pyrukynd®
(mitapivat) tablets
5 • 20 • 50 mg

Dosing Guide

INDICATION
PYRUKYND is a pyruvate kinase activator indicated for the treatment of hemolytic anemia in adults with pyruvate kinase (PK) deficiency.

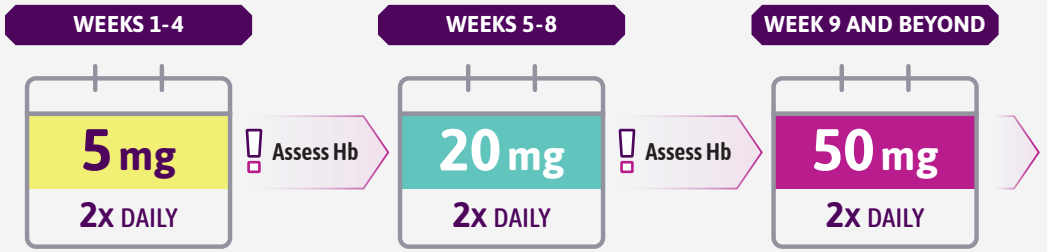
IMPORTANT SAFETY INFORMATION
Acute Hemolysis: Acute hemolysis with subsequent anemia has been observed following abrupt interruption or discontinuation of PYRUKYND in a dose-ranging study. Avoid abruptly discontinuing PYRUKYND. Gradually taper the dose of PYRUKYND to discontinue treatment if possible. When discontinuing treatment, monitor patients for signs of acute hemolysis and anemia including jaundice, scleral icterus, dark urine, dizziness, confusion, fatigue, or shortness of breath.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information for PYRUKYND in pocket.

Prescribing PYRUKYND®: One oral tablet, twice a day[1]

Assess hemoglobin (Hb) and transfusion requirement before dose increases and **up-titrate** to gradually increase Hb and maximize the effect.

EXAMPLE DOSE TITRATION SCHEDULE



In a study, **88%** of patients were maintained at 50 mg twice daily[1]

UP-TITRATE TO 50 mg TWICE-DAILY DOSE AS APPROPRIATE[1]*

- Titrate PYRUKYND every 4 weeks from 5 mg to 20 mg twice daily, and then to the maximum recommended dose of 50 mg twice daily
- If Hb is below normal range or patient was transfused in the previous 8 weeks, increase to the next dose. If the patient's Hb is within normal range and they have not required a recent transfusion, maintain current dose*
- If at any time the patient's Hb decreases, consider up-titrating to the maximum dose of 50 mg twice daily
- If a dose reduction is required for adverse event management, tolerability, or for Hb above normal, reduce to the next lower dose level

HOW TO TAKE PYRUKYND[1]

- Direct patients to take tablets orally, with or without food. Tablets should be swallowed whole
- Patients should not split, crush, chew, or dissolve the tablets

*Some patients may reach and maintain normal Hb levels at 5 mg twice daily or 20 mg twice daily.[1]

IMPORTANT SAFETY INFORMATION (cont.)

Adverse Reactions: Serious adverse reactions occurred in 10% of patients receiving PYRUKYND in the ACTIVATE trial, including atrial fibrillation, gastroenteritis, rib fracture, and musculoskeletal pain, each of which occurred in 1 patient. In the ACTIVATE trial, the most common adverse reactions including laboratory abnormalities (≥10%) in patients with PK deficiency were estrone decreased (males), increased urate, back pain, estradiol decreased (males), and arthralgia.

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Missed, interrupted, or discontinued treatment[1]

MISSED DOSE

Advise patient: If a PYRUKYND® dose is missed by 4 hours or less, take scheduled dose as soon as possible. If a dose is missed by more than 4 hours, do not take a replacement dose, and wait until the next scheduled dose. Subsequently, return to normal dose schedule.

TAPER DOSE TO GRADUALLY DISCONTINUE TREATMENT

To reduce the risk of acute hemolysis, avoid abrupt interruption or discontinuation of PYRUKYND. Dose taper packs are available.

IF CURRENT DOSE IS **50 mg TWICE DAILY**	IF CURRENT DOSE IS **20 mg TWICE DAILY**	IF CURRENT DOSE IS **5 mg TWICE DAILY**
Dose as 50 mg once daily for 7 days On day 8, down-titrate to 20 mg once daily for 7 days and then discontinue	Dose as 20 mg once daily for 7 days On day 8, down-titrate to 5 mg once daily for 7 days and then discontinue	Dose as 5 mg once daily for 7 days and discontinue

IN-TRIAL TAPERING

- In a phase 2 dose-finding study with doses as high as 300 mg twice daily, 2 out of 52 patients experienced acute hemolysis due to sudden discontinuation. Both patients experienced a rapid and large Hb increase during the first 3 weeks of treatment, followed by a sudden discontinuation of PYRUKYND without taper, resulting in acute hemolysis[2]
- In the trials, patients who missed only a few doses of PYRUKYND later in their treatment course, or for whom the dose was tapered, did not experience acute hemolysis[3]

Discontinue PYRUKYND if no benefit has been observed by 24 weeks (6 months), based on the hemoglobin and hemolysis laboratory results and transfusion requirements

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PYRUKYND® dosage modifications[1]

DRUG-DRUG INTERACTIONS

Strong CYP3A Inhibitors	Moderate CYP3A Inhibitors	Strong CYP3A Inducers	Moderate CYP3A Inducers
Avoid co-administration	Do not titrate above 20 mg twice daily	Avoid co-administration	▶ Consider alternatives ▶ Can titrate beyond 50 mg twice daily, as needed, but do not exceed 100 mg twice daily

SPECIAL POPULATIONS AND CIRCUMSTANCES[1]

HEPATIC IMPAIRMENT

- Avoid use of PYRUKYND in patients with moderate and severe hepatic impairment
- PYRUKYND undergoes extensive hepatic metabolism. Moderate and severe hepatic impairment is expected to increase the systemic exposure of PYRUKYND

RENAL IMPAIRMENT

- Steady state AUC of PYRUKYND in patients with eGFR 60 to <90 mL/min/1.73 m^2 was not significantly different compared to patients with eGFR ≥90 mL/min/1.73 m^2
- There are limited data available in patients with eGFR 30 to <60 mL/min/1.73 m^2 and no data available in patients with eGFR <30 mL/min/1.73 m^2

ADVERSE REACTIONS OR Hb ABOVE NORMAL†

- Reduce dose to the next lower dose twice daily

AUC=area under the curve; eGFR=estimated glomerular filtration rate.
†If discontinuation is required, follow the dose taper schedule on page 3.

Advise patients using hormonal contraceptives to use an alternative non-hormonal method or add a barrier method during treatment with PYRUKYND

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myAgios® Patient Support Services can educate on dose titration

myAgios can help ensure continuity of care during dose titration for enrolled patients

1. Prescribe 28-day Rx PYRUKYND for your patient enrolled in myAgios.
2. A dedicated PSM will proactively contact your office on Day 1, Day 15, and Day 20 after initial shipment with a reminder of your patient's upcoming refill or dose titration.
3. Clinician assessment of Hb and/or transfusion needs.
4. myAgios PSM confirms refill or dose titration based on clinician assessment. If dose titration is needed, myAgios PSM can warm transfer clinician to specialty pharmacy for new Rx.

INTRODUCING

myAgios Patient Support Services for adults with pyruvate kinase (PK) deficiency

A centralized enrollment for eligible patients, including prescription fulfillment, financial assistance, access, and adherence support.

To learn more, call 1-800-951-3889, Mon-Fri, 8 AM to 6 PM ET or visit PYRUKYND.myAgios.com/hcp

myagios

This program is not intended as medical advice and patients should consult their healthcare team with questions related to their treatment.

To learn more, visit PYRUKYND.com/hcp

IMPORTANT SAFETY INFORMATION (cont.)

Drug Interactions:

- Strong CYP3A Inhibitors and Inducers: Avoid concomitant use.
- Moderate CYP3A Inhibitors: Do not titrate PYRUKYND beyond 20 mg twice daily.
- Moderate CYP3A Inducers: Consider alternatives that are not moderate inducers. If there are no alternatives, adjust PYRUKYND dosage.
- Sensitive CYP3A, CYP2B6, CYP2C Substrates Including Hormonal Contraceptives: Avoid concomitant use with substrates that have narrow therapeutic index.
- UGT1A1 Substrates: Avoid concomitant use with substrates that have narrow therapeutic index.
- P-gp Substrates: Avoid concomitant use with substrates that have narrow therapeutic index.

Hepatic Impairment: Avoid use of PYRUKYND in patients with moderate and severe hepatic impairment.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information for PYRUKYND in pocket.

REFERENCES: 1. PYRUKYND. Prescribing information. Agios Pharmaceuticals, Inc.; 2022. **2.** Grace RF, Rose C, Layton DM, et al. Safety and efficacy of mitapivat in pyruvate kinase deficiency. *N Engl J Med.* 2019;381(10):933-944. **3.** Data on file. Agios Pharmaceuticals, Inc.

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