COVERAGE AUTHORIZATION GUIDE

KUVAN® (sapropterin dihydrochloride) Tablets or Powder for Oral Solution

INDICATION

KUVAN® (sapropterin dihydrochloride) Tablets for Oral Use and Powder for Oral Solution are indicated to reduce blood phenylalanine (Phe) levels in adult and pediatric patients one month of age or older with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin-(BH4-) responsive Phenylketonuria (PKU). KUVAN is to be used in conjunction with a Phe-restricted diet.

KUVAN®
(sapropterin dihydrochloride)
Tablets or Powder for Oral Solution

Please see Important Safety Information throughout and full Prescribing Information.

BIOMARIN®

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TABLE OF CONTENTS

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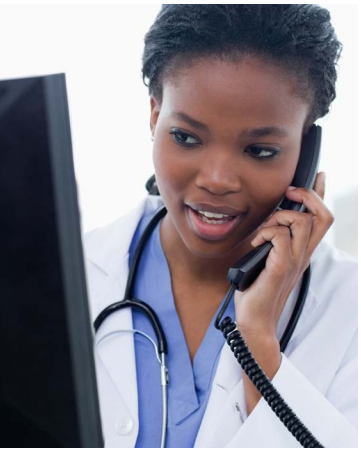
INTRODUCTION AND DISCLAIMER

BioMarin, the manufacturer of branded KUVAN® (sapropterin dihydrochloride) Tablets or Powder for Oral Solution, would like to help every individual for whom the product is medically appropriate to have access to it. We can provide assistance with managing the process of getting patients on KUVAN and work directly with patients to help educate them on the safe and appropriate use of BioMarin products.

We offer comprehensive product education and product access support to patients taking branded KUVAN, their caregivers, and healthcare providers through our services hub, BioMarin RareConnections™. In addition, BioMarin's support services include the KUVAN free 30-day response trial program, Clinical Coordinator product education and support, co-pay financial assistance for eligible, commercially insured patients, bridge and patient assistance programs for eligible patients, and ongoing logistics management to help patients obtain and remain compliant with their prescribed therapy.



If you decide that branded KUVAN is the right therapy option for your patients, make sure to sign the KUVAN Patient Enrollment Form (PEF) in the "dispense-as-written" box, and include any specific language as required by your state pharmacy laws.

If you are e-prescribing, help ensure that automatic substitution does not occur: select KUVAN from the medications list and indicate "dispense as written," or your state's required language, in your Electronic Health Records (EHR) platform.

Every patient's insurance plan and health benefits are different, so it is very important to contact each patient's plan for assistance when interpreting drug policies, billing and coding, and payment. These items vary greatly among insurance plans and are subject to change without notice because of frequently changing guidelines, laws, rules, and regulations. Some patients may change insurance plans during the year, so verify current insurance information at each patient visit. If your patient receives a denial, consult the insurance plan to help interpret the denial language, and provide the necessary information and documentation requested by the plan in a timely manner.

Some patients may change insurance plans during the year, so verify current insurance information at each patient visit.

Disclaimer

BioMarin has compiled this guide with information gathered from third-party sources and experienced insurance reimbursement experts to serve as a source of information to assist your practice in obtaining approval and ongoing authorization for branded KUVAN. While we have included some best practices for working with BioMarin RareConnections, insurance companies, and specialty pharmacies in this guide, BioMarin makes no guarantee that the use of this information will prevent denials, delays, or differences of opinion with insurance plans as to the correct information to submit for KUVAN authorization, or forms of billing that will expedite payment to providers of service. BioMarin provides this information as a convenience; it does not constitute legal advice or a recommendation regarding medical practice.

This guide covers only those Food and Drug Administration (FDA)-approved indications that are documented in the KUVAN Prescribing Information (see link below). Where reimbursement is sought for prescribed use and/or administration of this product that may be inconsistent with, or not expressly specified in, the FDA-cleared or FDA-approved labeling outlined in the KUVAN Prescribing Information, consult with your billing advisers or the patient's insurance plan on handling such issues.

Please see Important Safety Information throughout and full Prescribing Information.

COORDINATING WITH BIOMARIN RARECONNECTIONS™

BioMarin RareConnections is a resource for patients prescribed branded KUVAN® (sapropterin dihydrochloride) Tablets or Powder for Oral Solution.

BioMarin RareConnections™ helps patients and healthcare providers navigate the difficulties of managing serious and rare genetic diseases through a wide array of product support services throughout the treatment journey. Our dedicated and experienced Case Managers will provide guidance on how to gain access to branded KUVAN, including:

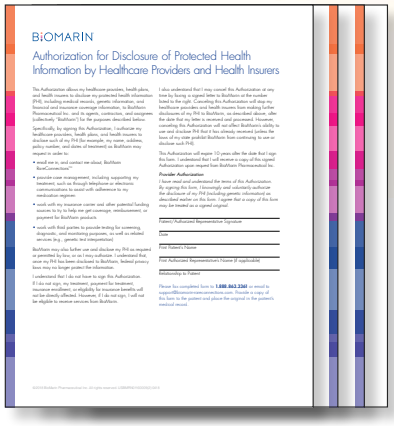
When you are ready to start a patient on KUVAN, contact BioMarin RareConnections at 1-866-906-6100 or email at support@biomarin-rareconnections.com

- Helping patients understand their insurance coverage and financial assistance options, including the KUVAN Co-Pay Assistance Program for commercially insured, eligible patients
- Providing ongoing product education and support for branded KUVAN
- Coordinating with a specialty pharmacy (SP) to deliver the patient's medication
- Assisting eligible* patients with a free 30-day trial of branded KUVAN to determine response

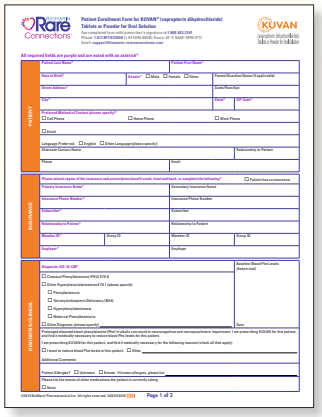
In order to access BioMarin RareConnections product support services, submit both the BioMarin RareConnections Patient Enrollment Form (PEF) and the Patient Authorization Form (PAF) and copies of the insurance cards (front and back).

With the KUVAN Co-Pay Assistance Program, 99% of participating patients in 2020 and 2021 paid $0 out of pocket for their prescription†

- **PAF:** The Patient Authorization Form provides authorization from the patient for the provider/clinic to provide patient-level information to BioMarin and for BioMarin RareConnections to use this patient-level information to communicate with payers and SPs to secure access to the prescribed product
- **PEF:** The Patient Enrollment Form serves as the prescription and provider authorization for BioMarin RareConnections to work on a patient's case


BIOMARIN

Authorization for Disclosure of Protected Health Information by Healthcare Providers and Health Insurers


Patient Enrollment Form for KUVAN® (sapropterin dihydrochloride) Tablets or Powder for Oral Solution

If you decide that branded KUVAN is the right therapy option for your patients, make sure to sign the KUVAN PEF in the "dispense-as-written" box and include any specific language as required by your state pharmacy laws.

If you are e-prescribing, help ensure that automatic substitution does not occur: select KUVAN from the medications list and indicate "dispense as written," or your state's required language, in your Electronic Health Records (EHR) platform.

*The free trial of KUVAN for up to 30 days is available only to individuals in the United States who are diagnosed with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin (BH4)-responsive PKU and have never used KUVAN previously.

†Based on 2020 and 2021 co-pay program data. The KUVAN Co-Pay Assistance Program can cover up to $15,750 in assistance per calendar year for eligible patients. Some restrictions apply.

BioMarin Rare Connections™

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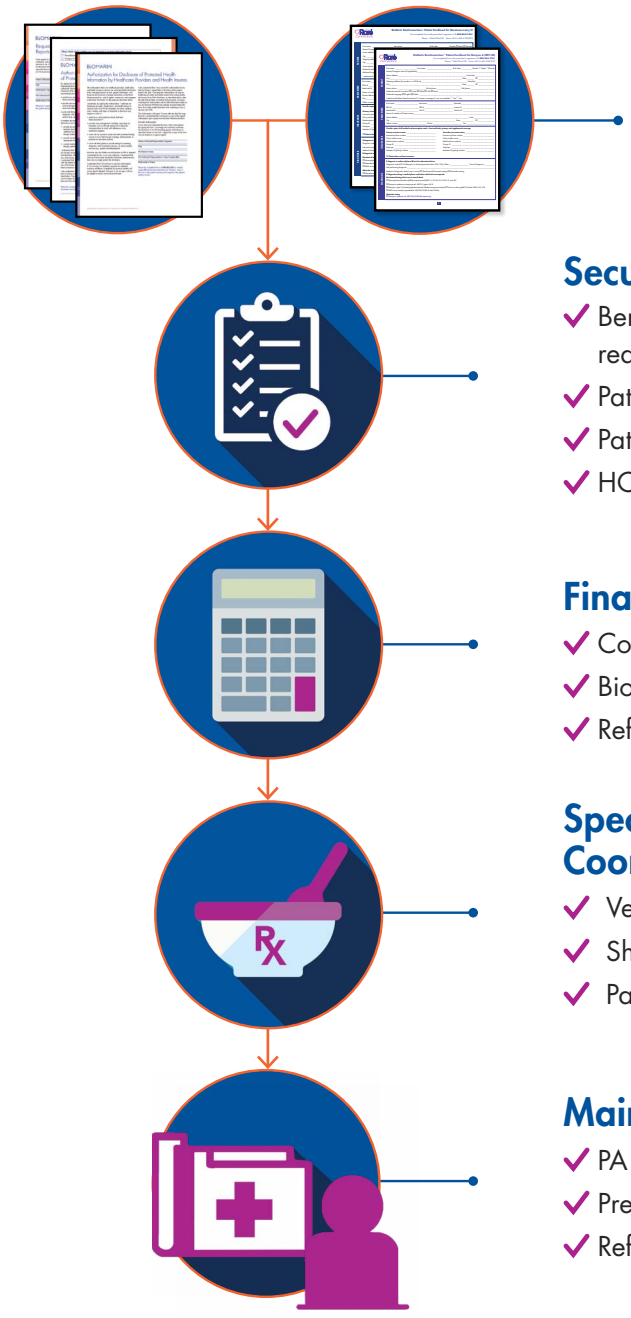
BIOMARIN RARECONNECTIONS™ AND SPECIALTY PHARMACY ROADMAP

FOR BRANDED KUVAN® (sapropterin dihydrochloride) Tablets or Powder for Oral Solution



Patient Enrollment: PAF + PEF

- ✓ HCP notification of PEF receipt
- ✓ Follow-up with HCP on missing information
- ✓ Patient notification of PAF received

Securing Coverage

- ✓ Benefits investigation (BI) and prior authorization (PA) requirements assessed
- ✓ Patient welcome call
- ✓ Patient notification of BI results
- ✓ HCP notification of BI results & PA requirements

Financial Assistance Support*

- ✓ Co-Pay program eligibility screening
- ✓ BioMarin patient assistance program eligibility screening
- ✓ Referrals to additional support options, if needed

Specialty Pharmacy Triage & Shipment Coordination

- ✓ Verification of prescription
- ✓ Shipment coordination with patients
- ✓ Packaging and delivery logistics

Maintaining Therapy†

- ✓ PA reauthorization
- ✓ Prescription expiration follow-up
- ✓ Refill reminders

*As appropriate for eligible patients.
†Specialty pharmacy–dependent processes.
HCP, healthcare provider; PAF, BioMarin RareConnections™ Patient Authorization Form; PEF, BioMarin RareConnections™ Patient Enrollment Form.

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INSURANCE VERIFICATION AND WORKING WITH BIOMARIN RARECONNECTIONS™

Does your patient have insurance coverage for branded KUVAN® (sapropterin dihydrochloride) Tablets or Powder for Oral Solution treatment?

Now that you and your patient have decided to use KUVAN to manage your patient's Phenylketonuria (PKU), it is important to understand how to gain coverage for the treatment. KUVAN tablets for oral use and powder for oral solution are indicated to reduce blood Phe levels in adult and pediatric patients one month of age or older with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin-(BH4-) responsive Phenylketonuria (PKU). KUVAN is a specialty medication to be used in conjunction with a Phe-restricted diet. Managing and accessing a specialty drug is quite different from a typical prescription filled at a local retail pharmacy. Additional steps and time are needed for a patient's insurance plan to authorize treatment with KUVAN. Understanding if and how your patient's insurance covers KUVAN is the first step, and BioMarin has included some suggestions below to help you.

Completing the prior authorization requirements

1 

Before a patient can be treated with KUVAN, the patient's insurance benefits should be verified

Verify the patient's insurance benefits

2 

Make copies of the medical and pharmacy benefit insurance cards, and upload the insurance information to your patient's medical record

3 

Always ask at each office visit if there have been changes to the patient's insurance

BioMarin RareConnections PKU Field Reimbursement Managers (FRMs) can work directly with you to share best practices for managing the KUVAN prescription fulfillment process. They can also provide insight on the patient's insurance plan, education on the access and reimbursement process, a checklist for prior authorization requirements provided by the plan, and support with the appeals process. The PKU FRM works in coordination with the patient's BioMarin RareConnections Case Manager and is your 1:1 in-person informational resource for clinics to educate on:

- Individualized reimbursement support for patients, including coordinated communication with BioMarin RareConnections Case Managers and facilitation of cases/situations as needed
- BioMarin RareConnections overview (program services and tools, including the ePAF, HCP portal, co-pay program, website)
- General reimbursement education (PA/appeal support, regional payer insights/trends, formulary changes)
- Specialty pharmacy education and support

HCP, healthcare provider; PAF, BioMarin RareConnections Patient Authorization Form

Please see Important Safety Information throughout and full Prescribing Information.

TREATMENT AUTHORIZATION AND REAUTHORIZATION

Prescribing branded KUVAN® (sapropterin dihydrochloride) Tablets or Powder for Oral Solution

KUVAN is a specialty drug, and specialty drugs often require additional verification steps from the patient's insurance plan. The insurance plan manages access to specialty drugs because they want to ensure these drugs are used in the appropriate patient population.

A prior authorization (PA) is a request for authorization of branded KUVAN by the insurance plan. It is usually a 1- to 2-page form that asks questions to confirm diagnosis, request medical documentation, and confirm treatment history. It is a written statement from the healthcare provider stating why branded KUVAN is the proper course of treatment for the patient.

After BioMarin RareConnections™ verifies the patient's insurance benefits, your office may be required to complete a PA request from the insurance plan. The insurance plan will review the completed PA and supporting medical documentation, and then provide a determination. A determination is either an approval or denial for the specialty drug, usually obtained within 24–72 hours.

KUVAN is dosed based on calculating the patient's body weight and the amount of drug needed. The powder or tablets are administered orally, once daily, with a meal to increase absorption, preferably at the same time each day. KUVAN is available in three dosing forms:

- 100 mg tablets
- 100 mg powder packets
- 500 mg powder packets

KUVAN is supplied in 100 mg tablets, 100 mg powder, or 500 mg powder.

The prescription and PA are typically written for one form of KUVAN, either tablets or powder. If both forms are prescribed for the patient, it may require additional insurance authorization and two total co-payments by the patient, depending on the patient's insurance plan. After the PA has been sent to the patient's insurance plan, it will be very important to monitor your phone, fax, email, and/or mail for any communication from the insurance plan or specialty pharmacy for every patient prescribed branded KUVAN. Insurance plans expect a high level of monitoring and oversight of these patients by their healthcare providers.

Requesting prior authorization for branded KUVAN

- Indicate on the KUVAN Patient Enrollment Form (PEF) if you plan to prescribe branded KUVAN tablets, powder, or both for your patient, and sign in the "dispense-as-written" box, including any specific language as required by your state pharmacy laws
- If you are e-prescribing and want to choose branded KUVAN for your patient: select KUVAN from the medications list and indicate "dispense as written," or your state's required language, in your Electronic Health Records (EHR) platform
- BioMarin RareConnections can provide the appropriate PA form and list of PA requirements to your office when available, based on its investigation of the patient insurance benefits

Please see Important Safety Information throughout and full Prescribing Information.

- The healthcare provider/clinic must complete the PA paperwork and gather the supporting medical documentation
  - Write a letter of medical necessity to the insurance plan's contact information listed on the PA; be sure to identify which dosage form(s) you are prescribing for the patient
  - Provide all baseline data requested by the patient's insurance plan
  - If you want BioMarin to send the PA package into the insurance plan, submit the complete PA package (e.g., PA and supporting documents) to BioMarin RareConnections™
- If the insurance plan requests additional documentation, it is important to provide it in a timely manner
- Monitor for any communication from the patient's insurance plan
- BioMarin RareConnections can help monitor approvals and denials. Denials may also be communicated by a letter mailed to the patient and the physician's office
- BioMarin RareConnections is available to assist with PA denials and appeals, if applicable

Examples of supporting medical documentation

- For initiation of treatment
  - ICD-10-CM codes pertinent to your patient's diagnosis
  - Patient's medical history or consultation report(s) discussing the patient's diagnosis and medical necessity for KUVAN treatment
  - Testing and laboratory results as required by the insurance plan
  - Treatment history
  - Diet records or notes by a dietitian
  - Baseline data for clinical assessments (e.g., blood phenylalanine levels prior to treatment)
  - Healthcare provider chart notes
- Other examples of supporting documentation
  - Any shared decision-making notes from multidisciplinary discussions or case conferences, which may include specific reasons for prescribing branded KUVAN

Reauthorization

Insurance plans typically authorize treatment for 1 year, so each year they may require the prescriber to issue a new prescription and reauthorize treatment with branded KUVAN. The patient's insurance plan may request data to demonstrate any changes in Phe levels from baseline, when being treated with KUVAN. BioMarin encourages providers to conduct ongoing assessments of their patients using the same instruments with which they gathered baseline measurements.

BioMarin RareConnections and specialty pharmacies also provide the following services for patients who are receiving their drug through the specialty pharmacy channel:

- Informing the patient and the prescriber if treatment reauthorization is required by the patient's health insurance
- Requesting prescribers to submit an updated prescription with any additional information to include in the reauthorization
- Informing the patient and the prescriber if treatment is reauthorized for another year, or if the insurance plan requires additional information

PRIOR AUTHORIZATION/ REAUTHORIZATION CHECKLIST

Checklist for branded KUVAN® (sapropterin dihydrochloride) Tablets or Powder for Oral Solution treatment

Utilize the following checklist to ensure that all relevant information is obtained before submitting the prior authorization (PA) package for KUVAN. All services requested from the patient's insurance benefits must be medically appropriate and properly supported by the patient's medical record, and most importantly, based on the medical diagnosis determined by the prescriber. Checklist does not constitute medical advice or guarantee coverage.

The following items may be requested by the patient's insurance plan to include in the PA/medical necessity request:

Key PA criteria
(information usually requested by insurance plans)

- ☐ ICD-10-CM diagnosis and description
- ☐ Genetic testing, if available
- ☐ Patient weight
- ☐ Patient height
- ☐ Blood phenylalanine (Phe) levels: baseline and current Phe levels with dates measured
- ☐ Clinical notes: medical and treatment history
- ☐ Response to prior treatment: documentation of therapeutic failure or intolerance
- ☐ Dietary records
- ☐ Specific reasons, if any, to continue to receive branded KUVAN vs generic per physician discretion

Disclaimer

BioMarin provides this information as a convenience; it does not constitute legal advice or a recommendation regarding medical practice.

SAMPLE LETTER OF MEDICAL NECESSITY FOR BRANDED KUVAN® (sapropterin dihydrochloride) Tablets or Powder for Oral Solution TREATMENT

- ✔ Date
- ✔ Patient Name
- ✔ Patient Mailing Address
- ✔ Patient Contact Phone Number
- ✔ Insurance Plan Name
- ✔ Insurance Plan Mailing Address
- ✔ Insurance Subscriber Name
- ✔ Insurance Subscriber ID Number
- ✔ Effective Date of Coverage

RE: Authorization of KUVAN® (sapropterin dihydrochloride) Tablets or Powder for Oral Solution Treatment

Dear Sir or Madam:

I am writing on behalf of my patient, [insert patient name], to request approved authorization and coverage from [insert insurance plan name] for branded KUVAN® (sapropterin dihydrochloride) Tablets or Powder for Oral Solution [insert tablets or powder]. My patient has been diagnosed with [insert diagnosis]. Individuals born with Phenylketonuria (PKU) have a defect in an enzyme called phenylalanine hydroxylase (PAH). The PAH enzyme uses tetrahydrobiopterin (BH4), a naturally occurring cofactor (or helper) in the body, to break down phenylalanine (Phe) into tyrosine. Tyrosine is a building block for many proteins and an important neurotransmitter that helps the brain function. In PKU, the PAH enzyme is not working properly and is unable to break down Phe in the body. When tyrosine is not produced and Phe builds up in the blood, it can cause a variety of signs and symptoms, including mental, behavioral, neurological, and physical problems.

KUVAN is a phenylalanine hydroxylase activator indicated to reduce blood Phe levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-) responsive PKU. KUVAN is used in conjunction with a Phe-restricted diet. Treatment with BH4 can activate residual PAH enzyme to improve metabolism of Phe and decrease blood Phe levels in patients who respond. This letter provides information about my patient's medical and treatment history, diagnosis, and details regarding the medical necessity for treatment with KUVAN.

Patient's medical history

My patient's current disease state, prior treatment, and response to those treatments, as well as other issues that impact my treatment decision are:

- ✔ *Insert brief description of patient: age, height, weight, functional and neurological status, PKU history, and prior treatment history*
- ✔ *Include essential labs and genetic history that verify diagnosis*
- ✔ *Include other factors that impact the treatment decision (e.g., comorbidities, work status, etc.)*
- ✔ *Include supporting medical documentation (e.g., patient's medical record, clinical notes, medication records, relevant lab results [e.g., blood Phe levels])*
- ✔ *Include specific reasons, if any, for patient to receive branded KUVAN vs a generic per physician discretion*

Disease and treatment information

I have attached the prescribing information for branded KUVAN, which was approved by the U.S. Food and Drug Administration (FDA) on December 13, 2007.

KUVAN is dosed based on calculating the patient's body weight and the amount of drug needed. The [insert tablets or powder] are [is] administered orally, once daily, with a meal to increase absorption, preferably at the same time each day. I am requesting approval for the dosage(s) that my patient will require for treatment.

In conclusion, I am requesting that you approve treatment for my patient, [insert patient name], with KUVAN. Please contact me with any additional questions or if you require additional information.

Sincerely,

[Insert prescriber name,
credentials, contact information]

SUGGESTED ENCLOSURES

- KUVAN prescribing information
- KUVAN published clinical studies
- Patient's medical history, clinical notes, and labs confirming diagnosis
- Relevant labs, e.g., genetic tests, baseline testing

MANAGING DENIALS AND APPEALS

Denials occur when the insurance plan does not have enough information to confirm that a patient is the right candidate for a specialty treatment. They can also occur if the patient does not meet the clinical criteria for approval, as specified by the insurance plan. Specialty drugs can often be denied following an initial authorization request, and it will require writing an appeal or conducting a peer-to-peer discussion. The insurance plan will provide a written rationale for the denial to both prescriber and patient, usually by mail. Read these letters carefully, as they will provide the reasons for denial, methods for appealing the denial, and timeframe to request an appeal. If you do not understand the denial letter, contact the patient's insurance plan to request additional information.

Additional insurance plan requests

The denial letter may include additional requests for medical information; this may include additional medical records, laboratory work, genetic testing records, and/or the healthcare provider's medical rationale for selecting branded KUVAN® (sapropterin dihydrochloride) Tablets or Powder for Oral Solution as medically necessary for your patient.

Evaluate the methods for appealing in the letter or contact the insurance plan directly to understand your appeal options. Often written appeals are the first option provided, but if a peer-to-peer discussion is available, this is the preferred and most expeditious means of appealing a denial that the prescriber can use.

Peer-to-peer appeals can be an expeditious means of appealing a denial.

Three types of appeals

1 

Appeal letter: A formal, written letter is the usual and customary first level of appeal. This letter is the first attempt to answer or provide additional information requested by the insurance plan. Adjudication for coverage will be returned in letter format.

2 

Peer-to-peer discussion: A peer-to-peer appeal is a phone call where the prescriber has the opportunity to verbally provide the missing data for the insurance plan and explain his/her rationale for selecting a particular treatment. Adjudication for coverage could be provided during the call or be issued in a letter format.

3 

External review: If the insurance plan denies authorization for branded KUVAN treatment multiple times, patients have the opportunity to appeal to an external court or administrative law judge for review of treatment authorization. The letter must be written by the patient, and if an in-person meeting is granted, it must be conducted by the patient or the patient's legal representative. The prescriber may also attend to provide additional detail to support the appeal. Policies and specifics for this level of denial are state-specific, and it is recommended that patients or caregivers seek legal advice.

Every insurance plan is different; remember to read the denial carefully and identify the appeal timelines.

SAMPLE APPEAL LETTER FOR BRANDED KUVAN® (sapropterin dihydrochloride) Tablets or Powder for Oral Solution TREATMENT

- ✔ Date
- ✔ Patient Name
- ✔ Patient Mailing Address
- ✔ Patient Contact Phone Number
- ✔ Insurance Plan Name
- ✔ Insurance Plan Mailing Address
- ✔ Insurance Subscriber Name
- ✔ Insurance Subscriber ID Number
- ✔ Effective Date of Coverage

RE: Denial of KUVAN® (sapropterin dihydrochloride) Tablets or Powder for Oral Solution Treatment

Dear Sir or Madam:

I am writing on behalf of my patient, [insert patient name] to appeal the [insert date] denial for coverage of branded KUVAN® (sapropterin dihydrochloride) Tablets or Powder for Oral Solution [insert tablets or powder]. My patient has been diagnosed with [insert diagnosis]. This letter provides the additional information requested by [insert insurance plan name] in the denial letter and is a formal request for appeal and expedited review of my request for KUVAN coverage for [insert patient name].

Disease and treatment information

Individuals born with PKU have a defect in an enzyme called phenylalanine hydroxylase (PAH). The PAH enzyme uses BH4, a naturally occurring cofactor (or helper) in the body, to break down Phe into tyrosine. Tyrosine is a building block for many proteins and an important neurotransmitter that helps the brain function. In PKU, the PAH enzyme is not working properly and is unable to break down Phe in the body. When tyrosine is not produced and Phe builds up in the blood, it can cause a variety of signs and symptoms, including mental, behavioral, neurological, and physical problems.

KUVAN is a PAH activator indicated to reduce blood phenylalanine (Phe) levels in patients with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-) responsive Phenylketonuria (PKU). KUVAN is used in conjunction with a Phe-restricted diet. Treatment with BH4 can activate residual PAH enzyme to improve metabolism of Phe and decrease blood Phe levels in patients who respond.

Patient's medical history

My patient's current disease state, prior treatment, and response to those treatments, as well as other issues that impact my treatment decision are:

- ✔ *Insert brief description of patient: age, height, weight, functional and neurological status, PKU history, and prior treatment history*
- ✔ *Include essential labs and genetic history that verify diagnosis*
- ✔ *Include other factors that impact the treatment decision (e.g., comorbidities, work status, etc)*
- ✔ *Include supporting medical documentation (e.g., patient's medical record, clinical notes, medication records, relevant lab results [e.g., blood Phe levels])*
- ✔ *Include specific reasons, if any, for patient to receive branded KUVAN vs generic based on your own medical discretion*

In conclusion, I am asking [insert insurance plan name] to reconsider your decision to deny my patient access to KUVAN. I request that [insert insurance plan name] issue approval for the dosage(s) my patient will require for treatment.

Please contact me with any additional questions or if you require additional information.

Sincerely,

[Insert prescriber name,
credentials, contact information]

SUGGESTED ENCLOSURES

- Copy of denial letter
- KUVAN prescribing information
- KUVAN published clinical studies
- Patient's medical history, clinical notes, and labs confirming diagnosis
- Relevant labs, e.g., genetic tests, blood phenylalanine testing

Please see Important Safety Information throughout and full Prescribing Information.

FINANCIAL ASSISTANCE SUPPORT AND SHIPMENT COORDINATION

KUVAN® (sapropterin dihydrochloride) Tablets or Powder for Oral Solution Free 30-Day Trial Program

BioMarin offers a free, 30-day trial of KUVAN for eligible patients diagnosed with PKU and new to therapy, to assess if it will help lower their blood Phe levels in combination with a low-Phe diet. BioMarin RareConnections™ can assist patients with determining eligibility and can coordinate delivery of the KUVAN trial shipment. BioMarin Clinical Coordinators can provide product education and support during the 30-day response trial, to reinforce patient adherence to your trial protocol and provide product education and guidance on the safe/appropriate use of the product.

Financial assistance

BioMarin Co-Pay Assistance Program: BioMarin RareConnections can help commercially insured patients determine eligibility for the KUVAN Co-Pay Assistance Program. The program helps cover 100% of co-pay costs, up to the patient's annual maximum benefit, for eligible patients. The KUVAN Co-Pay Assistance Program is for commercially insured patients only, and certain terms and conditions may apply.

With the KUVAN Co-Pay Assistance Program, 99% of participating patients in 2020 and 2021 paid $0 out of pocket for their prescription*

BioMarin Bridge Program

The Bridge Program provides temporary, free product to patients experiencing a temporary coverage or insurance delay for authorization of KUVAN treatment. BioMarin RareConnections can monitor the patient's prior authorization, and if a delay occurs, will reach out to the HCP to discuss writing a Bridge prescription. The Bridge Program has certain eligibility rules and limitations to the amount of Bridge product provided for each patient, and BioMarin RareConnections will discuss these directly with the patient and provider. BioMarin Bridge product will be delivered by BioMarin's free drug specialty pharmacy.

*Based on 2020 and 2021 co-pay program data. The KUVAN Co-Pay Assistance Program will cover up to $15,750 in assistance per calendar year for eligible patients. Some restrictions apply. Valid only for those with commercial insurance. Offer not valid for prescriptions eligible to be reimbursed, in whole or in part, by Medicare, Medicaid, or any other federal or state program (including any state prescription drug assistance programs) (e.g., VA, DoD, TriCare), for cash-paying patients, where product is not covered by patient's commercial insurance, or where plan reimburses you for entire cost of your prescription drug. No claim for reimbursement of the out-of-pocket expense amount covered by the program shall be submitted to any third-party payer, whether public or private. Offer is not valid where prohibited by law. Valid only in the United States and Puerto Rico. This program is not health insurance. Offer may not be combined with any other rebate, coupon, or offer. Co-payment assistance under the program is not transferable. BioMarin Pharmaceutical Inc. reserves the right to rescind, revoke, or amend the program without notice. Patient certifies responsibility for complying with applicable limitations, if any, of any commercial insurance and reporting receipt of program rewards, if necessary, to any commercial insurer. This program is subject to termination or modification at any time.

Please see Important Safety Information throughout and full Prescribing Information.

BioMarin Patient Assistance Program

The BioMarin Patient Assistance Program (PAP) provides free product to eligible patients who are uninsured or functionally uninsured. BioMarin RareConnections™ will work with the patient and provider to discuss eligibility. A PAP application and attestation must be completed by the patient and HCP, the patient must meet certain eligibility requirements as outlined by BioMarin, and the product will be delivered by BioMarin's free drug specialty pharmacy. Patients eligible for PAP are approved for 1 calendar year unless their insurance coverage changes.

Shipment coordination

Once the patient's prior authorization (PA) is approved and the financial elements are taken care of, KUVAN is delivered by the specialty pharmacy directly to the patient's home. BioMarin is contracted with a limited number of specialty pharmacies (SPs) to distribute KUVAN. The SPs are licensed in all 50 states and will coordinate shipment and logistics for ongoing refill management of KUVAN. The SPs also provide case management on KUVAN PA renewals, prescription changes, and dose modification.

Please see Important Safety Information throughout and full Prescribing Information.

CODING

Possible coding for KUVAN® (sapropterin dihydrochloride) Tablets or Powder for Oral Solution

The following coding examples are provided by BioMarin but are not considered a guarantee for reimbursement:

KUVAN

Code Type	Code(s)	Descriptors
ICD-10 Diagnosis Code	E70.0	Classical Phenylketonuria (PKU)
	E70.1	Other Hyperphenylalaninemias
KUVAN National Drug Code		KUVAN® (sapropterin dihydrochloride) Tablets or Powder for Oral Solution
	68135-0300-02	100 mg Tablet
	68135-0301-22	100 mg Powder
	68135-0482-11	500 mg Powder

Disclaimer

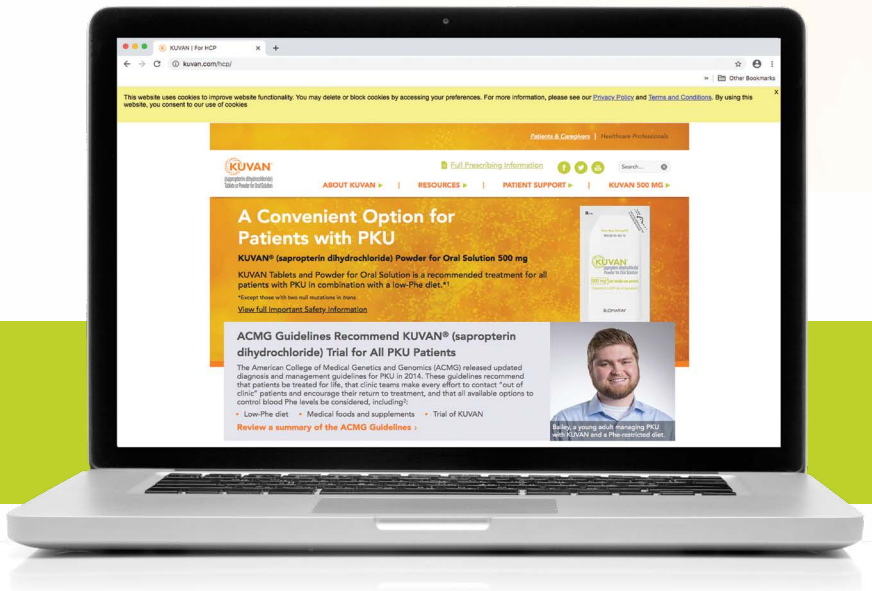
BioMarin makes no guarantee that the use of this information will prevent denials, delays, or differences of opinion with insurance plans as to the correct information to submit for KUVAN authorization, or forms of billing that will expedite payment to providers of service. BioMarin provides this information as a convenience; it does not constitute legal advice or a recommendation regarding medical practice.

This guide covers only those Food and Drug Administration (FDA)-approved indications that are documented in the KUVAN Prescribing Information (see link below). Where reimbursement is sought for prescribed use and/or administration of this product that may be inconsistent with, or not expressly specified in, the FDA-cleared or FDA-approved labeling outlined in the KUVAN Prescribing Information, consult with your billing advisers or the patient's insurance plan on handling such issues.

ADDITIONAL INFORMATION AND RESOURCES

KUVAN® (sapropterin dihydrochloride) Tablets or Powder for Oral Solution: Visit the product website at www.kuvan.com/hcp/ to find additional information about KUVAN resources, such as the following:

- KUVAN RareConnections™ Patient Enrollment Form
- BioMarin RareConnections™ Patient Authorization Form
- KUVAN dosage forms
- KUVAN dosing and administration information
- PKU treatment guidelines
- KUVAN patient education materials



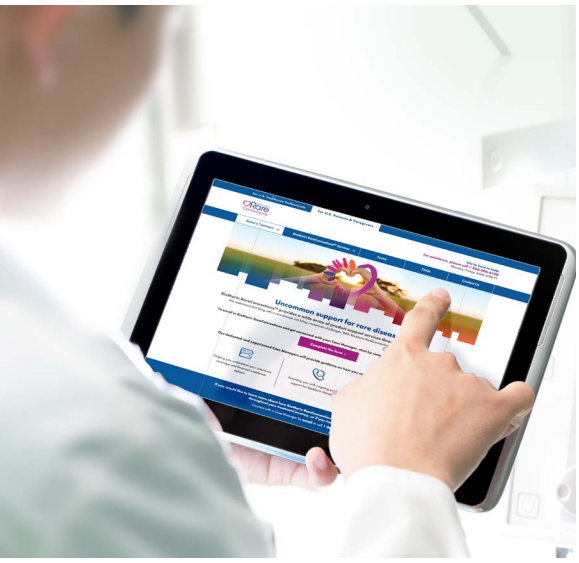
BIOMARIN Rare Connections™

Please see Important Safety Information throughout and full Prescribing Information.

BIOMARIN RARECONNECTIONS™

BioMarin RareConnections contact information:

- Phone: 1-866-906-6100
- Email: support@biomarin-rareconnections.com
- Hours: Monday–Friday, 6 AM–5 PM PT



For additional information about BioMarin RareConnections resources and contact information, visit the website www.biomarin-rareconnections.com.

Patients wishing to enroll in BioMarin RareConnections and get connected with a Case Manager can download and complete the BioMarin RareConnections Patient Authorization Form via the RareConnections website, or complete the form online at www.BioMarinPAF.com.

Patients interested in determining eligibility for the KUVAN® (sapropterin dihydrochloride) Tablets or Powder for Oral Solution Co-Pay Assistance program can visit www.biomarin-rareconnections.com/kuvan/co-pay-assistance/, or call 1-877-MY-KUVAN (1-877-695-8826) to speak with a BioMarin RareConnections Case Manager.

BioMarin RareConnections Healthcare Provider Portal: A single web-based site to access BioMarin RareConnections patient information for all healthcare providers in your clinic. www.BioMarinHCPPortal.com

- Access list of patients enrolled in BioMarin RareConnections and enroll new patients
- Review patient information, including insurance coverage, prior authorization, and appeal status
- Submit prescriptions online for new or existing patients
- Receive alerts for patients that require your attention

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IMPORTANT SAFETY INFORMATION

INDICATION

KUVAN® (sapropterin dihydrochloride) Tablets for Oral Use and Powder for Oral Solution are indicated to reduce blood phenylalanine (Phe) levels in adult and pediatric patients one month of age or older with hyperphenylalaninemia (HPA) due to tetrahydrobiopterin- (BH4-) responsive Phenylketonuria (PKU). KUVAN is to be used in conjunction with a Phe-restricted diet.

IMPORTANT SAFETY INFORMATION

Treatment with KUVAN should be directed by physicians knowledgeable in the management of PKU. Prolonged exposure to elevated blood Phe levels can result in severe neurologic damage in PKU patients.

The use of KUVAN does not eliminate the need for careful monitoring of blood Phe levels and ongoing dietary management to ensure adequate Phe control and nutritional balance. Response to KUVAN can only be determined by a therapeutic trial. Patients should be advised to notify their physicians in cases of overdose.

Warnings and Precautions

- **Hypersensitivity Reactions Including Anaphylaxis:** KUVAN is not recommended in patients with a history of anaphylaxis to KUVAN. Hypersensitivity reactions, including anaphylaxis and rash, have occurred. Signs of anaphylaxis include wheezing, dyspnea, coughing, hypotension, flushing, nausea, and rash. Discontinue KUVAN treatment in patients who experience anaphylaxis, and initiate appropriate medical treatment. Continue dietary Phe restrictions in patients who experience anaphylaxis.
- **Upper Gastrointestinal Mucosal Inflammation:** Gastrointestinal (GI) adverse reactions suggestive of upper GI mucosal inflammation have been reported with KUVAN. Serious adverse reactions included esophagitis and gastritis. If left untreated, these could lead to severe sequelae including esophageal stricture, esophageal ulcer, gastric ulcer, and bleeding, and such complications have been reported in patients receiving KUVAN. Monitor patients for signs and symptoms of upper GI mucosal inflammation.
- **Hypophenylalaninemia:** Some patients receiving KUVAN can experience significant drops in blood Phe levels, and children younger than 7 years old treated with KUVAN doses of 20 mg/kg per day are at an increased risk for low levels of blood Phe compared with children 7 years and older.
- **Monitoring Blood Phe Levels During Treatment:** Prolonged elevations of blood Phe levels in patients with PKU can result in severe neurologic damage, including severe intellectual disability, developmental delay, microcephaly, delayed speech, seizures, and behavioral abnormalities. Conversely, prolonged levels of blood Phe that are too low have been associated with catabolism and endogenous protein breakdown, which has been associated with adverse developmental outcomes. Active management of dietary Phe intake and frequent blood Phe monitoring while taking KUVAN is required to ensure adequate Phe control and nutritional balance, especially in the pediatric population.
- **Lack of Biochemical Response to KUVAN:** Not all patients with PKU respond to treatment with KUVAN. Biochemical response to KUVAN treatment cannot generally be pre-determined by laboratory testing (e.g., molecular testing), and should be determined through a therapeutic trial (evaluation) of KUVAN response.
- **Interactions with Levodopa:** In a post-marketing safety surveillance program for a non-PKU indication using another formulation of the same active ingredient (sapropterin), there have been reports of an interaction with levodopa causing seizures, exacerbation of seizures, over-stimulation, and irritability. Monitor patients who are receiving levodopa for a change in neurologic status during treatment with KUVAN.
- **Hyperactivity:** There have been post-marketing reports of hyperactivity with administration of KUVAN. Monitor patients for hyperactivity.

Adverse Reactions

- Most common: The most common adverse reactions (incidence ≥4%) were headache, rhinorrhea, pharyngolaryngeal pain, diarrhea, vomiting, cough, and nasal congestion.
- Additional adverse reactions reported in connection with worldwide marketing: hypersensitivity reactions including anaphylaxis and rash, esophagitis, gastritis, oropharyngeal pain, pharyngitis, esophageal pain, abdominal pain, dyspepsia, nausea, vomiting, and hyperactivity

Additional Drug Interactions

- Frequently monitor blood Phe levels when co-administering KUVAN with medications known to inhibit folate metabolism, such as methotrexate, valproic acid, phenobarbital, trimethoprim.
- Monitor patients for hypotension when co-administering KUVAN with medications known to affect nitric oxide–mediated vasorelaxation such as PDE-5 inhibitors including sildenafil, vardenafil, or tadalafil.

To report SUSPECTED ADVERSE REACTIONS, contact BioMarin Pharmaceutical Inc. at 1-866-906-6100, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please read the full Prescribing Information by clicking here.

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