Report Mitapivat - Pyrukynd®

Product & Mechanism of action

Substance: Mitapivat

Brand Name: Pyrukynd

Originator/licensee: Agios Netherlands B.V.

Classification: NCE

ATC code: B06AX04

Orphan Status:
Eu: Yes
Us: Yes

Mechanism of action: Mitapivat is a pyruvate kinase activator; it works by binding to the enzyme PK, thus stabilising the defective enzyme and helping it work better. This results in a reduction in disease symptoms [1].

Authorized indications Licensing status

Authorized Indication:
EMA: Mitapivat is indicated for the treatment of PK deficiency in adult patients [1].
FDA: Mitapivat is a PK activator indicated for the treatment of hemolytic anemia in adults with PK deficiency [2].

Route of administration: os

Licensing status
EU CHMP P.O. date: 15/09/2022
FDA M.A. date: 17/02/2022

EU Speed Approval Pathway: No
FDA Speed Approval Pathway: Yes

ABBREVIATIONS:
Ad: adjusted difference
AE: adverse event
CHMP: Committee for Medicinal Products for Human Use
CI: confidence interval
M.A.: marketing authorization
P: p-value
Pbo: placebo
P.O.: positive opinion
PK: pyruvate kinase
SAE: serious adverse event

Essential therapeutic features

Summary of clinical EFFICACY:
NCT03548220 was a phase III, randomized, placebo-controlled trial to evaluate the efficacy and safety of mitapitant in adults (≥ 18 years) with PK deficiency* who were not receiving regular red-cell transfution.
The primary end point was a hemoglobin response (an increase from baseline of ≥1.5 g per deciliter in the hemoglobin level) that was sustained at two or more scheduled assessments at weeks 16, 20, and 24.
The patients were assigned to receive either mitapivat (5 mg twice daily, with potential escalation to 20 or 50 mg twice daily) or pbo for 24 weeks.
16 of the 40 patients (40%) in the mitapivat group had a hemoglobin response, as compared with none of the 40 patients in the placebo group (ad, 39.3% points; 95% CI, 24.1 to 54.6; two-sided P<0.001).
The percentage of patients with a hemoglobin response was significantly higher in the mitapivat group than in the pbo group (40% vs. 0%; ad, 39.3% points [95% CI, 24.1 to 54.6]; two-sided P<0.001 by the Cochran–Mantel–Haenszel test)
Patients who received mitapivat had a greater response than those who received placebo [4].
*defined as the documented presence of at least two mutant alleles in PKLR, of which at least one was a missense mutation

Summary of clinical SAFETY:
The most common AEs in the mitapivat group were nausea and headache; the incidence of these events were similar to or lower than those in the pbo group.
The most common AEs of grade ≥ 3 in the mitapivat group were hypertriglyceridemia and hypertension.
SAEs in the mitapivat group were gastroenteritis, atrial fibrillation, rib fracture and musculoskeletal pain; SAEs in the pbo group were metapneumovirus infection and obstructive pancreatitis. In the mitapivat group, no adverse events led to death or to discontinuation, interruption, or reduction of the dose of mitapivat; two patients who received placebo had a dose interruption owing to an adverse event. There were no deaths [4].

AE	Any AE	TEAE	Grade ≥ 3 AE	Grade ≥ 3 TEAE	SAE
Mitapivat (N=40) N %	35 (88)	23 (58)	10 (25)	3 (8)	4 (10)
Pbo (N=39) N %	35 (90)	14 (36)	5 (13)	0	2 (5)

Ongoing studies:
- ***For the same indication:*** Yes
- ***For other indications:*** Yes [5].

Discontinued studies (for the same indication): No

NHS impact

Cost of therapy:
Price is not available yet.

Epidemiology:
The general prevalence of the disease is estimated 1-9 cases/100,000 people [6].

POSSIBLE PLACE IN THERAPY
There are currently no therapies with Marketing Authorisation approval in the EU for the treatment of PKD [7].

OTHER INDICATIONS IN DEVELOPMENT: Thalassaemia, Sickle cell anaemia, Inborn error pyruvate metabolism disorders, Hereditary spherocytosis [5]

SAME INDICATION IN EARLIER LINE(S) OF TREATMENT:
No

OTHER DRUGS IN DEVELOPMENT for the SAME INDICATION:
No

*Service reorganization: Yes
*Possible off label use: Yes

References:
[1]. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/pyrukynd
[2]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/216196s000lbl.pdf
[3]. https://www.nejm.org/doi/10.1056/NEJMoa2116634?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed
[4]. https://www.nejm.org/doi/10.1056/NEJMoa2116634?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed
[5]. https://adisinsight.springer.com/drugs/800040426
[6]. https://www.osservatoriomalattierare.it/malattie-rare/deficit-di-piruvato-chinasi#:~:text=La%20prevalenza%20generale%20della%20patologia,variabile%20da%20paziente%20a%20paziente.
[7]. https://www.io.nihr.ac.uk/wp-content/uploads/2022/01/11252-Mitapivat-for-Pyruvate-Kinase-Deficiency-V1.0-NOV2020.-non-CONF.pdf