely anaemic, to reduce the need for transfusion and/or to increase Hb (Iolascon et al, 2017). This procedure is practised in approximately 70% of patients diagnosed with PK deficiency between the ages of 5 and 18 years (Grace and Barcellini, 2020). However, in almost all patients, haemolysis and indirect hyperbilirubinemia persist after splenectomy, and patients remain at risk for gallstones and jaundice (Grace et al, 2019), leading to a 50% likelihood of a cholecystectomy after splenectomy (Grace et al, 2018a). In addition, splenectomy increases the risk of infection due to encapsulated organisms, requiring patients to undergo prolonged prophylactic antibiotic therapy and maintain strict vaccination compliance, and increases the risk of thrombosis, pulmonary hypertension, and iron overload (Crary and Buchanan, 2009; Evans, 1985; Jones et al, 2016). Moreover, patients with the most severe haemolysis and anaemia, or with two non-missense PKLR mutations, are least likely to respond to splenectomy. Up to 10% of patients have no improvement in haemoglobin or haemolysis; typically, in patients with more severe haemolysis pre-splenectomy (Grace et al, 2019).

Iron chelation is used to address the frequent iron overload in patients with PK deficiency and can occur even in patients who are not regularly transfused (van Beers et al, 2019; Porter et al, 2017). Compliance is often poor (as a result of tolerability issues), which limits its benefit. Chelating agents also have risks associated with their use (e.g., decreases in serum creatinine clearance and increases of transaminases), and the label contains warnings for hepatic toxicity including failure, and renal toxicity including failure, and gastrointestinal haemorrhage. Additionally, serious hypersensitivity reaction has also been reported (Exjade Summary of Product Characteristics, 2020). Paediatric growth retardation in younger children is a warning for desferroxamine (Desferrioxamine mesilate Summary of Product Characteristics, 2017).

Jaundice therapies such as rifampicin may be prescribed to prevent and/or reduce the jaundice commonly associated with PK deficiency. In the PK Deficiency NHS and mitapivat clinical studies

(AG348-C-003, AG348-C-006 and AG348-C--007), reported jaundice therapies included ursodiol and phenobarbital.

Hematopoietic allogeneic stem cell transplantation is rarely performed. Since, although potentially curative, the practice bears relatively high morbidity and mortality rate compared with supportive care (Grace and Barcellini, 2020; van Straaten et al, 2018). A worldwide review identified 16 PK deficiency patients in which the 2-year cumulative survival rate was 74% (van Straaten et al, 2018). The serious and often life-threatening complications associated with the procedure, particularly in very young children, make transplantation a difficult decision, and the benefit-risk determination is most often in favour of supportive care rather than transplant.

The COMP concluded that there is no approved pharmacological treatment or method that qualifies as a satisfactory treatment.

Significant benefit

Not applicable as there are no satisfactory treatments.

4. COMP list of issues

Not applicable.

5. COMP position adopted on 19 September 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 pyruvate kinase deficiency (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 0.5 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 due acute and long-term clinical complications associated with chronic haemolytic anaemia which could lead to fatigue, iron accumulation, jaundice and pruritis, gallstones, bone deformations due to extramedullary erythropoiesis and a reduction in life expectancy;
- there is, at present, no satisfactory method for the treatment of the condition that has been authorised in the European Union for patients affected by the condition.

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 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 Pyrukynd, mitapivat sulfate, for treatment of pyruvate kinase deficiency (EU/3/20/2270) is not removed from the Community Register of Orphan Medicinal Products.