



Imagine this for your red blood cells

The first and only targeted PK deficiency treatment

Jim, 22

Takes PYRUKYND®

All patients photographed may or may not still be on treatment.

Introducing PYRUKYND, a treatment of hemolytic anemia for adults with pyruvate kinase (PK) deficiency that targets the underlying cause of the disease and activates the defective enzyme.



Talk to your doctor about what PYRUKYND can do for you.

WHAT IS PYRUKYND?

PYRUKYND is a prescription medicine used to treat low red blood cell counts caused by the early breakdown of red blood cells (hemolytic anemia) in adults with pyruvate kinase (PK) deficiency.

It is not known if PYRUKYND is safe and effective in children.

IMPORTANT SAFETY INFORMATION

PYRUKYND may cause serious side effects, including:

- **Rapid breakdown of red blood cells (acute hemolysis)** has happened after suddenly interrupting or stopping treatment with PYRUKYND. **You should not suddenly stop taking PYRUKYND.** If you have to stop your treatment with PYRUKYND, your healthcare provider should monitor you closely. Tell your healthcare provider right away if you develop any signs or symptoms of breakdown of red blood cells including yellowing of the skin or the whites of your eyes (jaundice), dark colored urine, dizziness, confusion, feeling tired, or shortness of breath

Please see additional Important Safety Information throughout and [full Prescribing Information](#), including Patient Information, for PYRUKYND in pocket.



pyrukynd
(mitapivat) tablets
5 • 20 • 50 mg

What is PK deficiency?

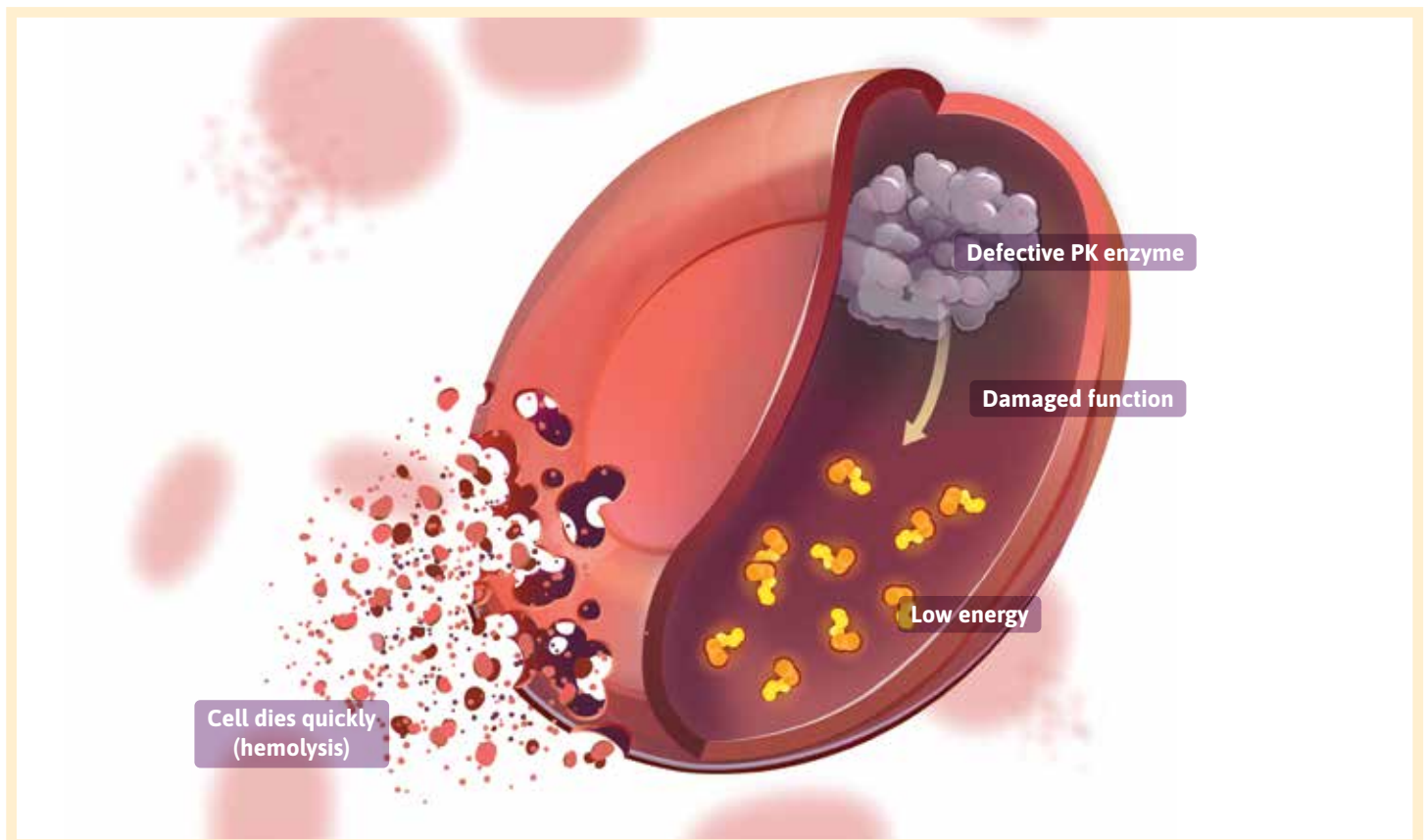
Understand the role that the PK enzyme plays in the health of your red blood cells (RBCs)

PK deficiency is a rare, inherited enzyme defect that causes RBCs to break down faster than they are made, which leads to lifelong hemolytic anemia.

The life of healthy RBCs

- After healthy RBCs are produced, they travel through the lungs, where oxygen binds to a molecule in each of the RBCs called hemoglobin
- The RBCs then transport oxygen to the rest of the body
- Healthy RBCs have enough ATP, or energy, made by the pyruvate kinase R (PKR) enzyme to survive this trip throughout the body
- Each RBC lives for about 120 days before being broken down and removed from circulation

PK-Deficient RBC



- People with PK deficiency have a PK enzyme that has a defect, causing their RBCs to break down sooner than normal. When RBCs break down, it's called hemolysis
- If PK deficiency is left untreated, RBCs continue to break down, and this may lead to symptoms of anemia like extreme fatigue, yellow skin/eye tone (jaundice), and complications like iron overload

KEY TERMS

Red blood cells

Cells that carry oxygen throughout the body

Anemia

A condition in which the blood has lower-than-normal levels of RBCs or hemoglobin

Hemoglobin (Hb)

A protein that helps RBCs carry the oxygen your body needs

Hemolytic anemia

A type of anemia that is caused by the early breakdown of RBCs in the bloodstream or by the spleen

Hemolysis

The breakdown of RBCs, which leads to the release of hemoglobin and bilirubin into the blood

Glycolysis

The process of RBCs converting glucose (sugar) into pyruvate and ATP

Enzyme

A protein that catalyzes chemical reactions that occur inside the body

PKR

The pyruvate kinase enzyme found in red blood cells

Adenosine triphosphate (ATP)

The primary source of energy for cells

Iron overload

An excess of iron in the body



If you have questions about the details of PK deficiency, a myAgios® Patient Support Manager is available to help at **1-800-951-3889**, Mon-Fri, 8 AM to 6 PM ET.

It's important to speak up about your PK deficiency symptoms

When talking with your doctor it can be helpful to prepare ahead of each appointment by knowing the key information to bring up.

Answer these questions about your PK deficiency journey to help guide the conversation.



What are your Hb levels?

How do these signs and symptoms affect you?



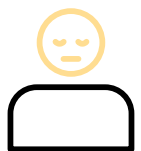
FATIGUE AND TIREDNESS

0	1	2	3	4	5
Not at all		Mild	Moderate		Severe



SHORTNESS OF BREATH

0	1	2	3	4	5
Not at all		Mild	Moderate		Severe



YELLOWING OF THE SKIN/EYES (JAUNDICE)

0	1	2	3	4	5
Not at all		Mild	Moderate		Severe

Do you have a history with transfusions? Yes No

If yes, when was the last one you received?

Think about different areas of your life and note any impact you feel due to PK deficiency:

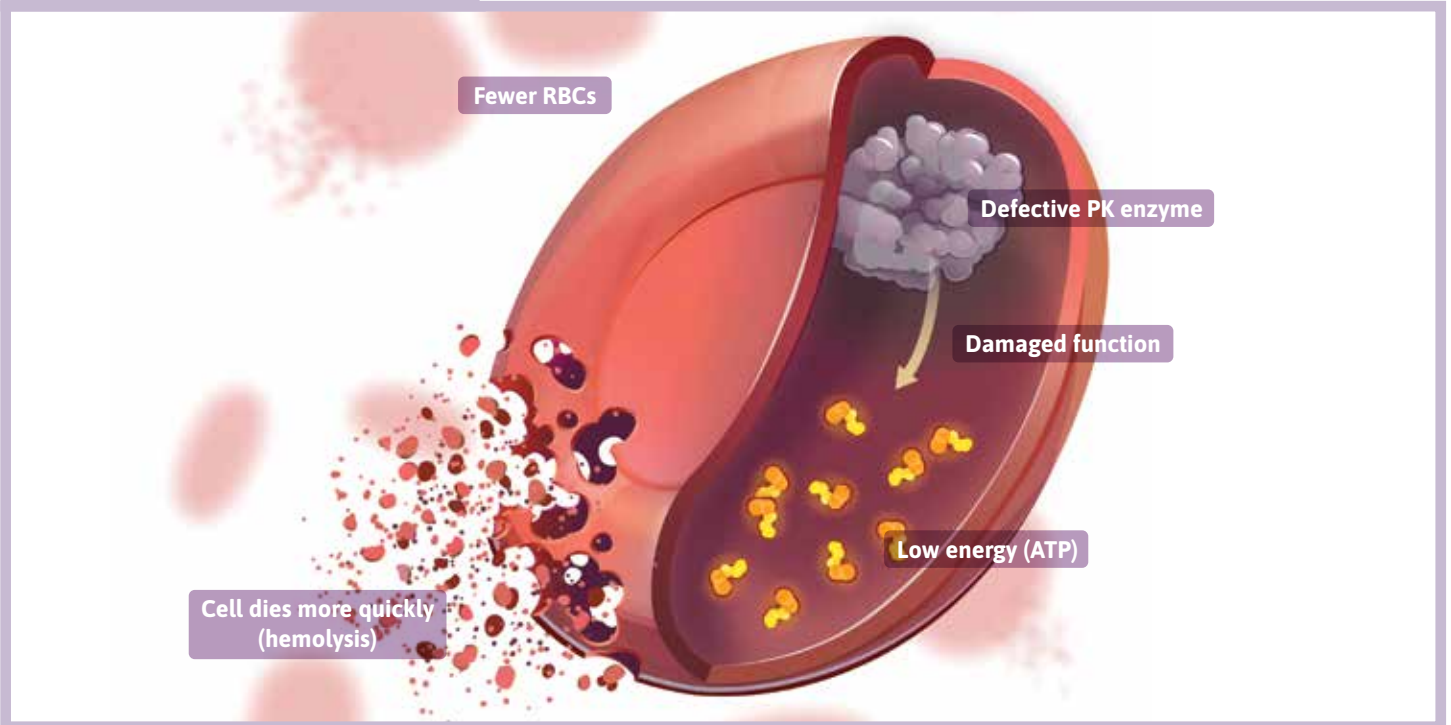


Bring this form to your next appointment to help paint a full picture of your PK deficiency experience for your doctor.

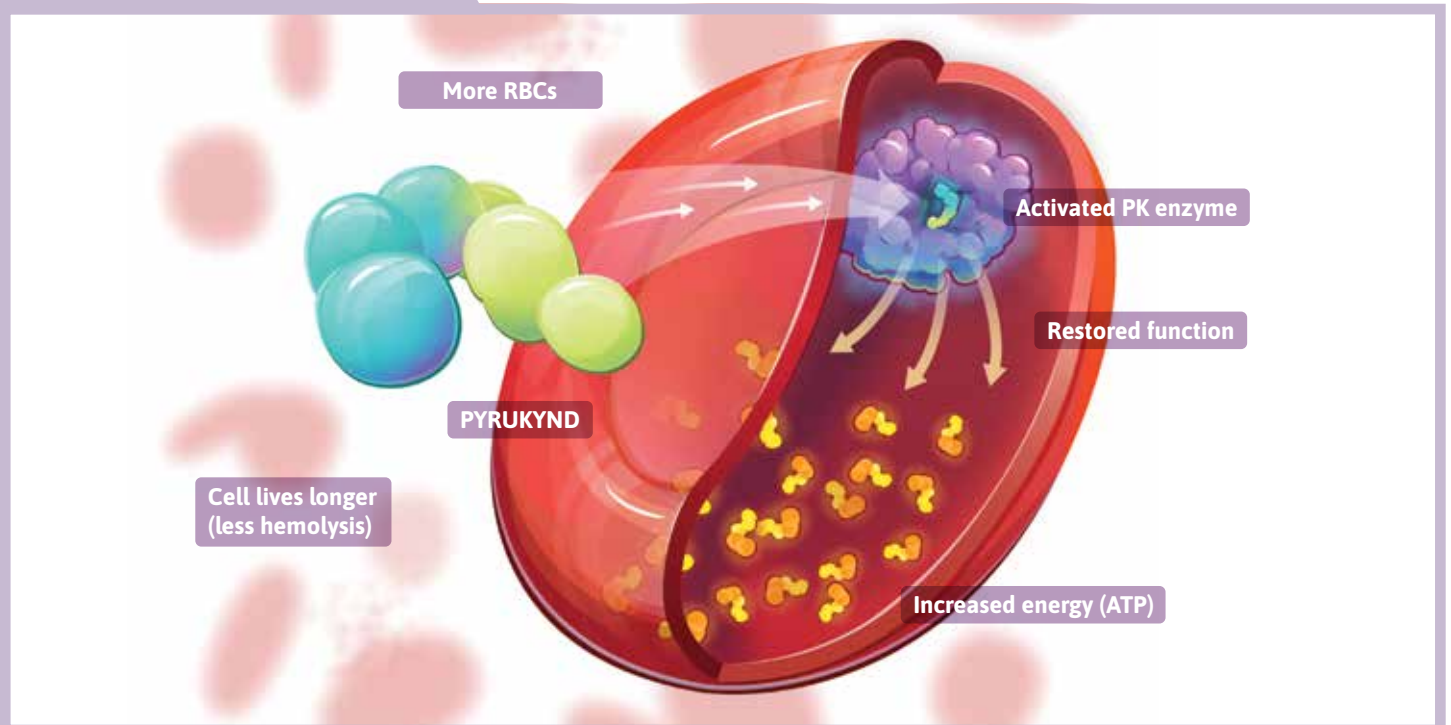
For more information about the symptoms and complications of PK deficiency, visit [KnowPKDeficiency.com](https://www.knowpkdeficiency.com).

Imagine the first and only treatment to target the cause of your PK deficiency

WITHOUT PYRUKYND®



WITH PYRUKYND



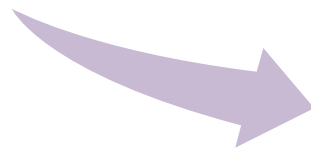
By activating the defective PK enzyme that causes the rapid breakdown of RBCs (hemolysis), PYRUKYND may help your RBCs live longer

Take a closer look at how PYRUKYND is thought to work:



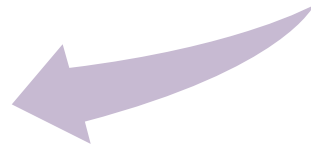
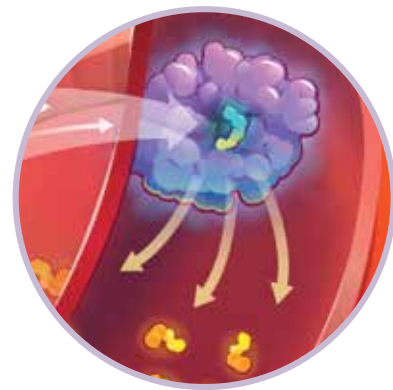
STEP ONE ATTACHES

PYRUKYND starts by attaching and binding to the defective PK enzyme



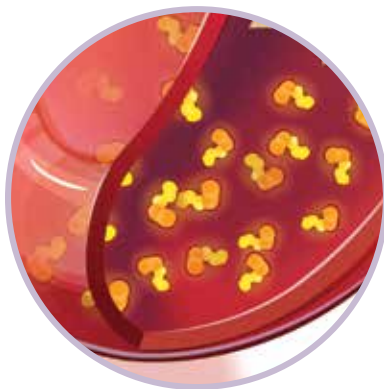
STEP TWO ACTIVATES

Once attached, PYRUKYND activates the PK enzyme to help improve its function, and increase energy, or ATP (as seen in healthy people without PK deficiency)



STEP THREE RESTORES ENERGY

Helps increase energy (ATP) to slow the process of RBC breakdown (hemolysis) and helps them live longer



IMPORTANT SAFETY INFORMATION (cont.)

The most common side effects of PYRUKYND were decrease in reproductive hormone (estrone) in men, increased salt from uric acid (urate) blood test, back pain, decrease in reproductive hormone (estradiol) in men, and joint pain (arthralgia).

These are not all the possible side effects of PYRUKYND. Call your healthcare provider for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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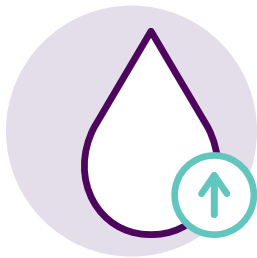
WHAT IS
PYRUKYND?

The safety and effectiveness of PYRUKYND[®] was studied in 2 clinical trials

STUDY 1 (ACTIVATE)

Adults with PK deficiency who were not regularly transfused
(defined as receiving 4 or fewer blood transfusions a year)

What were the main goals?

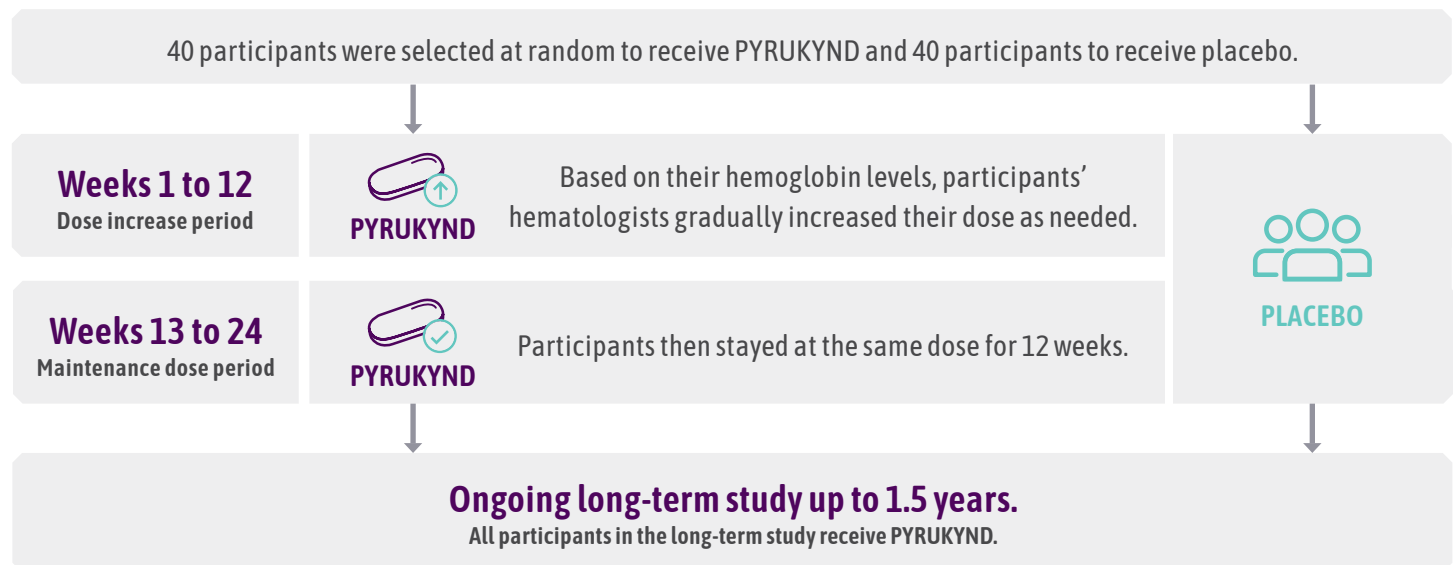


Study 1 measured:

- Changes in participants' hemoglobin and hemolysis levels
- Improvements in signs and symptoms of PK deficiency such as jaundice, tiredness, and shortness of breath

A response to PYRUKYND was measured by at least a 1.5 g/dL increase in hemoglobin during at least 2 of 3 checkups at weeks 16, 20, and 24.

How was the study set up?



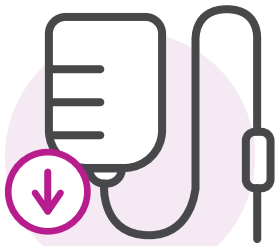
The safety of PYRUKYND has been studied up to 5 years in 4 clinical trials in 155 participants. [Learn more about how PYRUKYND was studied at PYRUKYND.com.](https://www.pyrukynd.com)

STUDY 2 (ACTIVATE-T)

Adults with PK deficiency who were regularly transfused

(defined as receiving 6 or more blood transfusions a year)

What was the main goal?



Study 2 measured changes in participants' need for transfusions

A response to PYRUKYND was measured by at least a 33% reduction in the number of transfusions required during the final 24-week period.

Transfusion reductions were measured in comparison to the number of RBC units they received in the year before the study.

How was the study set up?

All 27 participants received PYRUKYND. None received placebo.

Weeks 1 to 16
Dose increase period



Participants' doses of PYRUKYND were gradually increased over the course of 16 weeks.

Weeks 17 to 40
Maintenance dose period



Participants were then given the same dose of PYRUKYND for the next 24 weeks.

Ongoing long-term study up to 1.8 years.



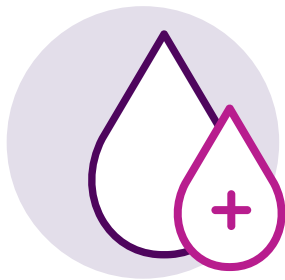
The most common side effects of PYRUKYND were decreases in reproductive hormones in males (estrone and estradiol), increased salt from uric acid (urate), back pain, and joint pain.

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What a change in hemoglobin levels means for your PK-deficient red blood cells

PYRUKYND® helps activate the PK enzyme to keep RBCs from breaking down too quickly and increase your hemoglobin (Hb) levels

Increased hemoglobin levels are a sign that anemia is improving



40% of patients

out of the 40 participants in Study 1 (ACTIVATE) responded to PYRUKYND compared to 0% receiving placebo, meaning their Hb increased by 1.5 g/dL or greater during at least 2 of 3 checkups at weeks 16, 20, and 24.

In Study 1 (ACTIVATE), initial increases in average Hb levels were seen as early as 2 weeks after starting treatment, and improvements generally continued over the course of the 6-month period.



PYRUKYND was also shown to slow the process of RBC breakdown (hemolysis), which could help RBCs live longer.

Blood tests are used to measure levels of hemolysis. In clinical studies, **PYRUKYND noticeably improved***:

- Bilirubin
- Haptoglobin
- Reticulocytes
- Lactate dehydrogenase (LDH)

*Participants on PYRUKYND showed a -1.5 mg/dL reduction in bilirubin, a 15.8 mg/dL increase in haptoglobin, a -10% reduction in reticulocytes percentage, and a -71 U/L reduction in LDH.

IMPORTANT SAFETY INFORMATION (cont.)

Before taking PYRUKYND, tell your healthcare provider about all of your medical conditions, including if you:

- have liver problems
- are pregnant or plan to become pregnant. It is not known if PYRUKYND will harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think that you are pregnant during treatment with PYRUKYND
- are breastfeeding or plan to breastfeed. It is not known if PYRUKYND passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with PYRUKYND

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A great day is when I get to hang out with my dog and do the things that fuel me. With my hemoglobin levels improving, I can see the difference.

—Jim, 22
Takes PYRUKYND



KEY TERMS

MEASURES OF HEMOLYSIS

Bilirubin

A substance released from RBCs when they break down, which can cause yellowing of the skin/eyes (jaundice). During hemolysis, bilirubin levels increase

Haptoglobin

A protein produced by the liver that the body uses to clear hemoglobin found outside of RBCs. During hemolysis, haptoglobin is low

Reticulocytes

RBCs that are still developing. During hemolysis, reticulocyte levels increase

Lactate dehydrogenase (LDH)

An enzyme found in RBCs as well as other cells. A high LDH level is a sign of hemolysis, as it indicates that RBCs may be breaking apart

HOW PYRUKYND HELPS



Treatment experiences and results with PYRUKYND will be different for everyone.



**Marissa, 24 & Lauryn, 19
Both take PYRUKYND**

It's nice to look in the mirror and see more impact
from PYRUKYND and less jaundice.

—Lauryn, 19

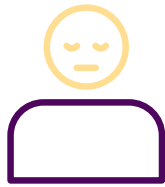
Everyone taking PYRUKYND is different, so individual results may vary.

A new day with PK deficiency and PYRUKYND®

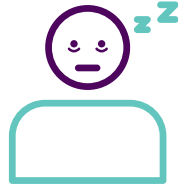
Treating your PK deficiency with PYRUKYND may change the way you think about your daily symptoms

Patients taking PYRUKYND saw improvements in signs and symptoms of PK deficiency.

Over the course of the clinical study, the PK Deficiency Diary (PKDD) was used to help track changes in signs and symptoms of PK deficiency compared to placebo, such as:



JAUNDICE



TIREDDNESS



SHORTNESS OF BREATH

Before PYRUKYND, my day revolved around my PK deficiency, but now I feel less tired and my anemia has improved.

—Marissa, 24

Everyone taking PYRUKYND is different, so individual results may vary.



IMPORTANT SAFETY INFORMATION (cont.)

Tell your healthcare provider about all the medicines that you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. PYRUKYND and certain other medicines may affect each other causing side effects. PYRUKYND may affect the way other medicines work, and other medicines may affect how PYRUKYND works. Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

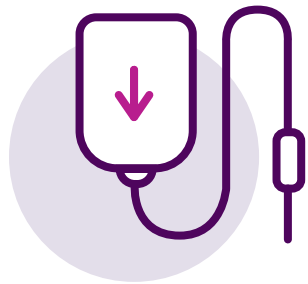
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Imagine an opportunity for fewer transfusions

Another possibility with PYRUKYND[®]

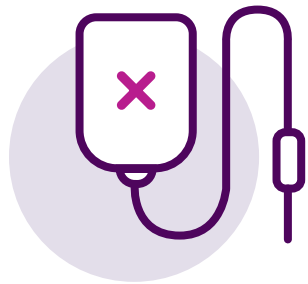
In some cases, people with PK deficiency receive regular transfusions. In Study 2 (ACTIVATE-T), the need for transfusions was evaluated in 27 participants who were regularly transfused.



Patients had the opportunity to have fewer transfusions.

33% of patients

experienced a $\geq 33\%$ reduction in the units transfused compared to their previous history*



And some were even transfusion free.

22% of patients

achieved transfusion-free status during the fixed-dose period of Study 2*

*Out of the 27 participants, 9 experienced a transfusion reduction and 6 became transfusion free.

IMPORTANT SAFETY INFORMATION (cont.)

The most common side effects of PYRUKYND were decrease in reproductive hormone (estrone) in men, increased salt from uric acid (urate) blood test, back pain, decrease in reproductive hormone (estradiol) in men, and joint pain (arthralgia).

These are not all the possible side effects of PYRUKYND. Call your healthcare provider for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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Kim, 52
Takes PYRUKYND





Jim, 22
Takes PYRUKYND

What are the most common side effects of PYRUKYND®?

We know that starting a treatment can be overwhelming, especially if the treatment is new. As the first approved treatment for PK deficiency, PYRUKYND has been closely monitored through clinical studies.

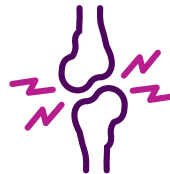
The most common side effects include:



decreases in reproductive hormones in males (estrone and estradiol)



increased salt from uric acid (urate)



joint pain



back pain



Tell your healthcare provider about the medicines you take.

PYRUKYND and certain other medicines may affect each other causing side effects.

PYRUKYND may affect the way other medicines work, and other medicines may affect how PYRUKYND works.

IMPORTANT SAFETY INFORMATION (cont.)

PYRUKYND may cause serious side effects, including:

- **Rapid breakdown of red blood cells (acute hemolysis)** has happened after suddenly interrupting or stopping treatment with PYRUKYND. **You should not suddenly stop taking PYRUKYND.** If you have to stop your treatment with PYRUKYND, your healthcare provider should monitor you closely. Tell your healthcare provider right away if you develop any signs or symptoms of breakdown of red blood cells including yellowing of the skin or the whites of your eyes (jaundice), dark colored urine, dizziness, confusion, feeling tired, or shortness of breath

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Getting started with PYRUKYND®



ONE ORAL TABLET, TWICE A DAY WITH OR WITHOUT FOOD

Check in with your doctor regularly to monitor your treatment progress and ask any questions you have while taking PYRUKYND.

Before starting PYRUKYND, your doctor will determine if your Hb is considered lower than normal and evaluate your need for transfusions. As you start treatment, your doctor may make adjustments as needed based upon changes in symptoms, Hb, need for transfusions, and potential side effects. If your Hb reaches a normal range, you'll stay at your current dose.

STEP ONE

Start at 5 mg twice a day

The starting dose for PYRUKYND is one 5-mg tablet taken orally twice daily for 4 weeks. Your doctor will assess your Hb after 3 weeks.

STEP TWO

Your doctor may increase your dose to 20 mg

After 4 weeks, your doctor may increase your dose of PYRUKYND to improve your body's Hb if:

- Your Hb stays below the normal range, or
- You've needed a transfusion within the last 8 weeks

If needed, your dose will increase from 5 mg twice daily to 20 mg twice daily.

STEP THREE

Your doctor may increase your dose to 50 mg

After 8 weeks, your doctor may increase your dose of PYRUKYND to 50 mg twice daily to increase your body's response if:

- Your Hb stays below the normal range after taking 20 mg of PYRUKYND twice daily, or
- You've needed a transfusion within the last 8 weeks

Your doctor will determine if other medications you're taking may cause your dosage to go above 50 mg twice daily.

Remember that PK deficiency is a chronic, genetic disease, which means it is persistent through life. Once treatment has started, it's important to continue with it.

Missing a dose

- If you miss a dose of PYRUKYND, there are ways to get back on track. If it's been 4 hours or less since the time you usually take it, take your dose as soon as possible
- If it's been over 4 hours since your missed dose, wait until your next scheduled dose and then return to your normal schedule

Stopping treatment

- **Make sure to discuss any changes with your doctor before you stop taking PYRUKYND. If you stop treatment abruptly, there is a risk of acute hemolysis.** Acute hemolysis is when large numbers of red blood cells are destroyed over a short time
- If you and your doctor decide you should stop taking PYRUKYND, you'll follow a schedule that slowly decreases your doses



Contact your healthcare provider immediately if you discontinue treatment and develop signs or symptoms of acute hemolysis, which include yellowing of the skin or eyes, darkening of the urine, dizziness, confusion, fatigue, and shortness of breath



Your myAgios® Patient Support Manager is available to help you. They can provide tips to stay on track with dosing and offer support if you lose or forget your prescription.

To schedule a phone or video call with your Patient Support Manager, call **1-800-951-3889**, Mon-Fri, 8 AM to 6 PM ET.

IMPORTANT SAFETY INFORMATION (cont.)

Tell your healthcare provider about all the medicines that you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. PYRUKYND and certain other medicines may affect each other causing side effects. PYRUKYND may affect the way other medicines work, and other medicines may affect how PYRUKYND works. Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

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myAgios[®] Patient Support Services is here to help

A customized support program for people living with PK deficiency and being treated with PYRUKYND[®] (mitapivat) tablets

Nefar Moran

Patient Support Manager
Cambridge, MA



Elisabeth Herdic

Patient Support Manager
Cambridge, MA

What is myAgios?

It's a patient support program for people living with PK deficiency and their caregivers, including those prescribed PYRUKYND. Experienced Patient Support Managers are available to support you throughout your journey, whether you've just been diagnosed or have had the condition for a long time. This program is free of charge. Please call our Patient Support Managers when you're ready to enroll and participate in the program.

If you and your doctor agree PYRUKYND is the right medicine to treat your PK deficiency, your doctor will complete and fax the enrollment form to myAgios. Your signature is needed to finish the enrollment, so your Patient Support Manager will work with you to get your signature and begin the next steps to start treatment.

IMPORTANT SAFETY INFORMATION (cont.)

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How do Patient Support Managers help?

Your dedicated Patient Support Manager will listen to understand the challenges you experience living with PK deficiency and is here to provide tailored help, including:



Financial support

- Verifying coverage with your insurance company and out-of-pocket costs for PYRUKYND
- Connecting with your healthcare provider to discuss your health insurance company's requirements or questions your insurance company has while determining your coverage
- Discussing your eligibility for certain financial assistance programs



Patient support

- Support while on treatment with PYRUKYND, including tips to help you stay on track with your treatment



Building a community

- Helping you advocate for yourself and working with you to prepare for upcoming doctor's appointments with your hematologist and care team
- Connecting you with the PK deficiency community through a series of patient-focused webinars. You can sign up at PYRUKYND.com, KnowPKDeficiency.com, or by calling your Patient Support Manager directly at 1-800-951-3889, Mon-Fri, 8 AM to 6 PM ET



Staying informed

- Providing PK deficiency disease education and connecting you with educational resources through KnowPKDeficiency.com

The purpose of this program is NOT to offer medical or treatment-related advice.
For these types of questions, contact your doctor.



We're ready when you are.
Get your questions answered by calling
our Patient Support Managers at
1-800-951-3889, Mon-Fri, 8 AM to 6 PM ET.



myAgios[®] financial assistance

Get the information and answers you need

If you do not have insurance, myAgios Patient Support Managers can assist you with financial and coverage support to help you access PYRUKYND[®]. Available information includes:



The PYRUKYND Copay Program

- If you're eligible, this program can lower the copay to \$0 per prescription
- Patients participating in government healthcare insurance are not eligible



The Patient Assistance Program

- For eligible patients, Agios' Patient Assistance Program can offer access to medication if you are uninsured or underinsured



Coverage Interruption

- If you are on PYRUKYND, but experience an interruption in prescription coverage by your health insurance, you may be eligible for the Coverage Interruption Program
- Patients participating in government healthcare insurance are not eligible




Please visit PYRUKYND.myAgios.com/financial-support to learn more about financial assistance options and to see full Terms and Conditions.

Please see full Terms and Conditions on myAgios.com/PYRUKYND

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Marissa, 24
Takes PYRUKYND



Reimagine your PK deficiency with PYRUKYND[®], the first and only targeted treatment



Increased hemoglobin levels and improved hemolytic anemia (see page 10)*



Showed improvements in signs and symptoms of PK deficiency (see page 13)*†



Reduced need for transfusions (see page 14)‡



PYRUKYND is an oral tablet taken twice a day



Learn more about PYRUKYND and explore additional resources at [PYRUKYND.com](https://www.pyrukynd.com).

*Study 1 (ACTIVATE) measured hemoglobin level changes in 80 adults who were not regularly transfused (4 or fewer blood transfusions a year). A hemoglobin increase of at least 1.5 grams per deciliter in at least 2 of the 3 checkups (at weeks 16, 20, or 24) was counted as a response. In Study 1, 40% of participants responded to PYRUKYND, compared to 0% receiving placebo.

†In Study 1 (ACTIVATE), changes in signs and symptoms of PK deficiency (jaundice, tiredness, and shortness of breath) were measured.

‡Study 2 (ACTIVATE-T) measured whether the need for transfusions changed in 27 regularly transfused adults (6 or more blood transfusions a year). Once they reached a maintenance dose of PYRUKYND, a 33% or greater decrease in the number of red blood cell units received was counted as a response. In Study 2, 33% of patients responded to PYRUKYND.

WHAT IS PYRUKYND?

PYRUKYND is a prescription medicine used to treat low red blood cell counts caused by the early breakdown of red blood cells (hemolytic anemia) in adults with pyruvate kinase (PK) deficiency.

It is not known if PYRUKYND is safe and effective in children.

IMPORTANT SAFETY INFORMATION (cont.)

Tell your healthcare provider about all the medicines that you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. PYRUKYND and certain other medicines may affect each other causing side effects. PYRUKYND may affect the way other medicines work, and other medicines may affect how PYRUKYND works. Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PYRUKYND safely and effectively. See full prescribing information for PYRUKYND.

PYRUKYND® (mitapivat) tablets, for oral use
Initial U.S. Approval: 2022

INDICATIONS AND USAGE

PYRUKYND is a pyruvate kinase activator indicated for the treatment of hemolytic anemia in adults with pyruvate kinase (PK) deficiency. (1)

DOSAGE AND ADMINISTRATION

- Starting dosage: 5 mg orally twice daily with or without food. (2.1)
- See Full Prescribing Information for dose titration and taper schedule. (2.1, 2.3)
- The tablet should be swallowed whole. (2.1)

DOSAGE FORMS AND STRENGTHS

Tablets: 5 mg, 20 mg, and 50 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

Acute Hemolysis: Avoid abrupt interruption or abrupt discontinuation of PYRUKYND to minimize the risk of acute hemolysis. A gradual reduction in dosing rather than abrupt cessation is recommended when possible. (5.1)

ADVERSE REACTIONS

The most common adverse reactions including laboratory abnormalities ($\geq 10\%$) in patients with PK deficiency were estrone decreased (males), increased urate, back pain, estradiol decreased (males), and arthralgia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Agios Pharmaceuticals at 1-833-228-8474 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong CYP3A Inhibitors and Inducers: Avoid concomitant use. (7.1)
- Moderate CYP3A Inhibitors: Do not titrate PYRUKYND beyond 20 mg twice daily. (7.1)
- Moderate CYP3A Inducers: Consider alternatives that are not moderate inducers. If there are no alternatives, adjust PYRUKYND dosage. (7.1)
- Sensitive CYP3A, CYP2B6, CYP2C substrates including hormonal contraceptives: Avoid concomitant use with substrates that have narrow therapeutic index. (7.2)
- UGT1A1 Substrates: Avoid concomitant use with substrates that have narrow therapeutic index. (7.2)
- P-gp Substrates: Avoid concomitant use with substrates that have narrow therapeutic index. (7.2)

USE IN SPECIFIC POPULATIONS

Hepatic Impairment: Avoid use of PYRUKYND in patients with moderate or severe hepatic impairment. (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 2/2022

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

PYRUKYND is taken with or without food and swallowed whole. Do not split, crush, chew, or dissolve the tablets.

The starting dosage for PYRUKYND is 5 mg orally twice daily. To gradually increase hemoglobin (Hb), titrate PYRUKYND from 5 mg twice daily to 20 mg twice daily, and then to the maximum recommended dose of 50 mg twice daily, with these dose increases occurring every 4 weeks (see Table 1). Assess Hb and transfusion requirement before increasing to the next dose level, as some patients may reach and maintain normal Hb at 5 mg twice daily or 20 mg twice daily.

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

Table 1: Dose Titration Schedule

Duration	Dosage
Week 1 through Week 4	5 mg twice daily
Week 5 through Week 8	If Hb is below normal range or patient has required a transfusion within the last 8 weeks: <ul style="list-style-type: none">• Increase to 20 mg twice daily and maintain for 4 weeks. If Hb is within normal range and patient has not required a transfusion within the last 8 weeks: <ul style="list-style-type: none">• Maintain 5 mg twice daily.
Week 9 through Week 12	If Hb is below normal range or patient has required a transfusion within the last 8 weeks: <ul style="list-style-type: none">• Increase to 50 mg twice daily and maintain thereafter. If Hb is within normal range and patient has not required a transfusion within the last 8 weeks: <ul style="list-style-type: none">• Maintain current dose (5 mg twice daily or 20 mg twice daily).
Maintenance	If Hb decreases, consider up-titration to the maximum of 50 mg twice daily as per the above schedule.

2.2 Missed Dose

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

2.3 Interruption or Discontinuation

To reduce the risk of acute hemolysis, avoid abrupt interruption or abrupt discontinuation of PYRUKYND when possible [see *Warnings and Precautions (5.1)*]. Taper the dose to gradually discontinue the medication (see Table 2). Monitor patients for signs of acute hemolysis and worsening of anemia.

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

Abbreviations: N/A = not applicable.

2.4 Recommended Dosage for Hepatic Impairment

Avoid use of PYRUKYND in patients with moderate or severe hepatic impairment [see *Use in Special Populations (8.6)* and *Clinical Pharmacology (12.3)*].

2.5 Recommended Dosage for Drug Interactions

Strong CYP3A Inhibitors

Avoid co-administration of strong CYP3A inhibitors with PYRUKYND [see *Drug Interactions (7.1)* and *Clinical Pharmacology (12.3)*].

Moderate CYP3A Inhibitors

Monitor Hb and for increased risks of adverse reactions from PYRUKYND. When used with a moderate CYP3A inhibitor, do not titrate PYRUKYND beyond 20 mg twice daily [see *Drug Interactions (7.1)* and *Clinical Pharmacology (12.3)*].

Strong CYP3A Inducers

Avoid co-administration of strong CYP3A inducers with PYRUKYND [see *Drug Interactions (7.1)* and *Clinical Pharmacology (12.3)*].

Moderate CYP3A Inducers

Consider alternative therapies that are not moderate CYP3A inducers during treatment with PYRUKYND. If there are no alternative therapies, monitor Hb and titrate beyond the 50 mg twice daily dose, if necessary, but do not exceed a maximum recommended dose of 100 mg twice daily [see *Drug Interactions (7.1)* and *Clinical Pharmacology (12.3)*].

2.6 Dose Modifications for Adverse Reactions and Hemoglobin Levels Above Normal

If a dose reduction is required because of an adverse reaction or tolerability, or for Hb above normal, 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 PYRUKYND, the dose taper schedule (Table 2) should be followed. In situations where the risk to the patient due to the adverse reaction or Hb above normal is greater than the risk of acute hemolysis due to sudden withdrawal of the drug, treatment may be stopped without taper and patients should be monitored for signs of acute hemolysis.

3 DOSAGE FORMS AND STRENGTHS

- 5 mg tablets: round, blue, film-coated tablets with "M5" printed on one side.
- 20 mg tablets: round, blue, film-coated tablets with "M20" printed on one side.
- 50 mg tablets: oblong, blue, film-coated tablets with "M50" printed on one side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Acute Hemolysis with Abrupt Treatment Interruption

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 [*see Dosage and Administration (2.3, 2.6)*]. 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.

6 ADVERSE REACTIONS

The following clinically significant adverse reaction is described elsewhere in labeling:

- Acute Hemolysis with Abrupt Treatment Discontinuation [*see Warnings and Precautions (5.1)*].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 155 patients received PYRUKYND, 79% of whom were exposed for longer than 24 weeks. PYRUKYND was administered up to 50 mg orally twice daily in 67 patients with PK

deficiency in the ACTIVATE trial (N=40) and the ACTIVATE-T trial (N=27) [see *Clinical Studies (14)*].

ACTIVATE Trial

In the ACTIVATE trial patients with PK deficiency who were not regularly transfused received PYRUKYND in incremental doses up to 50 mg twice daily (N=40) or placebo (N=39).

Serious adverse reactions occurred in 10% of patients receiving PYRUKYND in the ACTIVATE Trial, including atrial fibrillation, gastroenteritis, rib fracture, and musculoskeletal pain, which each occurred in 1 patient.

In the ACTIVATE trial, the most common adverse reactions including laboratory abnormalities ($\geq 10\%$) in patients with PK deficiency were estrone decreased (males), increased urate, back pain, estradiol decreased (males), and arthralgia.

Table 3 summarizes the adverse reactions in the ACTIVATE trial.

Table 3: Adverse Reactions ($\geq 5\%$) in Patients Receiving PYRUKYND in ACTIVATE

Adverse Reactions	PYRUKYND (N=40)		Placebo (N=39)	
	All Grades (%)	Grade ≥ 3 (%)	All Grades (%)	Grade ≥ 3 (%)
Back pain ^a	15%	0	8%	0
Arthralgia ^b	10%	0	5%	0
Hypertriglyceridemia ^c	8%	5%	3%	0
Gastroenteritis	8%	3%	0	0
Hot flush ^d	8%	0	0	0
Oropharyngeal pain	8%	0	5%	0
Hypertension	5%	5%	0	0
Arrhythmia ^e	5%	0	0	0
Breast discomfort	5%	0	0	0
Constipation	5%	0	0	0
Dry mouth ^f	5%	0	0	0
Paresthesia	5%	0	0	0

Grades: Per the CTCAE definition.

Grouped Term Definitions

^a Includes back pain, sciatica, and flank pain.

^b Includes arthralgia and joint swelling.

^c Includes hypertriglyceridemia and blood triglycerides increased.

^d Includes hot flush and flushing.

^e Includes arrhythmia, tachycardia, heart rate increased and atrial fibrillation.

^f Includes dry mouth and dry lip.

Laboratory abnormalities of PYRUKYND included increased urate (15%).

Variations in Reproductive Hormones

In ACTIVATE, increases in serum testosterone and decreases in serum estrone and estradiol were observed in men receiving PYRUKYND (Table 4). These changes in hormones persisted throughout the study period. In patients who discontinued PYRUKYND and had follow-up hormone measurements, the hormone changes returned close to the baseline levels 28 days after discontinuing PYRUKYND. In female patients, sex hormone analysis was limited due to physiologic variations in hormones during the menstrual cycle and the use of hormonal contraceptives.

Table 4: Laboratory Abnormalities in Reproductive Hormones in Men Receiving PYRUKYND

Parameter	ACTIVATE	
	PYRUKYND (16 males) n (%)	Placebo (15 males) n (%)
<i>Reproductive hormone analyses^a</i>		
Estrone decreased (males)	9 (56.3)	0
Estradiol decreased (males)	2 (12.5)	1 (6.7)
Blood testosterone increased (males)	1 (6.3)	1 (6.7)

^a Decreases in estrone and estradiol to below the lower limit of the reference range and increases in testosterone to above the upper limit of the reference range where baseline was within normal limits.

ACTIVATE-T Trial

The adverse reactions reported in the population of patients who were regularly transfused (ACTIVATE-T) were consistent with that seen in ACTIVATE.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on PYRUKYND

Strong CYP3A Inhibitors	
Clinical Impact	<ul style="list-style-type: none">• Co-administration of PYRUKYND with strong CYP3A inhibitors increased mitapivat plasma concentrations [see <i>Clinical Pharmacology (12.3)</i>].• Increased mitapivat plasma concentrations may increase the risks of adverse reactions of PYRUKYND.
Prevention or Management	<ul style="list-style-type: none">• Avoid co-administration of strong CYP3A inhibitors with PYRUKYND [see <i>Dosage and Administration (2.5)</i>].
Moderate CYP3A Inhibitors	
Clinical Impact	<ul style="list-style-type: none">• Co-administration of PYRUKYND with moderate CYP3A inhibitors will increase mitapivat plasma concentrations [see <i>Clinical Pharmacology (12.3)</i>].

Prevention or Management	<ul style="list-style-type: none"> • Monitor Hb and for increased risks of adverse reactions with PYRUKYND. • Do not titrate PYRUKYND beyond 20 mg twice daily [<i>see Dosage and Administration (2.5)</i>].
Strong CYP3A Inducers	
Clinical Impact	<ul style="list-style-type: none"> • Co-administration of PYRUKYND with strong CYP3A inducers decreased mitapivat plasma concentrations [<i>see Clinical Pharmacology (12.3)</i>]. • Decreased mitapivat plasma concentrations will reduce the efficacy of PYRUKYND.
Prevention or Management	<ul style="list-style-type: none"> • Avoid co-administration of strong CYP3A inducers with PYRUKYND [<i>see Dosage and Administration (2.5)</i>].
Moderate CYP3A Inducers	
Clinical Impact	<ul style="list-style-type: none"> • Co-administration of PYRUKYND with moderate CYP3A inducers will decrease mitapivat plasma concentrations [<i>see Clinical Pharmacology (12.3)</i>].
Prevention or Management	<ul style="list-style-type: none"> • Consider alternative therapies that are not moderate CYP3A inducers during treatment with PYRUKYND. If there are no alternative therapies, monitor Hb and titrate beyond 50 mg twice daily, if necessary, but do not exceed a maximum recommended dose of 100 mg twice daily [<i>see Dosage and Administration (2.5)</i>].

7.2 Effect of PYRUKYND on Other Drugs

CYP3A Substrates	
Clinical Impact	<ul style="list-style-type: none"> • PYRUKYND induces CYP3A. Co-administration of PYRUKYND will decrease systemic concentrations of drugs that are sensitive CYP3A substrates, including hormonal contraceptives (e.g., ethinyl estradiol) [<i>see Clinical Pharmacology (12.3)</i>].
Prevention or Management	<ul style="list-style-type: none"> • Monitor patients for loss of therapeutic effect of sensitive CYP3A substrates with narrow therapeutic index when co-administered with PYRUKYND. • Advise patients using hormonal contraceptives to use an alternative non-hormonal contraceptive method or add a barrier method of contraception during treatment with PYRUKYND.

CYP2B6 and CYP2C Substrates	
Clinical Impact	<ul style="list-style-type: none"> • PYRUKYND induces CYP2B6, CYP2C8, CYP2C9, and CYP2C19 enzymes <i>in vitro</i>, and may decrease systemic concentrations of drugs that are sensitive substrates of these enzymes [see <i>Clinical Pharmacology (12.3)</i>].
Prevention or Management	<ul style="list-style-type: none"> • Monitor patients for loss of therapeutic effect of sensitive substrates of these enzymes with narrow therapeutic index when co-administered with PYRUKYND.
UGT1A1 Substrates	
Clinical Impact	<ul style="list-style-type: none"> • PYRUKYND induces UGT1A1 <i>in vitro</i> and may decrease systemic concentrations of drugs that are UGT1A1 substrates [see <i>Clinical Pharmacology (12.3)</i>].
Prevention or Management	<ul style="list-style-type: none"> • Monitor patients for loss of therapeutic effect of UGT1A1 substrates with narrow therapeutic index when co-administered with PYRUKYND.
P-gp Substrates	
Clinical Impact	<ul style="list-style-type: none"> • PYRUKYND inhibits the P-gp transporter <i>in vitro</i> and may increase systemic concentrations of drugs that are P-gp substrates [see <i>Clinical Pharmacology (12.3)</i>].
Prevention or Management	<ul style="list-style-type: none"> • Monitor patients for adverse reactions of P-gp substrates with narrow therapeutic index when co-administered with PYRUKYND.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Available data from clinical trials of PYRUKYND are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes.

In animal reproduction studies, mitapivat orally administered twice daily to pregnant rats and rabbits during organogenesis was not teratogenic at doses up to 13 and 3 times the maximum recommended human dose (MRHD) of 50 mg twice daily, respectively. Mitapivat administered orally to pregnant rats twice daily during organogenesis through lactation did not result in adverse developmental effects at doses up to 13 times the MRHD (*see Data*).

The estimated background risk of major birth defects for the indicated population is unknown. Estimated frequencies for other important background risks in the population are as follows: miscarriage 18%, growth retardation 24%, preterm birth 56%. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Disease-Associated Maternal Risk

Untreated PK deficiency in pregnant women may precipitate acute hemolysis, pre-term labor, miscarriage and severe anemia requiring frequent transfusion. Additionally, preeclampsia and severe hypertension have been reported.

Data

Animal Data

In an embryo-fetal development study in rats, mitapivat was administered at doses of 5, 10, 25, and 100 mg/kg twice daily by oral gavage during the period of organogenesis (gestation days 6 to 17). There was a statistically significant 14% decrease in maternal net body weight gain at the high dose with associated decrease in food consumption. Enlarged or fused placenta and/or a distended amniotic sac, an increase in post-implantation loss (early and late resorptions), a decrease in the mean number of viable fetuses, lower mean fetal weights, and external, visceral, and skeletal malformations were observed at the high dose (100 mg/kg twice daily, 63 times the MRHD, based on area under the plasma drug concentration-time curve [AUC]). No maternal or embryo-fetal toxicity was observed up to 25 mg/kg twice daily (13 times the MRHD, based on AUC).

In an embryo-fetal development study in rabbits, mitapivat was administered at doses of 12.5, 30, and 62.5 mg/kg twice daily by oral gavage during the period of organogenesis (gestation days 7 to 20). Lower fetal weight was observed at 62.5 mg/kg twice daily (3 times MRHD, based on AUC) and correlated with reduced maternal body weight gain. No effects on fetal morphology were observed.

In a pre- and post-natal development study in rats, mitapivat was administered at doses of 5, 10, 25, and 100 mg/kg twice daily by oral gavage during the period of organogenesis and continuing to weaning (gestation day 7 to lactation day 20). Dystocia was observed at ≥ 25 mg/kg twice daily (≥ 13 x MRHD, based on AUC). At 100 mg/kg twice daily (63x MRHD, based on AUC) decreased maternal body weight gain, prolonged parturition, and dystocia occurred and resulted in maternal mortality, complete litter loss, decreased pup viability and decreased pup body weight. No adverse effects on pup growth and development, and reproductive performance were observed up to 50 mg/kg (13 times the MRHD, based on AUC).

8.2 Lactation

Risk Summary

There are no data on the presence of PYRUKYND or its metabolites in human or animal milk, the effects on the breastfed child, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PYRUKYND and any potential adverse effects on the breastfed child from PYRUKYND or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

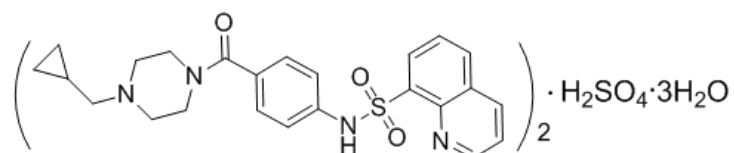
Clinical studies of PYRUKYND did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects.

8.6 Hepatic Impairment

Mitapivat undergoes extensive hepatic metabolism. Moderate and severe hepatic impairment is expected to increase the systemic exposure of mitapivat. Avoid use of PYRUKYND in patients with moderate and severe hepatic impairment [see *Dosage and Administration (2.4) and Clinical Pharmacology (12.3)*].

11 DESCRIPTION

The active ingredient of PYRUKYND is mitapivat, a pyruvate kinase activator, present as mitapivat sulfate. The chemical name of mitapivat sulfate is 8-quinolinesulfonamide, N-[4-[[4-(cyclopropylmethyl)-1-piperazinyl]carbonyl]phenyl]-, sulfate, hydrate (2:1:3). The chemical structure of mitapivat sulfate is:



The molecular formula is $(C_{24}H_{26}N_4SO_3)_2 \cdot H_2SO_4 \cdot 3H_2O$, and the molecular weight is 1053.23 for mitapivat sulfate. Mitapivat sulfate is a white to off-white solid and is slightly soluble in water.

PYRUKYND is available as 5 mg, 20 mg, and 50 mg tablets for oral administration. Each tablet contains 5 mg, 20 mg, or 50 mg mitapivat free base, provided as 5.85 mg, 23.4 mg, or 58.5 mg, respectively, of the sulfate hydrate salt, and the following inactive ingredients: croscarmellose sodium, mannitol, microcrystalline cellulose, and sodium stearyl fumarate. The tablet film coating contains the inactive ingredients FD&C Blue No. 2, hypromellose, lactose monohydrate, titanium dioxide, and triacetin. The tablets are imprinted with black ink containing the inactive ingredients ammonium hydroxide, ferrous ferric oxide, isopropyl alcohol, n-butyl alcohol, propylene glycol, and shellac glaze.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Mitapivat is a pyruvate kinase activator that acts by allosterically binding to the pyruvate kinase tetramer and increasing pyruvate kinase (PK) activity. The red blood cell (RBC) form of pyruvate kinase (PK-R) is mutated in PK deficiency, which leads to reduced adenosine triphosphate (ATP), shortened RBC lifespan, and chronic hemolysis.

12.2 Pharmacodynamics

Mitapivat decreases 2,3 diphosphoglycerate (2,3-DPG) and increases ATP in healthy volunteers.

Cardiac Electrophysiology

At a dose 6 times the maximum recommended dose, mitapivat did not prolong the QT interval to any clinically relevant extent.

12.3 Pharmacokinetics

Mitapivat exposure increased in an approximately dose proportional manner over the clinically relevant dose range of 5 mg to 50 mg twice daily.

The population pharmacokinetic model simulated C_{max} , C_{trough} , AUC_{0-12} and accumulation ratio of mitapivat at recommended dosages are listed in the table below.

Table 5: Steady State Mitapivat Exposure at Recommended Dosages^a

Mitapivat Dosage	C_{max} (ng/mL)	C_{trough} (ng/mL)	AUC_{0-12} (ng*h/mL)	Accumulation Ratio
5 mg twice daily	101.2 (17%)	10.1 (74%)	450.4 (28%)	1.2
20 mg twice daily	389.9 (18%)	32.3 (77%)	1623.8 (28%)	1.1
50 mg twice daily	935.2 (18%)	62.1 (80%)	3591.4 (28%)	1.0

^a Pharmacokinetic parameters are presented as geometric mean (CV%). The simulations were performed until 100 days after first dose. The interval of the last 12 hours was selected for steady state PK parameters calculation. Residual error was not included during simulation.

Absorption

Median t_{max} values at steady state were 0.5 to 1.0 hour post-dose across the dose range of 5 mg to 50 mg twice daily.

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

Effect of Food

Following administration of a single dose of PYRUKYND in healthy subjects, 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) did not change the exposure (AUC_{inf}) of mitapivat, but reduced the rate of mitapivat absorption, with a 42% reduction in C_{max} and a delay in t_{max} of 2.3 hours when compared to dosing under fasted conditions.

Distribution

Mitapivat is highly protein bound (97.7%) in plasma with low RBC distribution (RBC-to-plasma ratio of 0.37). The mean volume of distribution at steady state (V_{ss}) was 42.5 L.

Elimination

The mean effective half-life ($t_{1/2}$) of mitapivat ranged from 3 to 5 hours following multiple dose administrations of 5 mg twice daily to 20 mg twice daily in patients with PK deficiency. 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.

Metabolism

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

Excretion

After a single oral administration of radiolabeled mitapivat to healthy subjects, the total recovery of administered radioactive dose was 89.2%, with 49.6% in the urine (2.6% unchanged) and 39.6% in the feces (<1% unchanged).

Specific Populations

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

Pediatric Population

The pharmacokinetics of mitapivat in children and adolescents (<18 years old) have not been studied.

Hepatic Impairment

Mitapivat undergoes extensive hepatic metabolism. Moderate and severe hepatic impairment is expected to increase the systemic exposure of mitapivat. The pharmacokinetics of mitapivat in patients with hepatic impairment have not been studied.

Renal Impairment

The effects of renal impairment on mitapivat pharmacokinetics were assessed with population pharmacokinetic analyses. Steady state AUC of mitapivat in patients with eGFR 60 to <90 mL/min/1.73 m² was not significantly different compared to patients with eGFR ≥90 mL/min/1.73 m². There are limited data available in patients with eGFR 30 to <60 mL/min/1.73 m² and no data available in patients with eGFR <30 mL/min/1.73 m².

Drug Interaction Studies

Clinical Studies and Model-Based Approaches

Effect of Strong CYP3A Inhibitors on PYRUKYND

Itraconazole (a strong CYP3A inhibitor) increased mitapivat AUC_{inf} and C_{max} by 4.9-fold and 1.7-fold, respectively, following a single PYRUKYND dose of 20 mg. Itraconazole increased mitapivat AUC₀₋₁₂ and C_{max} by 3.6-fold and 2.2-fold, respectively, following PYRUKYND 50 mg twice daily. Ketoconazole (a strong CYP3A inhibitor) increased mitapivat AUC₀₋₁₂ and C_{max} by approximately 3.9-fold and 2.4-fold, respectively, following PYRUKYND doses of 5, 20 or 50 mg twice daily.

Effect of Moderate CYP3A Inhibitors on PYRUKYND

Fluconazole (a moderate CYP3A inhibitor) increased mitapivat AUC₀₋₁₂ and C_{max} by approximately 2.6-fold and 1.6-fold, respectively, following PYRUKYND doses of 5, 20 or 50 mg twice daily.

Effect of Strong CYP3A Inducers on PYRUKYND

Rifampin (a strong CYP3A inducer) decreased mitapivat AUC_{inf} and C_{max} by 91% and 77%, respectively, following a single PYRUKYND dose of 50 mg. Rifampin decreased mitapivat AUC₀₋₁₂ and C_{max} by approximately 95% and 85%, respectively, following PYRUKYND doses of 5, 20 or 50 mg twice daily.

Effect of Moderate CYP3A Inducers on PYRUKYND

Efavirenz (a moderate CYP3A4 inducer) decreased mitapivat AUC₀₋₁₂ and C_{max} by approximately 60% and 30%, respectively, following PYRUKYND doses of 5 or 20 mg twice daily. Efavirenz decreased mitapivat AUC₀₋₁₂ and C_{max} by 55% and 24%, respectively, following PYRUKYND doses of 50 mg twice daily.

Effect of PYRUKYND on CYP3A substrates

Midazolam (a CYP3A substrate) AUC_{inf} and C_{max} decreased by 21% and 19%, respectively, following co-administration of midazolam with PYRUKYND 5 mg twice daily. Midazolam AUC_{inf} and C_{max} decreased by 43% and 39%, respectively, following co-administration with PYRUKYND 20 mg twice daily, and 57% and 52%, respectively, with PYRUKYND 50 mg twice daily.

Effect of PYRUKYND on P-gp Substrates

Co-administration of PYRUKYND with drugs that are substrates of P-gp may result in a clinically relevant increase in plasma concentrations of these substrates.

In vitro Studies

CYP450 and UGT Enzymes

Mitapivat induces CYP2B6, CYP2C8, CYP2C9, CYP2C19, and UGT1A1.

Drug Transporter Systems

Mitapivat is a substrate and an inhibitor of P-gp.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Mitapivat was not carcinogenic in transgenic rasH2 mice up to the highest doses tested at 500 mg/kg/day in males and at 250 mg/kg/day in females when given orally for 26 weeks.

Mitapivat was not carcinogenic in rats when given orally up to 300 mg/kg/day in males and 200 mg/kg/day in females, at systemic exposures 47 times and > 100 times the MRHD, respectively, based on AUC.

Mutagenesis

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 or in an *in vivo* rat bone marrow micronucleus assay.

Fertility

In a fertility and early embryonic development study, oral administration of mitapivat twice daily in male rats prior to and during mating at doses up to 300 mg/kg/day, which represents 45 times the MRHD of 50 mg twice daily, based on AUC, did not result in adverse effects on fertility or reproductive function. In female rats, twice daily oral administration of mitapivat prior to mating and continuing through organogenesis, at doses up to 200 mg/kg/day, which represents 48 times the MRHD of 50 mg twice daily, based on AUC, did not result in adverse effects on fertility or reproductive function.

14 CLINICAL STUDIES

Patients with PK Deficiency

Patients Not Regularly Transfused

The efficacy of PYRUKYND was evaluated in ACTIVATE, a multinational, randomized, double-blind, placebo-controlled clinical study (NCT03548220) of 80 adults 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 variant alleles in the pyruvate kinase liver and red blood cell (PKLR) gene, of which at least 1 was a missense variant, and Hb less than or equal to 10 g/dL. Patients who were homozygous for the c.1436G>A (p.R479H) variant or had 2 non-missense variants (without the presence of another missense variant) 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 dose-ranging study. Randomization was stratified by average screening Hb (<8.5 vs ≥ 8.5 g/dL) and PKLR gene variant category (missense/missense vs. missense/non-missense).

Among the 80 patients with PK deficiency, 40 patients were randomized to PYRUKYND. Following a period of dose titration up to 50 mg twice daily, patients continued a fixed dose of PYRUKYND for 12 weeks. Eighty-eight percent of patients were maintained on 50 mg twice daily.

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 and <28 weeks. Among the 80 randomized patients, the median age was 33 years (range 18 to 78) and 40% were male; race was reported in 88% of patients: 75% were White, 10% Asian, 1.3% Native Hawaiian/Other Pacific Islander and 1.3% were other races. The median baseline hemoglobin was 8.5 g/dL (range: 6.4 to 10.2 g/dL). There were 55 patients (69%) with the missense/missense PKLR gene variant category, and 25 patients (31%) with the missense/non-missense PKLR gene variant category. There were 58 patients (73%) who had a history of splenectomy. Complications and comorbidities associated with PK deficiency included iron overload with a median baseline ferritin of 479 ng/mL (range: 21 to 5890 ng/mL), chelation therapy use in the year before the first dose of study treatment in 15 patients (19%), decreased bone mineral density in 64 patients (80%) who had a baseline femoral neck T-score or lumbar spine T-score <-1.0 , and history of cholecystectomy in 58 patients (73%).

Efficacy was based upon Hb response, defined as a ≥ 1.5 g/dL increase in Hb from baseline sustained at 2 or more scheduled assessments (Weeks 16, 20, and 24) during the fixed dose period without transfusions. The efficacy results, including changes in markers of hemolysis are shown in Table 6.

Table 6: Efficacy Results in Patients with PK Deficiency Who Were Not Regularly Transfused (ACTIVATE)

Endpoint	PYRUKYND N=40	Placebo N=40	Difference^{1, 2} p-value
Hb Response, n (%)	16 (40%)	0	39 (24, 55) <0.0001
Hemoglobin (g/dL) Baseline Mean (SD) LS Mean Change (95% CI)	8.6 (1.0) 1.7 (1.3, 2.1)	8.5 (0.8) -0.1 (-0.6, 0.3)	1.8 (1.2, 2.4) <0.0001
Indirect bilirubin (mg/dL) Baseline Mean (SD) LS Mean Change (95% CI)	4.8 (3.6) -1.2 (-1.7, -0.7)	5.2 (3.6) 0.3 (-0.2, 0.8)	-1.5 (-2.2, -0.9) <0.0001
Reticulocyte (fraction of 1) Baseline Mean (SD) LS Mean Change (95% CI)	0.37 (0.24) -0.10 (-0.13, -0.07)	0.40 (0.22) 0 (-0.02, 0.03)	-0.10 (-0.14, -0.06) <0.0001
LDH (U/L) Baseline Mean (SD) LS Mean Change (95% CI)	348 (276) -92 (-124, -60)	260 (140) -21 (-53, 11)	-71 (-116, -26) 0.003
Haptoglobin (mg/dL) Baseline Mean (SD) LS Mean Change (95% CI)	8.2 (10.7) 16.9 (8.8, 25.1)	8.3 (13.8) 1.2 (-7.0, 9.4)	15.8 (4.3, 27.3) 0.008

CI: confidence interval, Hb: hemoglobin, LDH: lactate dehydrogenase, LS Mean Change: least square mean change from baseline, SD: standard deviation

¹ All results are statistically significant.

² For Hb response, the difference is adjusted for randomization stratification factors, which included average screening Hb (<8.5, ≥8.5 g/dL) and PKLR gene variant category (missense/missense, missense/non-missense). The two-sided p-value is based on the Mantel-Haenszel stratum weighted method adjusting for the randomization stratification factors.

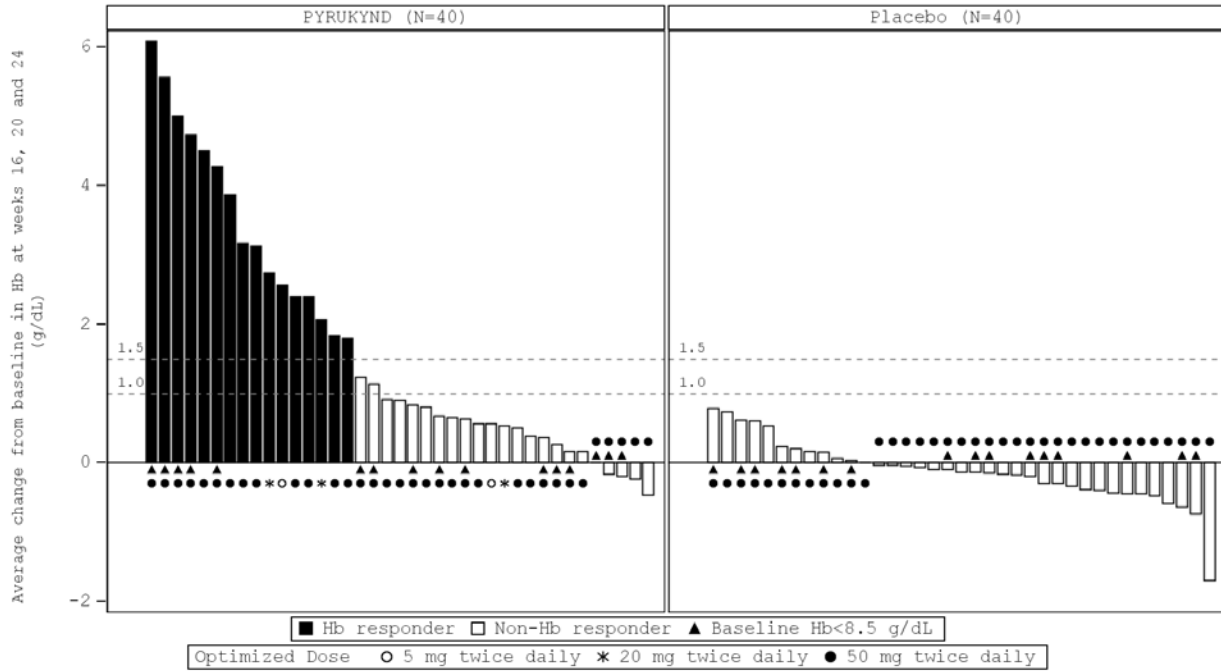
For the endpoints of average change from baseline at Weeks 16, 20, and 24 for hemoglobin, indirect bilirubin, reticulocytes, LDH, and haptoglobin, the two-sided p-value is based on the mixed-effect model repeat measurement (MMRM) method, which included change from baseline as the dependent variable, baseline as a covariate, and treatment arm, visit, treatment-by-visit interaction, and the randomization stratification factors as fixed factors and subject as the random effect. All scheduled visits were included in the model.

In ACTIVATE, the LS Mean change from baseline with PYRUKYND compared to placebo was -0.4 (standard error [SE] 0.1) for jaundice (scale: 0-4), -1.1 (SE 0.4) for tiredness (scale: 0-10),

and -0.3 (SE 0.3) for shortness of breath (scale: 0-10), assessed with the daily Pyruvate Kinase Deficiency Diary (PKDD) where lower scores represent less sign/symptom severity.

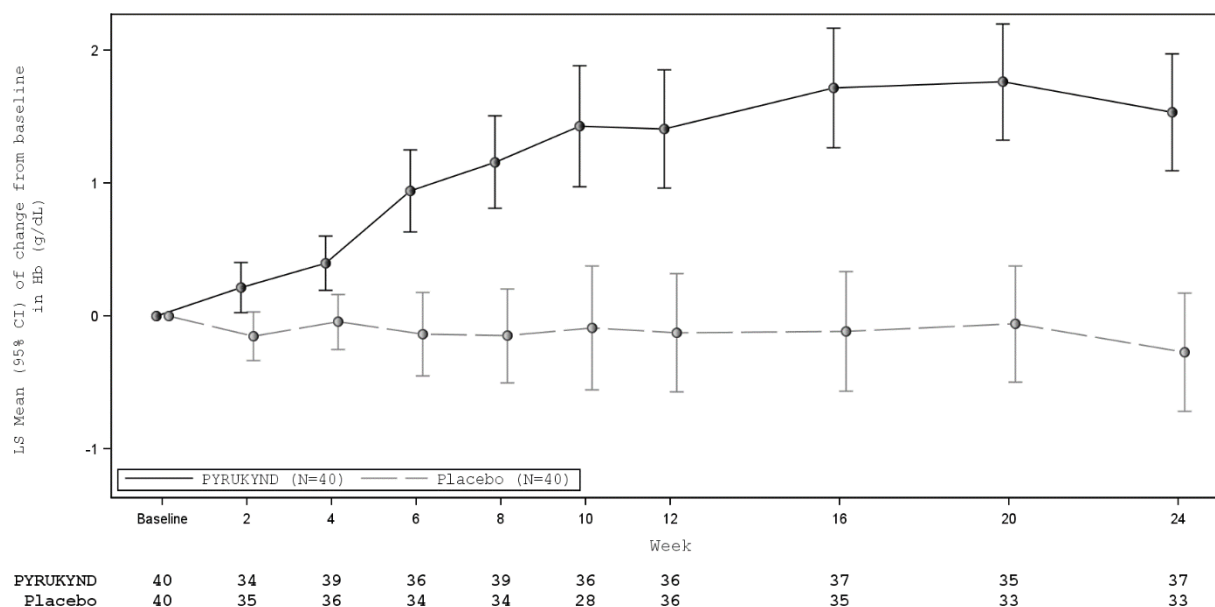
In ACTIVATE, the majority of PYRUKYND-treated patients experienced an increase in Hb, while the majority of patients in the placebo arm experienced a decrease in Hb as measured by average change from baseline at weeks 16, 20, and 24 (Figure 1).

Figure 1: Average Change at Weeks 16, 20, and 24 from Baseline in Hemoglobin (Hb) by Patient - All Randomized Patients (ACTIVATE)^a



^aApproximately 99% of all randomized patients completed 24 weeks of treatment.

Figure 2: LS Mean Change from Baseline in Hemoglobin Over Time - All Randomized Patients (ACTIVATE)



CI: confidence interval, Hb: hemoglobin, LS: least square

Fifteen of the 16 patients with a 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 ≥ 1.5 g/dL 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, 18.4+).

Patients Who Were Regularly Transfused

The efficacy of PYRUKYND in patients with PK deficiency who were regularly transfused was evaluated in ACTIVATE-T, a multinational single-arm clinical trial (NCT03559699) of 27 adults with PK deficiency who had a minimum of 6 transfusion episodes in the 52-week period prior to informed consent. Patients were included if they had documented presence of at least 2 variant alleles in the PKLR gene, of which at least 1 was a missense variant. Patients who were homozygous for the c.1436G>A (p.R479H) variant or had 2 non-missense variants (without the presence of another missense variant) in the PKLR gene were excluded. Following a period of dose titration up to 50 mg twice daily, patients continued on a fixed dose of PYRUKYND for 24 weeks.

The median duration of treatment with PYRUKYND was 40.3 weeks (range 16.3 to 46.3 weeks). Overall, 20 (74%) patients were exposed to PYRUKYND for >40 weeks and <47 weeks. The median age was 36 years (range 18 to 68) and 26% were male; race was reported in 85% of patients: 74% were White and 11% Asian. The median baseline hemoglobin was 9.1 g/dL (range: 7.4 to 10.9 g/dL). Patients had a median of 9 transfusion episodes (range: 6 to 17 episodes) in the 52 weeks before the first dose of study treatment and a median of 7 red blood cell units transfused (range: 3 to 20 units) standardized to 24 weeks. There were 20 patients (74%) with the missense/missense PKLR gene variant category, and 7 patients (26%) with the missense/non-missense PKLR gene variant category. There were 21 patients (78%) who had a

history of splenectomy. Patients had evidence of complications and comorbidities associated with PK deficiency including iron overload (median baseline ferritin was 1324 ug/L; range: 163 to 5357 ng/mL), chelation therapy use in the year before the first dose of study treatment in 24 patients (89%), decreased bone mineral density in 20 patients (74%) who had a baseline femoral neck T-score or lumbar spine T-score <-1.0, and history of cholecystectomy in 23 patients (85%).

Efficacy was based on transfusion reduction response and was defined as $\geq 33\%$ reduction in the number of red blood cell (RBC) units transfused during the fixed dose period compared with the patient's historical transfusion burden.

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)

Endpoints	PYRUKYND N=27
Patients with Transfusion Reduction Response	
n (%)	9 (33)
95% CI	(17, 54)
Patients who were Transfusion Free	
n (%)	6 (22)
95% CI	(9, 42)

CI: confidence interval, RBC: red blood cell
CI is based on Clopper-Pearson method.

All 6 (22%) patients 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 months (range: 11.5+, 21.8+).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

<u>PYRUKYND 28-Day Packs</u>			
Tablet Strength	Description	Imprint	NDC
5 mg	Round, blue, film-coated tablets	"M5" printed on one side	71334-205-05
20 mg	Round, blue, film-coated tablets	"M20" printed on one side	71334-210-20
50 mg	Oblong, blue, film-coated tablets	"M50" printed on one side	71334-215-50

<u>PYRUKYND Taper Packs</u>				
Tablet strength(s)	Blister Wallet Configuration	Tablet Description	Imprint	NDC
5 mg	<ul style="list-style-type: none"> 5 mg blister wallet containing 7 tablets 	round, blue, film-coated tablets	"M5" printed on one side	71334-220-11
20 mg and 5 mg	<ul style="list-style-type: none"> 20 mg blister wallet containing 7 tablets 5 mg blister wallet containing 7 tablets 	round, blue, film-coated tablets round, blue, film-coated tablets	"M20" printed on one side "M5" printed on one side	71334-225-12
50 mg and 20 mg	<ul style="list-style-type: none"> 50 mg blister wallet containing 7 tablets 20 mg blister wallet containing 7 tablets 	oblong, blue, film-coated tablets round, blue, film-coated tablets	"M50" printed on one side "M20" printed on one side	71334-230-13

Storage

Store at 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (59°F and 86°F) [see *USP Controlled Room Temperature*]. Store the blister wallets in the original carton until use.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Acute Hemolysis with Abrupt Treatment Interruption

Inform patients of the risk of developing acute hemolysis and subsequent anemia following abrupt interruption or discontinuation of PYRUKYND. Inform patients to follow their healthcare provider's instructions for discontinuing PYRUKYND. Upon discontinuing PYRUKYND, tell patients to immediately report any symptoms suggestive of acute hemolysis including jaundice, scleral icterus, dark urine, dizziness, confusion, fatigue, or shortness of breath to their healthcare provider for further evaluation [see *Warnings and Precautions (5.1)*].

Drug Interactions

Advise patients to inform their healthcare providers of all concomitant medications, including over-the-counter medications, vitamins, and herbal products [see *Drug Interactions (7)*].

Dosing and Storage Instructions

- Instruct patients to swallow the tablets whole with or without food and not to split, crush, chew, or dissolve the tablets.

- Advise patients if a dose of PYRUKYND is missed by 4 hours or less, to take the scheduled dose as soon as possible. If a dose of PYRUKYND is missed by more than 4 hours, advise the patient to not take a replacement dose and wait until the next scheduled dose.

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Manufactured for and Distributed by:

Agios Pharmaceuticals, Inc.
Cambridge, MA 02139

AG-PI-001

PATIENT INFORMATION
PYRUKYND (pye roo' kind)
(mitapivat)
tablets, for oral use

What is PYRUKYND?

PYRUKYND is a prescription medicine used to treat low red blood cell counts caused by the early breakdown of red blood cells (hemolytic anemia) in adults with pyruvate kinase deficiency (PK Deficiency).

It is not known if PYRUKYND is safe and effective in children.

Before taking PYRUKYND, tell your healthcare provider about all your medical conditions, including if you:

- have liver problems.
- are pregnant or plan to become pregnant. It is not known if PYRUKYND will harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think that you are pregnant during treatment with PYRUKYND.
- are breastfeeding or plan to breastfeed. It is not known if PYRUKYND passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with PYRUKYND.

Tell your healthcare provider about all the medicines that you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

PYRUKYND and certain other medicines may affect each other causing side effects. PYRUKYND may affect the way other medicines work, and other medicines may affect how PYRUKYND works.

Know the medicines you take. Keep a list of them to show your healthcare provider or pharmacist when you get a new medicine.

How should I take PYRUKYND?

- Take PYRUKYND exactly as your healthcare provider tells you to take it.
- Take PYRUKYND with or without food.
- Swallow PYRUKYND tablets whole. Do not split, chew, crush, or dissolve the tablets.
- Do not change your dose or stop taking PYRUKYND without talking to your healthcare provider. Your healthcare provider will give you instructions for stopping PYRUKYND. See **“What are the possible side effects of PYRUKYND?”**
- If you miss a dose of PYRUKYND by 4 hours or less, take your dose as soon as possible. If more than 4 hours have passed since your regularly scheduled dose, wait for the next dose. Return to your normal schedule at the next dose.

What are the possible side effects of PYRUKYND?

PYRUKYND may cause serious side effects, including:

- **Rapid breakdown of red blood cells (acute hemolysis)** has happened after suddenly interrupting or stopping treatment with PYRUKYND. **You should not suddenly stop taking PYRUKYND.** If you have to stop your treatment with PYRUKYND, your healthcare provider should monitor you closely. Tell your healthcare provider right away if you develop any signs or symptoms of breakdown of red blood cells including:
 - yellowing of the skin or the whites of your eyes (jaundice)
 - dark colored urine
 - dizziness
 - confusion
 - feeling tired
 - shortness of breath

The most common side effects of PYRUKYND include:

- decrease in reproductive hormone (estrone) in men
- decrease in reproductive hormone (estradiol) in men
- increased salt from uric acid (urate) blood test
- joint pain (arthralgia)

- back pain

These are not all of the possible side effects of PYRUKYND.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store PYRUKYND?

- Store PYRUKYND at room temperature between 68°F to 77°F (20°C to 25°C).
- Store the blister wallets in the original carton until use.

Keep PYRUKYND and all medicines out of the reach of children.

General information about the safe and effective use of PYRUKYND.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use PYRUKYND for a condition for which it was not prescribed. Do not give PYRUKYND to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about PYRUKYND that is written for healthcare professionals.

What are the ingredients in PYRUKYND?

Active ingredient: mitapivat

Inactive ingredients: croscarmellose sodium, mannitol, microcrystalline cellulose, and sodium stearyl fumarate.

The tablet film coating contains: FD&C Blue No. 2, hypromellose, lactose monohydrate, titanium dioxide, and triacetin.

The tablets printed with black ink contains: ammonium hydroxide, ferrousferic oxide, isopropyl alcohol, n-butyl alcohol, propylene glycol, and shellac glaze.

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Agios Pharmaceuticals, Inc.
Cambridge, MA 02139

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For more information, visit www.pyrukynd.com or call 1-833-228-8474.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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