SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Pyrukynd 20 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 20 mg of mitapivat (as sulfate).

Excipient with known effect

Each film-coated tablet contains 1.4 mg of lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Blue, round film-coated tablets of approximately 8 mm in diameter with “M20” printed in black ink on one side and plain on the reverse.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Pyrukynd is indicated for the treatment of pyruvate kinase deficiency (PK deficiency) in adult patients (see section 4.4).

4.2 Posology and method of administration

Posology

The recommended starting dose is 5 mg taken orally twice daily.

To gradually increase haemoglobin (Hb) levels and maximise the effect, Pyrukynd should be titrated through sequential doses of 5 mg twice daily, 20 mg twice daily and 50 mg twice daily, with sequential dose increases occurring every 4 weeks (see Table 1). Hb level and transfusion requirement should be assessed before increasing to the next dose level as some patients may reach and maintain normal Hb levels at 5 mg twice daily or 20 mg twice daily. The maximum recommended dose is 50 mg twice daily.

Treatment with Pyrukynd is intended to be long-term. Pyrukynd should be discontinued if a patient does not experience an improvement of haemolytic anaemia at the maximum recommended dose, based on the totality of laboratory results and clinical status of the patient, unless there is another explanation for response failure (e.g. bleeding, surgery, other concomitant illnesses).

Table 1: Dose titration and maintenance schedule

Duration	Dose titration and maintenance
Day 1 to Week 4	**All patients:** • 5 mg twice daily
Week 5 to Week 8	If Hb level is below normal range or patient has required a transfusion within the last 8 weeks: • Increase to 20 mg twice daily and maintain for 4 weeks. If Hb level is within normal range and patient has not required a transfusion within the last 8 weeks: • Maintain 5 mg twice daily.
Week 9 to Week 12	If Hb level is below normal range or patient has required a transfusion within the last 8 weeks: • Increase to 50 mg dose twice daily and maintain thereafter. If Hb level is within normal range and patient has not required a transfusion within the last 8 weeks: • Maintain current dose (5 mg twice daily or 20 mg twice daily).

Maintenance	If Hb level decreases, consider up-titration to the maximum of 50 mg twice daily as per the above schedule.

Interruption or discontinuation

To minimise the risk of acute haemolysis, abrupt interruption or discontinuation of Pyrukynd should be avoided. The dose should be tapered to gradually discontinue the medicinal product over a 1-2 week period (see Table 2). Patients should be monitored for signs of acute haemolysis with worsening of anaemia (see sections 4.4 and 4.8).

Table 2: Dose taper schedule

Current dose	**Dose taper schedule**		
	Day 1-7	**Day 8-14**	**Day 15**
5 mg twice daily	5 mg **once** daily	Discontinue	N/A
20 mg twice daily	20 mg **once** daily	5 mg **once** daily	Discontinue
50 mg twice daily	50 mg **once** daily	20 mg **once** daily	Discontinue

N/A: not applicable.

Missed dose

If a dose of Pyrukynd is missed by 4 hours or less, the dose should be administered as soon as possible. If a dose is missed by more than 4 hours, a replacement dose should not be administered, and the patient should wait until the next scheduled dose. Subsequently, the patient should return to their normal dosing schedule.

Dose adjustments due to adverse events

If a dose reduction is required for adverse event management and/or tolerability, the dose may be reduced to the next lower dose level, 20 mg twice daily or 5 mg twice daily.

If a patient needs to discontinue the medicinal product due to an adverse event, the dose taper schedule (Table 2) should be followed. In situations where the risk to the patient due to the adverse event is greater than the risk of acute haemolysis due to sudden withdrawal of the medicinal product, treatment may be stopped without taper and patients should be monitored for signs of acute haemolysis with worsening of anaemia.

Special populations

Elderly

There are limited data available in elderly patients. No dose modifications are recommended in elderly patients (see sections 5.1 and 5.2).

Hepatic impairment

There are no data available in patients with hepatic impairment. No dose recommendations can be made.

Renal impairment

There are limited data available in patients with mild or moderate renal impairment. No dose modifications are recommended in patients with mild or moderate renal impairment (see section 5.2.).

There are no data available in patients with severe renal impairment. No dose recommendations can be made.

Paediatric population

The safety and efficacy of Pyrukynd in children and adolescents less than 18 years old have not been established. No data are available. Non-clinical studies in juvenile animals have been conducted (see section 5.3).

Method of administration

For oral use.

Pyrukynd may be taken with or without food. The tablets should be swallowed whole. The tablets should not be split, crushed, chewed or dissolved because there are no data currently available to support other methods of administration.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Acute haemolysis

Acute haemolysis with subsequent anaemia has been observed following abrupt interruption or discontinuation of Pyrukynd (see section 4.8). Abrupt interruption or discontinuation of treatment with Pyrukynd should be avoided. A gradual reduction in dosing rather than abrupt cessation is recommended (see section 4.2). If discontinuing treatment abruptly, patients should be monitored for signs of acute haemolysis and

anaemia which may include among other symptoms and signs: jaundice, scleral icterus and dark urine.

Efficacy across mutation types

The 2 Phase 3 clinical studies *ACTIVATE* and *ACTIVATE-T* excluded 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. In the Phase 2 clinical study, there were 10 subjects with 2 non-missense mutations (without the presence of another missense mutation) in the PKLR gene, and 5 subjects homozygous for the R479H mutation. Patients with these mutations are less likely to respond to treatment with Pyrukynd (see section 5.1). Treatment should be discontinued if clinical benefit is not observed (see section 4.2).

Drug-drug interactions

Hormonal contraceptives

Mitapivat may decrease the systemic exposure of hormonal contraceptives that are sensitive substrates of cytochrome P450 3A4 (CYP3A4) (e.g. ethinylestradiol) (see section 4.5). Women of childbearing potential should be counselled regarding the use of additional or alternative contraception methods (see section 4.6).

Co-administration of other medicinal products

Co-administration of specific medicinal products with mitapivat may result in increased risk of insomnia or changes in efficacy of mitapivat or changes in efficacy of the co-administered medicinal products (see section 4.5). Potential drug-drug interactions should be considered whenever beginning or discontinuing treatment with mitapivat or other medicinal products concomitantly administered with mitapivat.

Lactose

Pyrukynd contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Mitapivat is primarily metabolised by CYP3A4 and is a substrate for P-glycoprotein (P-gp). Mitapivat induces CYP3A4 and may also induce CYP2B6, CYP2C8, CYP2C9, CYP2C19 and uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). Mitapivat may inhibit CYP3A4. Mitapivat may induce and inhibit P-gp (see section 5.2).

Effects of other medicinal products on Pyrukynd

CYP3A4 inhibitors

The effect of itraconazole (a strong CYP3A4 inhibitor) on the pharmacokinetics of a single dose of mitapivat was evaluated in a Phase 1 study. Itraconazole increased mitapivat AUC_{0-t}, AUC_{∞} and C_{max} by 4.7-fold, 4.9-fold and 1.7-fold, respectively. Increased mitapivat plasma exposures may increase the risk of insomnia. The concomitant use of CYP3A4 inhibitors with Pyrukynd should be avoided (see section 4.4). If concomitant use of a CYP3A4 inhibitor is unavoidable, patients should be monitored for increased risk of insomnia (see section 4.2).

CYP3A4 inducers

The effect of rifampicin (a strong CYP3A4 inducer) on the pharmacokinetics of a single dose of mitapivat was evaluated in a Phase 1 study. Rifampicin decreased mitapivat AUC_{0-t}, AUC_{∞} and C_{max} by 91%, 91% and 77%, respectively. Decreased mitapivat plasma exposures may reduce the efficacy of Pyrukynd. The concomitant use of CYP3A4 inducers with Pyrukynd should be avoided (see section 4.4). If concomitant use of a CYP3A4 inducer is unavoidable, patients should be monitored for reduced efficacy of mitapivat.

Gastric acid-reducing agents

Mitapivat exhibits pH-dependent solubility (see section 5.2) and coadministration with gastric acid-reducing agents (e.g. famotidine) may decrease mitapivat absorption (see section 4.4). Concomitant use of Pyrukynd with medicinal products that elevate gastric pH was not evaluated in a clinical drug-drug interaction study. If concomitant use of gastric acid-reducing agents is unavoidable, patients should be monitored for reduced efficacy of mitapivat.

Effect of Pyrukynd on other medicinal products

CYP3A4 substrates

Mitapivat induces and may inhibit CYP3A4 (see section 5.2) and co-administration with sensitive CYP3A4 substrates (e.g. midazolam) may alter systemic exposure of these medicinal products. Concomitant use of Pyrukynd with substrates of this enzyme was not evaluated in a clinical drug-drug interaction study. Alternative therapies that are not sensitive substrates of CYP3A4 should be considered during treatment with Pyrukynd (see section 4.4). If co-administration of Pyrukynd with sensitive CYP3A4 substrates is unavoidable, patients should be carefully monitored

especially for those substrates with a narrow therapeutic index (e.g. alfentanil, carbamazepine, cyclosporine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus).

Hormonal contraceptives

Mitapivat may alter the systemic exposure of hormonal contraceptives that are sensitive substrates of CYP3A4 (e.g. ethinylestradiol) (see section 4.4) and may affect their efficacy (see section 4.6).

UGT1A1, CYP2B6 and CYP2C substrates

Based on *in vitro* data, mitapivat may induce UGT1A1, CYP2B6, CYP2C8, CYP2C9 and CYP2C19 (see section 5.2) and may decrease systemic exposure to substrates of these enzymes (e.g. irinotecan [UGT1A1]; bupropion [CYP2B6]; omeprazole [CYP2C19]; repaglinide [CYP2C8]; warfarin [CYP2C9]). Concomitant use of Pyrukynd with substrates of these enzymes was not evaluated in a clinical drug-drug interaction study. Alternative therapies that are not UGT1A1 substrates or sensitive substrates of CYP2B6 or CYP2C should be considered during treatment with Pyrukynd (see section 4.4). If co-administration is unavoidable, patients should be monitored for loss of therapeutic effect of substates of these enzymes, especially for those with a narrow therapeutic index (e.g. irinotecan [UGT1A1]; cyclophosphamide [CYP2B6]; valproic acid [CYP2C19]; paclitaxel [CYP2C8]; warfarin, phenytoin [CYP2C9]).

P-gp substrates

Based on *in vitro* data, mitapivat may induce and inhibit P-gp (see section 5.2) and may alter systemic exposure of substrates (e.g. dabigatran etexilate) of this transporter. Concomitant use of Pyrukynd with substrates of P-gp was not evaluated in a clinical drug-drug interaction study. Alternative therapies that are not P-gp substrates should be considered during treatment with Pyrukynd (see section 4.4). If co-administration of Pyrukynd with P-gp substrates is unavoidable, patients should be carefully monitored especially for those substrates with a narrow therapeutic index (e.g. colchicine, digoxin).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in females

Women of childbearing potential should avoid becoming pregnant while receiving Pyrukynd.

Women of childbearing potential should use contraception during treatment with Pyrukynd and for at least 1 month after the last dose. Mitapivat may decrease the systemic exposure of hormonal contraceptives that are sensitive substrates of CYP3A4 (see sections 4.4 and 4.5). Additional or alternative methods of contraception should be considered.

Pregnancy

There are no or limited amount of data from the use of mitapivat in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3).

Pyrukynd is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether mitapivat and/or its metabolites are excreted in human milk. A risk to newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to abstain from Pyrukynd therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no human data on the effect of mitapivat on fertility. Animal studies have shown reversible effects on reproductive organs of males and females (see section 5.3). While taking mitapivat, there may be an impact on the ability of a woman and a man to conceive.

4.7 Effects on ability to drive and use machines

Pyrukynd has a minor influence on the ability to drive and use machines. Patients should be advised to be cautious when driving or using machines in case they experience insomnia during treatment with Pyrukynd (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The safety evaluation of Pyrukynd is based on experience from a randomised, double-blind, placebo-controlled clinical study of adult patients with PK deficiency who were not regularly transfused (*ACTIVATE*) and a single-arm clinical study of adult patients with PK deficiency who were regularly transfused (*ACTIVATE-T*).

The most common adverse reaction across both studies was insomnia (19.4%) and the most common laboratory abnormalities observed were oestrone decreased (males) (43.5%) and oestradiol decreased (males) (8.7%).

Tabulated list of adverse reactions

The adverse reactions associated with Pyrukynd as identified in clinical studies of patients with PK deficiency are tabulated below.

Adverse reactions are listed by MedDRA system organ class and frequency: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Adverse reactions

System organ class	**Very common**	**Common**
Psychiatric disorders	Insomnia	
Gastrointestinal disorders	Nausea	
General disorders and administration site conditions		Hot flush
Investigations	Oestrone decreased (males)	Blood testosterone increased (males) Oestradiol decreased (males)

Description of selected adverse reactions

Acute haemolysis

Abrupt interruption or discontinuation of Pyrukynd can lead to acute haemolysis (see section 4.4). For guidance on how to interrupt or discontinue treatment see section 4.2.

In a Phase 2 study, 2 of 52 patients (3.8%) experienced haemolysis upon sudden withdrawal of Pyrukynd, including 1 serious adverse event of acute haemolysis. In both patients who received an initial Pyrukynd dose of 300 mg twice daily, a rapid and large Hb increase was observed during the first 3 weeks of treatment. This was followed by a sudden discontinuation of Pyrukynd without taper, which resulted in acute haemolysis with anaemia. Patients who missed a few doses of Pyrukynd later in their treatment course, or for whom the dose was tapered, did not experience events of acute haemolysis.

Changes in sex hormone levels

Mitapivat is a weak aromatase inhibitor *in vitro*. In *ACTIVATE*, 1 of 16 (6.3%) males experienced increases in testosterone to above normal levels and 2 of 16 (12.5%) and 9 of 16 (56.3%) males experienced decreases in oestradiol and oestrone below the lower limit of normal, respectively. In *ACTIVATE-T*, 1 of 7 males (14.3%) experienced oestrone decrease below the lower limit of normal. These changes in hormone levels were maintained throughout the study period. In patients who discontinued Pyrukynd at the end of the core period, the hormone changes were reversible. Sex hormone analysis in female patients was limited due to physiological variations in hormone levels expected throughout the normal menstrual cycle and the various types of hormonal contraceptives used by patients.

Insomnia

In *ACTIVATE*, insomnia was reported with a similar incidence between patients who received Pyrukynd and patients who received placebo and was reported in 6 of 27 (22.2%) patients in *ACTIVATE-T*. In a Phase 2 study, 5 of 27 (18.5%) patients treated at 50 mg twice daily and 16 of 25 (64%) patients treated at 300 mg twice daily experienced insomnia during the core period.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In clinical studies in patients with PK deficiency, doses of mitapivat were assessed up to 300 mg twice daily. Healthy volunteers received up to 2 500 mg as a single dose and 700 mg twice daily for 14 days. One patient in a clinical study took 150 mg twice daily, a dose greater than the recommended dose in that study (50 mg twice daily) and did not experience any associated adverse events.

Patients who received higher than the recommended maximum dose of 50 mg twice daily in clinical studies reported adverse events consistent with the safety profile of mitapivat in all patients.

In case of overdose, patients should be treated symptomatically and provided with appropriate supportive measures as needed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other haematological agents, ATC code: B06AX04

Mechanism of action

Mitapivat is a pyruvate kinase activator and acts by directly binding to the pyruvate kinase tetramer. The red blood cell (RBC) form of pyruvate kinase (PKR) is mutated in PK deficiency, which leads to reduced adenosine triphosphate (ATP) levels, shortened RBC lifespan and chronic haemolysis. Mitapivat improves RBC energy homeostasis by increasing PKR activity.

Pharmacodynamic effects

In healthy volunteers, decreases in 2,3 diphosphoglycerate and increases of ATP concentrations were observed after dosing mitapivat to steady state. Changes to these pharmacodynamic markers are not considered significant for the assessment of activity in subjects with PK deficiency that should rely on clinical parameters only.

Clinical efficacy and safety

The efficacy of Pyrukynd was evaluated in 2 multinational Phase 3 clinical studies in patients with PK deficiency: *ACTIVATE* and *ACTIVATE-T*.

Patients with PK deficiency who were not regularly transfused (ACTIVATE)

The efficacy of Pyrukynd was studied in a multinational, randomised, double-blind, placebo-controlled clinical study (*ACTIVATE*) of 80 adult patients with PK deficiency who were not regularly transfused, defined as having had no more than 4 transfusions in the 52-week period prior to treatment and no transfusions in the 3-month period prior to treatment. Patients were included if they had documented presence of at least 2 mutant alleles in the PKLR gene, of which at least 1 was a missense mutation, and a Hb concentration less than or equal to 100 g/L. Patients homozygous for the R479H mutation or with 2 non-missense mutations (without the presence of another missense mutation) in the PKLR gene were excluded because these patients did not achieve Hb response (change from baseline in Hb $\geq$ 1.5 g/dL at > 50% assessments) in the Phase 2 dose-ranging study. Randomisation was stratified by average of screening Hb concentrations (< 85 vs $\geq$ 85 g/L) and PKLR gene mutation category (missense/missense vs missense/non-missense). Following a dose titration period with 2 sequential steps for dose level increase up to 50 mg twice daily, patients continued on a fixed dose of Pyrukynd for 12 weeks.

Among the 80 patients with PK deficiency, 40 patients were randomised to Pyrukynd. Thirty-five out of the 40 (87.5%) patients who received Pyrukynd received an optimised dose of 50 mg twice daily following the dose titration period. The median duration of treatment with Pyrukynd was 24.1 weeks (range 23.6 to 27.4 weeks). Overall, 30 (75%) patients were exposed to Pyrukynd for > 24 weeks. Among the 80 randomised patients, the median age was 32.5 years (range 18 to 78) and 40% were male; race was reported in 87.5% of patients including 75% White, 10% Asian, 1.3% Native Hawaiian/Other Pacific Islander and 1.3% were other races.

The baseline disease characteristics are shown in Table 4.

Table 4: Baseline disease characteristics in patients with PK deficiency who were not regularly transfused (*ACTIVATE*)

Baseline disease characteristics[1]	**Total N=80**
Haemoglobin (g/L), n	80
Median	85.08
(min, max)	(64.0, 102.3)
PKLR genotype, n (%)	
Missense/missense	55 (68.8)
Missense/non-missense	25 (31.3)
Reticulocyte (fraction of 1), n	80
Median	0.4009
(min, max)	(0.038, 0.827)
Indirect bilirubin (µmol/L), n	76
Median	74.647
(min, max)	(11.03, 294.7)
LDH (U/L), n	79
Median	223.5
(min, max)	(101.0, 1190.5)
Haptoglobin (g/L), n	80
Median	0.030
(min, max)	(0.03, 0.70)
Ferritin (µg/L), n	77
Median	479.420
(min, max)	(21.36, 5890.25)

Baseline disease characteristics[1]	**Total** **N=80**
Femoral T-Score category by DXA, n (%)	
≤ -2.5	5 (6.3)
> -2.5 - < -1.0	36 (45.0)
≥ -1.0	38 (47.5)
Missing	1 (1.3)
Prior history of splenectomy, n (%)	58 (72.5)
Prior history of cholecystectomy, n (%)	58 (72.5)
Prior chelation therapy, n (%)	15 (18.8)

DXA: dual-energy X-ray absorptiometry, LDH: lactate dehydrogenase.
[1] n is the number of patients with non-missing data.

The primary endpoint of Hb response was defined as a ≥ 15 g/L increase in Hb concentration from baseline sustained at 2 or more scheduled assessments (Weeks 16, 20 and 24) during the fixed-dose period without transfusions. The efficacy results are shown in Table 5.

Table 5: Efficacy results in patients with PK deficiency who were not regularly transfused (*ACTIVATE*)

	Pyrukynd[1] N=40	**Placebo[1] N=40**	**Difference[1]**	
Primary endpoint	**n (%)**	**n (%)**	**Adjusted difference[2] (95% CI)**	**p-value**
Hb response	16 (40%)	0	39.3 (24.1, 54.6)	< 0.0001
Secondary endpoints[3]	**LS mean 95% CI**	**LS mean 95% CI**	**LS mean difference (95% CI)**	**p-value**
Haemoglobin (g/L)	16.73 (12.60, 20.86)	-1.48 (-5.63, 2.67)	18.21 (12.41, 24.01)	< 0.0001
Indirect bilirubin (µmol/L)	-21.16 (-29.59, -12.72)	5.10 (-3.00, 13.21)	-26.26 (-37.82, -14.70)	< 0.0001
Reticulocytes (fraction of 1)	-0.0973 (-0.1252, -0.0694)	0.0038 (-0.0239, 0.0315)	-0.1011 (-0.1391, -0.0632)	< 0.0001
LDH (U/L)	-91.99 (-124.47, -59.50)	-21.18 (-53.30, 10.94)	-70.81 (-115.88, -25.74)	0.0027
Haptoglobin (g/L)	0.169 (0.088, 0.251)	0.012 (-0.070, 0.094)	0.158 (0.043, 0.273)	0.0079

CI: confidence interval, Hb: haemoglobin, LDH: lactate dehydrogenase, LS: least square.
[1] All p-values are 2-sided.
[2] Difference adjusted for randomisation stratification factors.
[3] Secondary endpoints are the average change from baseline at Weeks 16, 20 and 24 for Hb, indirect bilirubin, reticulocytes, LDH and haptoglobin.

During the study, 2 (5.0%) patients in the Pyrukynd arm and 7 (17.5%) patients in the placebo arm received transfusions.

Fifteen of the 16 patients with an Hb response in *ACTIVATE* continued in a long-term extension study and were evaluable for maintenance of response. Thirteen maintained increases in Hb concentration from baseline above the response threshold of ≥ 15 g/L at the last available Hb assessment without requiring any transfusions. The median duration of response for the 16 patients with Hb response was 6.9 months (range 3.3 to 18.4+ months).

Patients with PK deficiency who were regularly transfused (ACTIVATE-T)

The efficacy of Pyrukynd was studied in a multinational, single-arm clinical study (*ACTIVATE-T*) of 27 adult patients with PK deficiency who were regularly transfused. Patients who were regularly transfused were defined as having had a minimum of 6 transfusion episodes and a history of transfusions occurring on average no more frequently than once every 3 weeks during the 52-week period prior to informed consent. There were no limitations on the amount of RBC units received during the 52-week period prior to informed consent. Patients were included if they had documented presence of at least 2 mutant alleles in the PKLR gene, of which at least 1 was a missense mutation. Patients homozygous for the R479H mutation or with 2 non-missense mutations (without the presence of another missense mutation) in the PKLR gene were excluded because these patients did not achieve Hb response (change from baseline in Hb ≥ 1.5 g/dL at > 50% assessments) in the Phase 2 dose-ranging study. Following a dose titration period with 2 sequential steps for dose level increase up to 50 mg twice daily, patients continued on a fixed dose of Pyrukynd for 24 weeks.

Among the 27 patients treated, the median duration of treatment with Pyrukynd was 40.3 weeks (range 16.3 to 46.3 weeks). Overall, 20 (74.1%) patients were exposed to Pyrukynd for > 40 weeks. Twenty-five out of the 27 (92.6%) patients who received Pyrukynd received an optimised dose of 50 mg twice daily following the dose titration period. The median age was 36 years (range 18 to 68 years), and 25.9% were male; race was reported in 85.2% of patients including 74.1% White, and 11.1% Asian. The baseline disease characteristics are shown in Table 6.

Table 6: Baseline disease characteristics in patients with PK deficiency who were regularly transfused (*ACTIVATE-T*)

Baseline disease characteristics[1]	**Pyrukynd N=27**
Haemoglobin (g/L), n	27
Median	91.0
(min, max)	(74, 109)
PKLR genotype, n (%)	
Missense/missense	20 (74.1)
Missense/non-missense	7 (25.9)
Ferritin (µg/L), n	18
Median	748.445
(min, max)	(163.42, 5357.04)

Baseline disease characteristics[1]	**Pyrukynd N=27**
Transfusion burden	
Number of transfusion episodes standardised to 24 Weeks, n	27
Median	4.15
(min, max)	(2.8, 7.8)
Number of RBC units transfused standardised to 24 Weeks, n	27
Median	6.92
(min, max)	(2.8, 20.3)
Femoral T-score category by DXA, n (%)	
≤ -2.5	1 (3.7)
> -2.5 - < -1.0	15 (55.6)
≥ -1.0	10 (37.0)
Missing	1 (3.7)
Prior history of splenectomy, n (%)	21 (77.8)
Prior history of cholecystectomy, n (%)	23 (85.2)
Prior chelation therapy, n (%)	24 (88.9)

DXA: dual-energy X-ray absorptiometry, RBC: red blood cell.
[1] n is the number of patients with non-missing data.

The primary endpoint of transfusion reduction response was defined as ≥ 33% reduction in the number of RBC units transfused during the fixed-dose period compared with the historical transfusion burden standardised to 24 weeks.

Efficacy results for patients with PK deficiency who were regularly transfused are presented in Table 7.

Table 7: Efficacy results in patients with PK deficiency who were regularly transfused (*ACTIVATE-T*)

Endpoint	**Pyrukynd N=27**
Patients with transfusion reduction response, n (%)	10 (37.0)
95% CI	(19.4, 57.6)
Percent reduction in RBC units from baseline[1]	
≥ 33 to < 50%, n (%)	1 (3.7)
≥ 50%, n (%)[2]	10 (37.0)

Endpoint	Pyrukynd N=27
Patients who were transfusion free, n (%)	6 (22.2)
95% CI	(8.6, 42.3)

CI: confidence interval, RBC: red blood cell.
[1] Calculated as the total number of RBC units transfused in the 52 weeks prior to informed consent standardised to 24 weeks.
[2] One patient with ≥ 50% reduction in RBC units from baseline was a non-responder in the analysis of the primary endpoint (transfusion reduction response) since they received < 12 weeks of treatment in the fixed-dose period.

All 6 (22.2%) subjects who were transfusion free in *ACTIVATE-T* remained transfusion free in a long-term extension study. The median duration of response for the 6 patients was 17.0 months (range 11.5+ to 21.8+ months).

Paediatric population

The Medicines and Healthcare products Regulatory Agency has deferred the obligation to submit the results of studies with Pyrukynd in one or more subsets of the paediatric population in the treatment of PK deficiency (see section 4.2 for information on paediatric use).

Elderly

Clinical studies of Pyrukynd did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients.

5.2 Pharmacokinetic properties

The pharmacokinetics of mitapivat have been characterised in healthy adults and patients with PK deficiency. Mitapivat is readily absorbed, extensively distributed and exhibits low clearance following oral administration.

Autoinduction of mitapivat clearance was evident upon repeat dosing.

The pharmacokinetics of mitapivat showed low to moderate variability in healthy adult subjects.

Absorption

Mitapivat was readily absorbed after single and multiple doses both in healthy subjects and in patients with PK deficiency. Median T_{max} values at steady state were 0.5 to 1 hour post dose across the dose range studied (5 mg to 700 mg twice daily).

The absolute bioavailability after a single dose was approximately 73%.

Mitapivat exhibits pH-dependent solubility. High solubility is observed up to pH 5.5, with decreasing solubility at higher pH which may decrease mitapivat absorption.

Effect of food

Following administration of a single dose in healthy subjects, and a high-fat meal (approximately 900 to 1 000 total calories, with 500 to 600 calories from fat, 250 calories from carbohydrate and 150 calories from protein) there was no change in AUC_{inf} while mitapivat C_{max} decreased by 42%. Administration of Pyrukynd with a high-fat meal had no clinically meaningful effect on mitapivat pharmacokinetics.

Distribution

Mitapivat is highly protein bound (97.7%) in plasma with low RBC distribution. The mean volume of distribution (Vz) was 135 L.

Biotransformation

In vitro studies showed that mitapivat is primarily metabolised by CYP3A4. Following a single oral dose of 120 mg of radiolabelled mitapivat to healthy subjects, unchanged mitapivat was the major circulating component.

In vitro drug interaction studies

Metabolic pathways

Mitapivat induces CYP3A4 and may also induce CYP2B6, CYP2C8, CYP2C9, CYP2C19 and UGT1A1. Mitapivat may inhibit CYP3A4.

Drug transporter systems

Mitapivat is a substrate for P-gp and may induce and inhibit P-gp.

Elimination

Mitapivat has a mean $t_{1/2}$ ranging from 16.2 to 79.3 hours following single oral dose administrations (5 to 2 500 mg) under fasted conditions to healthy subjects. Population pharmacokinetics derived median CL/F at steady state was 11.5, 12.7 and

14.4 L/h for the 5 mg twice daily, 20 mg twice daily, and 50 mg twice daily regimens, respectively.

After a single oral administration of radiolabelled mitapivat to healthy subjects, the total recovery of administered radioactive dose was 89.1%, with 49.6% in the urine (2.6% unchanged) and 39.6% in the faeces (less than 1% unchanged).

Linearity/non-linearity

The AUC and C_{max} of mitapivat increased in a dose-proportional manner over the clinically relevant dose range of 5 to 50 mg twice daily in healthy subjects and in patients with PK deficiency.

Special populations

No clinically meaningful effects on the pharmacokinetics of mitapivat were observed based on age, sex, race or body weight.

Elderly

There were 5 patients 65 years of age or older who received mitapivat in the clinical studies *ACTIVATE* and *ACTIVATE-T*. No differences in the pharmacokinetics were observed in these patients compared to younger patients.

Hepatic impairment

The pharmacokinetics of mitapivat in patients with mild, moderate or severe hepatic impairment have not been studied.

Renal impairment

The effects of renal impairment on mitapivat pharmacokinetics were assessed as part of the population pharmacokinetic analyses. There were 24 patients with mild (estimated glomerular filtration rate [eGFR] $\geq$ 60 to $<$ 90 mL/min/1.73 m^2) and 4 with moderate (eGFR $\geq$ 30 to $<$ 60 mL/min/1.73 m^2) renal impairment. Steady-state AUC was similar between patients with normal renal function and mild renal impairment. Geometric mean for steady-state AUC from the small number of patients with moderate renal impairment was higher than that for patients with normal renal function but within the range of steady-state AUCs observed for patients with normal renal function (see section 4.2). There are no data available in patients with severe renal impairment.

Paediatric population

The pharmacokinetics of mitapivat in children and adolescent patients less than 18 years old have not been studied.

5.3 Preclinical safety data

Mitapivat was not carcinogenic in transgenic rasH2 mice when administered twice daily for a minimum of 26 weeks up to the highest total daily dose of 500 mg/kg/day in male mice (6.4-fold difference in human exposure) and 250 mg/kg/day in female mice (2.6-fold difference in human exposure).

In the 2-year rat carcinogenicity study, proliferative and neoplastic lesions were observed in the liver, thyroid, ovaries and pancreas. Findings in the liver and thyroid were attributed to CYP enzyme induction and were considered rodent-specific. In the ovaries, an increased incidence and/or severity of granulosa and/or luteal/granulosa cell hyperplasia was noted at mitapivat AUC0-12hr values > 100 fold above the range observed in humans at the maximum recommended human dose (MRHD) of 50 mg twice daily. Benign acinar hyperplasia and adenoma in the exocrine pancreas were observed at an increased incidence and/or severity in males from all dose groups (30, 100 and 300 mg/kg/day): a no-effect level was not determined. The incidence of the pancreatic findings was only outside the range observed historically in the test strain at 300 mg/kg/day (47-fold the human AUC0-12hr at the MRHD). The relevance of the pancreatic findings for humans is unknown.

Mitapivat was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay. Mitapivat was not clastogenic in an in vitro human lymphocyte micronucleus assay nor in an in vivo rat bone marrow micronucleus assay.

In embryo-foetal development studies, foetal adverse events were observed at AUC0-12 values 63-fold (rats) and 3.1-fold (rabbits) above the human AUC0-12hr value at the MRHD.

In a rat embryo-foetal toxicity study, oral administration of mitapivat was associated with foetal adverse events, including a decrease in the mean number and litter proportion of viable foetuses, lower mean foetal weights, and test article-related external, soft tissue and skeletal malformations. The maternal and foetal no-observed adverse effect level (NOAEL) occurred at a dose of 50 mg/kg/day (13-fold the human AUC 0 12hr at the MRHD).

In a rabbit embryo-foetal toxicity study, oral administration of mitapivat resulted in lower mean foetal body weights. No effects on foetal morphology were observed. The maternal and foetal NOAEL occurred at a dose of 60 mg/kg/day (1.5-fold the human AUC0-12hr at the MRHD).

In rats, mitapivat was shown to induce perinatal mortality in relation to drug-induced dystocia/prolonged parturition in both the pre-and post-natal development and juvenile toxicity studies at doses ≥ 50 mg/kg/day (≥ 20-fold the human AUC0-12hr at the MRHD).

In a fertility and early embryonic development study, oral administration of mitapivat twice daily at doses up to 300 mg/kg/day in male rats and 200 mg/kg/day in female rats prior to and during mating, and continuing in females through organogenesis, resulted in no adverse events on fertility in male or female animals. Reversible findings related to the reproductive organs of males and females were observed, which were considered related to aromatase inhibition. In males, reversible microscopic findings (degeneration of the seminiferous tubules, spermatid retention, atypical residual bodies in the testes, and increased incidence of cellular debris in the epididymides) correlating with abnormal sperm evaluation findings (decreased sperm motility and density, increased numbers of abnormal sperm) were observed at AUC0-12hr values ≥ 23-fold above the human exposure at the MRHD. In females, decreased number of oestrus stages before cohabitation was observed at AUC0-12hr values 49-fold above the human exposure at the MRHD, and this change resolved upon cessation of dosing.

In repeat dose toxicity studies in male and female rats, reproductive organ changes were observed and were attributable to aromatase inhibition. In males, lower accessory sex gland weights and higher testis weights, as well as microscopic findings in the testis and accessory sex glands were seen at AUC0-12hr values ≥ 4.7 fold the human exposure at the MRHD. In females, higher ovarian weights and lower uterus weights, and microscopic findings in the ovary and vagina occurred at AUC0-12hr values 3.0-fold the human exposure. All findings were reversible.

In a juvenile toxicology study initiated in rats aged 7 days and treated up to sexual maturity, most treatment-related findings were considered related to aromatase inhibition. In males, microscopic findings in the testis were observed from the low-dose level of 30 mg/kg/day (1.5-fold the human AUC0-12hr at the MRHD) and delayed sexual maturity, abnormal sperm evaluation findings, and mating and fertility changes were observed at ≥ 150 mg/kg/day (≥ 22-fold the human AUC0-12hr at the MRHD). In females, oestrous cycle changes were observed at the high-dose level of 200 mg/kg/day (60-fold the human AUC0-12hr at the MRHD). All evaluable reproductive changes were reversible or partially reversible. Treatment-related decrease and increase in body weights were observed in males and females, respectively, at ≥ 20-fold the human AUC0-12hr at the MRHD and were not reversed in females. Bone changes, including lower bone density and mass, were observed at ≥ 1.5- and ≥ 20-fold the human exposure in males and females, respectively. These changes were fully reversible in females; in males, they were fully reversible at 1.5-fold the human exposure and partially reversible at higher exposure levels.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Microcrystalline cellulose

Croscarmellose sodium

Mannitol (E421)
Sodium stearyl fumarate

Film-coating

Hypromellose (E464)
Titanium dioxide (E171)
Lactose monohydrate
Triacetin
Indigo carmine aluminium lake (E132)

Printing ink

Shellac (E904)
Black iron oxide (E172)
Ammonium hydroxide (E527)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

Mitapivat tablets are supplied in PVC/PCTFE/Al blister wallets in cartons.

Dose titration and maintenance packs:

Pyrukynd 5 mg film-coated tablets

Carton containing 56 film-coated tablets in 4 blister wallets, each containing 14 film-coated tablets.

Pyrukynd 20 mg film-coated tablets

Carton containing 56 film-coated tablets in 4 blister wallets, each containing 14 film-coated tablets.

Pyrukynd 50 mg film-coated tablets

Carton containing 56 film-coated tablets in 4 blister wallets, each containing 14 film-coated tablets.

Dose taper packs:

Pyrukynd 5 mg film-coated tablets

Carton containing 7 film-coated tablets in a blister wallet.

Pyrukynd 20 mg film-coated tablets + Pyrukynd 5 mg film-coated tablets

Each carton of 14 film-coated tablets contains:

7 film-coated tablets of Pyrukynd 20 mg

7 film-coated tablets of Pyrukynd 5 mg

Pyrukynd 50 mg film-coated tablets + Pyrukynd 20 mg film-coated tablets

Each carton of 14 film-coated tablets contains:

7 film-coated tablets of Pyrukynd 50 mg

7 film-coated tablets of Pyrukynd 20 mg

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Agios Netherlands B.V.
Zuidplein 36
Regus Amsterdam WTC
1077XV Amsterdam
The Netherlands

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 52779/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/12/2022

10 DATE OF REVISION OF THE TEXT

20/12/2022