Subject: Kuvan (sapropterin dihydrochloride)	Original Effective Date: 11/20/08
Policy Number: MCP-062	Revision Date(s): 5/13/15
Review Date(s): 12/15/2016; 6/22/2017	

DISCLAIMER

This Medical Policy is intended to facilitate the Utilization Management process. It expresses Molina's determination as to whether certain services or supplies are medically necessary, experimental, investigational, or cosmetic for purposes of determining appropriateness of payment. The conclusion that a particular service or supply is medically necessary does not constitute a representation or warranty that this service or supply is covered (i.e., will be paid for by Molina) for a particular member. The member's benefit plan determines coverage. Each benefit plan defines which services are covered, which are excluded, and which are subject to dollar caps or other limits. Members and their providers will need to consult the member's benefit plan to determine if there are any exclusion(s) or other benefit limitations applicable to this service or supply. If there is a discrepancy between this policy and a member's plan of benefits, the benefits plan will govern. In addition, coverage may be mandated by applicable legal requirements of a State, the Federal government or CMS for Medicare and Medicaid members. CMS's Coverage Database can be found on the CMS website. The coverage directive(s) and criteria from an existing National Coverage Determination (NCD) or Local Coverage Determination (LCD) will supersede the contents of this Molina medical coverage policy (MCP) document and provide the directive for all Medicare members.

SUMMARY

This policy addresses the coverage of Kuvan (sapropterin dihydrochloride) treatment of phenylketonuria (PKU) in conjunction with a phenylalanine-restricted diet when appropriate criteria are met.

- The standard treatment for patients with phenylketonuria (PKU) is maintaining a diet with low phenylalanine (Phe) content. Guidelines have not been updated since the approval of Kuvan.

- Untreated PKU is associated with severe mental retardation, psychological issues and neurologic damage. The blood Phe concentration associated with optimal neurodevelopmental outcome is uncertain.[B,C,10] However there is no consensus regarding the optimal blood Phe level. The National Institutes of Health (NIH) Consensus Statement and more recent practice guidelines from The American College of Medical Genetics and Genomics (ACMG) differ in recommendations:[B,C,10]

  - The ACMG currently recommends that blood phenylalanine levels be maintained in the 120–360 micromoles/liter range for all individuals.[C] Liberalization of blood phenylalanine levels in adults is no longer advised as elevated levels of phenylalanine may lead to psychological issues such as depression, anxiety, and phobias. For the 25% to 50% of individuals who are sapropterin hydrochloride responsive, Kuvan may play a pivotal role in the management of their phenylalanine hydroxylase (PAH) deficiency disorder.

  - The 2000 NIH Consensus Statement on PKU includes recommendations such as target blood Phe ranges of 2-6 mg/dL for infants through 12 years of age, 2-15 mg/dL after 12 years of age, and 6 mg/dL three months pre-conception and maintained at 2-6 mg/dL throughout pregnancy.

- There is insufficient evidence on how to identify the type of patients most likely to benefit because there is no standardized clinical protocol to select potential patients who might be responsive to saproterin treatment.

  - Approximately 25% to 50% of patients with PAH deficiency are sapropterin-responsive. "Patients with mild PAH deficiency are most likely to respond because some stable protein is required for sapropterin to function;

nonetheless, responsive patients are identified among those with complete PAH deficiency." Since prediction of sapropterin responsiveness by genotype-phenotype correlation is not exact, the American College of Medical Genetics and Genomics (ACMG) recommends, *"that every PAH-deficient patient should be offered a trial of sapropterin therapy to assess responsiveness except those with two null mutations in trans."*

- The clinical trials demonstrated saproterin can lower the blood Phe levels in some patients with PKU. However, there are no sufficient details on how to identify the type of patients that would get improvements. There are different definitions of responses ranging from a 20% to 50% reduction in blood Phe levels.[5] Saproterin responsiveness in clinical trials was defined as ≥ 30% blood Phe levels reductions, however this definition is arbitrary and many clinicians consider a 20% reduction in Phe clinically beneficial.

- Currently there are no other medications used in the treatment of PKU, so comparison to other medications is not possible. Additionally, there are no studies comparing the use of sapropterin to a Phe-restricted diet.

- There is insufficient evidence on the long-term effects of saproterin and no clear evidence of effectiveness in severe PKU.

FDA INDICATIONS

Hyperphenylalaninemia: To reduce blood phenylalanine levels in patients with hyperphenylalaninemia caused by tetrahydrobiopterin (BH4)–responsive phenylketonuria in conjunction with a phenylalanine-restricted diet.
NOTE: Sapropterin is designated by the FDA as an orphan drug for this indication.

Available as: 100mg disintegrating tablet (equivalent to 76.8 mg sapropterin), 100mg powder for oral solution

FDA Approved: December 2007

Black Box Warnings: *None at the time of this writing*

CLASSIFICATION: Endocrine Metabolic Agent

RECOMMENDATIONS/COVERAGE CRITERIA

Kuvan (sapropterin dihydrochloride) may be authorized for members who meet **ALL** of the following criteria **[ALL]**

1. Prescriber specialty [ONE]

- ❒ Prescribed by, or in consultation with, a board-certified medical geneticist or physician experienced in the management of metabolic disorders or phenylketonuria (PKU).[a] Submit consultation notes if applicable.
  NOTE: Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. Diagnosis/Indication [ONE]
Clinical documented diagnosis of (*includes clinical notes from the member's medical records including any applicable labs and/or tests, supporting the diagnosis*):

- ❒ Diagnosis of hyperphenylalaninemia (HPA) due to tetrahydrobiopterin-(BH4-) responsive phenylketonuria (PKU)

3. Age/Gender/Other restrictions [ALL]

- ❒ 4 years of age or older

4. Step/Conservative Therapy/Other condition Requirements [ALL]

- ❑ Therapy includes dietary intervention (phenylalanine-restriction) in conjunction with Kuvan (sapropterin dihydrochloride). Documentation that phenylalanine levels canNOT be maintained within the recommended maintenance range with dietary intervention alone despite strict compliance required.

- ❑ Baseline phenylalanine level (***prior*** to initiation of therapy with Kuvan) is above the recommended Phe levels [All ages: 2-6 mg/dL (120-360 mcmol/L)]. Submit copy of recent phenylalanine lab test report dated within 30 days of request.
  - ➢ *The American College of Medical Genetics and Genomics (ACMG) currently recommends that blood phenylalanine levels be maintained in the 120–360 micromoles/liter range for all individuals.[C] Liberalization of blood phenylalanine levels in adults is no longer advised as elevated levels of phenylalanine may lead to psychological issues such as depression, anxiety, and phobias. For the 25% to 50% of individuals who are sapropterin hydrochloride responsive, Kuvan may play a pivotal role in the management of their phenylalanine hydroxylase (PAH) deficiency disorder.*

5. Contraindications/Exclusions/Discontinuations

Authorization will <u>not</u> be granted if ANY of the following conditions apply [ANY]

- ❒ Non-FDA approved indications
- ❒ Hypersensitivity to sapropterin dihydrochloride or any of its components

**There are no contraindications listed in the manufacturer's labeling although the product should not be used in patients with a known severe allergy to any of the product ingredients (ascorbic acid, crospovidone, dibasic calcium phosphate, D-mannitol, riboflavin, sodium stearyl fumarate).[a-d]*

6. Labs/Reports/Documentation required [ALL]

All documentation for determination of medical necessity must be submitted for review. Prescriber to submit medical records and specific labs, chart notes, and documentation as indicated in the criteria above. Letters of support and/or explanation are often useful, but are not sufficient documentation unless ALL specific information required by this MCP is included. Additional documentation, rationale, and/or supporting evidence may be requested for review as deemed necessary or appropriate by Molina Medical/Pharmacy staff.

NOTE: Not all individuals with PKU respond to treatment with Kuvan.[a] Response to treatment cannot be pre-determined by laboratory testing (e.g., molecular testing), and can only be determined by a therapeutic trial of Kuvan**.** Patients whose blood phenylalanine (Phe) does not decrease after 1 month of treatment at 20 mg/kg per day are referred to as 'non-responders' and treatment with Kuvan should be **discontinued** in these patients.

- *There are currently no pharmacogenomic tests to identify patients most likely to respond to Kuvan. -*
- *Blood Phe levels should be monitored routinely during treatment to ensure adequate Phe control and prevent the member from prolonged exposure to elevated levels that can injure the brain and reduce the brain function. -*
- *Phenylalanine blood levels; at baseline[3], after 1 week of therapy, periodically for 1 month after initiation or dose increase, and routinely throughout treatment; frequent monitoring recommended in pediatric patients and patients treated with agents known to affect folate metabolism[a-e] -*

CONTINUATION OF THERAPY

Kuvan (sapropterin dihydrochloride) may be authorized for continuation of therapy if meet **ALL** of the following criteria are met: **[ALL]**

1. Initial Coverage Criteria [ALL]

- ❑ Member currently meets ALL initial coverage criteria
  EXCEPTION: Therapy may be authorized for members who have been on Kuvan (sapropterin dihydrochloride) therapy prior to their effective date of coverage by Molina Healthcare with documentation supporting the continuation of therapy coverage criteria and stability on therapy. Additional documentation may also be requested by the Medical Reviewer depending on the length of time the member has been receiving Kuvan therapy.

- ❑ Consultation notes must be submitted for initial request and for continuation of treatment requests at least ONCE annually.

2. Compliance [ALL]

- ❒ Remaining compliant/adherent to a phenylalanine-restricted diet **in conjunction with** Kuvan therapy
  - ➢ *All members receiving sapropterin should also be treated with a Phe-restricted diet as the initiation of sapropterin therapy does not eliminate the need for ongoing dietary management.*

3. Labs/Reports/Documentation required [ALL]

NOTE: Not all individuals with PKU respond to treatment with Kuvan.[a] Response to treatment cannot be pre-determined by laboratory testing (e.g., molecular testing), and can only be determined by a therapeutic trial of Kuvan**.** Patients whose blood phenylalanine (Phe) does not decrease after 1 month of treatment at 20 mg/kg per day are referred to as 'non-responders' and treatment with Kuvan should be **discontinued** in these patients.

- *Blood Phe levels should be monitored routinely during treatment to ensure adequate Phe control and prevent the member from prolonged exposure to elevated levels that can injure the brain and reduce the brain function.*
- *Phenylalanine blood levels; at baseline[3], after 1 week of therapy, periodically for 1 month after initiation or dose increase, and routinely throughout treatment; frequent monitoring recommended in pediatric patients and patients treated with agents known to affect folate metabolism[a-e]*

- ❒ Dosage of Kuvan and member's current weight must be submitted
  NOTE: Doses exceeding 20 mg/kg/day are considered investigational and will NOT be authorized.

- ❒ At least **ONE (1)** of the following criteria confirming significant reduction in phenylalanine (Phe) levels during first month of therapy to determine responsiveness to Kuvan therapy for continuation of therapy. Submit baseline Phe level and follow-up Phe levels during first month of therapy, or documentation of improvement to support responsiveness to Kuvan therapy as follows: [ONE]

  - ❍ At least 30% decrease in Phe levels from baseline
    - *Measure blood Phe concentrations at baseline, **after 1 week of treatment initiation,** and periodically thereafter to ensure maintenance of blood Phe concentrations within the desired range. Frequent blood monitoring is recommended in pediatric patients.*
    - *Clinicians have attempted to develop a uniform and practical approach to the use of saproterin for treating PKU in conjunctions with diet although a national consensus is still lacking. The most widely accepted standard of response to BH4 is a ≥ 30% reduction in blood phenylalanine level. However, it*

is recognized that a lower degree of responsiveness, e.g. 20% might also be considered sufficient in some individual circumstances.

- Less than a 30% reduction of phenylalanine levels, however **documented** continuing improvement as evidenced by: [AT LEAST ONE]
  - Increase in Phe tolerance [Increase in tolerance is determined by maintenance of low blood Phe levels or improvement in neuropsychiatric symptoms with increased dietary Phe. In some individuals, the increase in tolerance may be two to three times above baseline.]
    - *Patients with a baseline Phe level at the lower end of the treatment range (180 µmol/l or lower) rarely show a significant decline in blood Phe level, even if they are sapropterin-responsive.[C] In these patients, responsiveness must be determined by adding additional PHE to the diet in a stepwise fashion to determine if an increase in Phe tolerance is achieved, i.e., maintenance of low blood Phe levels on increased dietary Phe.[4] In some patients, the increase in dietary Phe can be substantial (two- to threefold over baseline) and has an impact on quality of life. An improvement in neuropsychiatric symptoms or increase in Phe tolerance without a decrease in blood Phe in any patient constitutes sufficient justification to continue therapy.*
  - Improvement in neuropsychiatric symptoms (i.e. depression, anxiety, or attention disorders) [C]
  - Improvements in behavior, psychiatric symptomology or seizure control

- *An improvement in neuropsychiatric symptoms or increase in Phe tolerance without a decrease in blood Phe in any patient constitutes sufficient justification to continue therapy. [C] For patients who are able to maintain blood Phe levels in the desired range with dietary treatment alone, the major benefit of treatment with sapropterin is that it increases dietary protein and Phe tolerance in responsive patients, allowing for the inclusion of more natural protein in the diet.[C] In some patients, the increase in dietary Phe can be substantial (two- to threefold over baseline) and has an impact on quality of life. For most sapropterin-responsive patients, the benefits of treatment are such that long-term therapy with sapropterin should be maintained.*

4. Discontinuation of Treatment [ANY]

Discontinue treatment if ANY of the following conditions applies: [ANY]

- Intolerable adverse effects or drug toxicity
- Persistent and uncorrectable problems with adherence to treatment
- Poor response to treatment as evidenced by laboratory documentation, physical findings or clinical symptoms
- **Non-responders to Sapropterin therapy** [defined as less than a 30% decrease in blood phenylalanine (Phe) levels after one month of treatment at 20 mg/kg/day]: After 1 month of treatment at 20 mg/kg/day blood PHE levels has **not** decreased at least 30% from baseline, the individual is considered a non-responder to Sapropterin therapy and treatment with Sapropterin should be discontinued in these patients.
  - *Current literature cites a 30% reduction in PHE levels as evidence for responsiveness to Sapropterin*.
- Contraindications/Exclusions to therapy
  - Non-FDA approved indications
  - Hypersensitivity to sapropterin dihydrochloride or any of its components

ADMINISTRATION, QUANTITY LIMITATIONS, AND AUTHORIZATION PERIOD

1. Recommended Dosage [ALL]

Initial, 10 to 20 mg/kg once daily; if phenylalanine (Phe) levels do not decrease after 1 month at 10 mg/kg, increase to 20 mg/kg/day; if phenylalanine levels do not decrease after 1 month at 20 mg/kg/day, discontinue use. Phe levels should be checked after 1 week of Kuvan treatment and periodically for up to a month. Doses exceeding 20 mg/kg/day will not be authorized.

- *The efficacy and safety of higher doses of Kuvan, above 20mg/kg/day, have not been evaluated in clinical trials.*
- *Children younger than 7 years treated with dosages of 20 mg/kg/day are at increased risk for low levels of blood phenylalanine (hypophenylalaninemia).*

❒ Recommended dose [ONE]

- ❍ Initial recommended dose: 10 mg/kg/day orally once daily
- ❍ Maintenance dose: Doses of Kuvan may be adjusted in the range of 5-20mg/kg taken once daily. Doses of Kuvan above 20mg/kg/day have not been evaluated in clinical trials.

❒ Dosage Adjustments [ONE]

- ❍ **If a 10 mg/kg/day initial dose** is utilized then response to therapy is determined by change in Phe following treatment for a period of **2 months:**
  - If Phe levels do not decrease after 1 month at 10 mg/kgday: Increase to 20 mg/kg/day
  - If Phe levels do not decrease after 1 month at 20 mg/kg/day: Discontinue use
    - *Patients whose Phe does not decrease after 1 month of treatment at 20 mg/kg per day are considered 'non-responders' and treatment with Kuvan should be discontinued in these patients.*
- ❍ **If a 20 mg/kg/day initial dose** is utilized then response to therapy is determined by change in Phe following treatment for a period of **1 month:**
  - If Phe levels do not decrease after 1 month of treatment at 20 mg/kg per day: Discontinue. Member is considered 'non-responder'.

❒ Once responsiveness to Kuvan has been established: Dosage may be adjusted within the range of **5 to 20 mg/kg per day** according to response to therapy. Blood phenylalanine levels (baseline, after 1 week of treatment, periodically for first month, regularly thereafter); children may require more frequent monitoring

❒ **DISCONTINUATION OF THERAPY:** Individuals whose blood Phe does **not** decrease after 1 month of treatment at 20 mg/kg/day is considered non-responders and treatment should be **discontinued**

- *In clinical trials, patients were considered responders to Kuvan if blood Phe levels decreased at least 30% from baseline. Some members do not respond to Kuvan therapy. If blood Phe does not decrease 30% from baseline on the 10 mg/kg/day dose, the dose may be increased to 20 mg/kg/day. If after one month of treatment at 20 mg/kg/day blood Phe levels have not decreased at least 30%, the member is considered a non-responder and further treatment will not be authorized. Documentation of Phe level at the end of the trial period is required.*

2. Authorization Limit [ALL]

- ❒ Quantity limit: The dose of sapropterin does **not** exceed 20 mg/kg/day, based on the member's current weight. All doses will be rounded to the nearest 100 mg. MOLINA REVIEWER: Authorize total amount of tablets (or powder packets for solution) based on daily prescribed dosage rounded to the nearest 100mg.

- ❒ Dispensing limit: Only a 1-month supply may be dispensed at a time

- ❒ Duration of initial authorization: [ONE]
  - ❍ If dose 5-10 mg/kg/day: 2 months
  - ❍ If initial dose is 20 mg/kg/day: 1 month

- ❒ Continuation of treatment: Re-authorization for continuation of treatment is required every **6 months** to determine continued need based on documented positive clinical response.
  NOTE: Subsequent authorization will be granted based on response to therapy as determined by changes in blood Phe following treatment. Refer to 'Continuation of Therapy' section for specific criteria.

- ❒ Duration of continuation of treatment: May be authorized up to **6 months** at a time

3. Route of Administration [ALL]

- ❒ Kuvan (sapropterin dihydrochloride) is deemed appropriate for **self-administration** or administration by a caregiver (i.e., not a healthcare professional). Therefore, coverage/administration in a provider-administered setting such as an outpatient hospital, ambulatory surgical suite, physician office, or emergency facility will not be authorized.
  - *Treatment with Kuvan must be supervised by a physician knowledgeable in the management of children and adults with PKU*

- ❒ If member meets all criteria and approval for therapy is granted, medication will be dispensed by a specialty pharmacy vendor at the discretion of Molina Healthcare. Self-administered medications may not be dispensed for self-administration and billed through the medical benefit by a provider; they must be dispensed through a participating pharmacy.

COVERAGE EXCLUSIONS

This policy only addresses the indication of Kuvan (sapropterin dihydrochloride) for the treatment of phenylketonuria (PKU) in conjunction with a phenylalanine-restricted diet when appropriate criteria are met.

All other uses of Kuvan (sapropterin dihydrochloride) that are not an FDA-approved indication or not included in the 'Coverage Criteria' section of this policy are considered experimental/investigational or not a covered benefit of this policy. This subject to change based on research and medical literature, or at the discretion of Molina Healthcare.

SUMMARY

Phenylketonuria (PKU), also referred to as phenylalanine hydroxylase (PHA) deficiency, is a genetic disorder characterized by a deficiency or absence of the hepatic enzyme phenylalanine hydroxylase (PAH) resulting in an increase in blood phenylalanine (Phe) concentrations. PAH deficiency is inherited in an autosomal-recessive manner; affected individuals inherit two mutations in the PAH gene, one from each parent. PAH is required for the conversion of the essential amino acid phenylalanine (Phe) to tyrosine. Due to deficiency in PAH, individuals with PKU have an overabundance of phenylalanine, which plays an integral role in the development of normal brain function. Elevated blood Phe concentrations can cause severe neurological damage. Conversely, prolonged blood Phe concentrations that are too low may lead to catabolism and protein breakdown. The clinical consequences can vary widely between patients, as can blood Phe levels, but untreated PKU can lead to severe learning disabilities and mental retardation due to neurological poisoning from Phe.[6]

The primary goal of therapy should be to lower blood Phe, and any interventions, including medications, or combination of therapies that help to achieve that goal in an individual, without other negative consequences, should be considered appropriate therapy. Secondary goals should include improved dietary Phe tolerance, amelioration of symptoms, and improved quality of life. Effects of adjuvant therapies on Phe tolerance require continued careful clinical and laboratory monitoring.

Pharmacologic Agents/Conventional Therapy
PKU requires lifelong treatment to reduce and prevent adverse consequences associated with the excessive accumulation of PHE. The cornerstone of PKU treatment is a Phe-restricted diet, which severely limits the intake of protein from meat, fish, dairy, and grain products. PKU is currently treated by dietary restriction of phenylalanine. This requires almost complete elimination of protein rich foods from diets with the substitution of specially prepared dietary supplements resulting in a low-Phe diet. However compliance with the special diet is often suboptimal. [7-9] Dietary restriction of Phe throughout life is required for optimal neurological and developmental outcomes. However, long-term use of the restrictive diet has been associated with complications of low bone mass such as osteopenia, osteoporosis, and fractures.[1,2]

In December 2007, Kuvan (sapropterin) received approval from the US Food and Drug Administration making it the first pharmacologic agentfor the treatment of PKU patients. Kuvan (sapropterin) is an orally administered medication used in conjunction with a Phe-restricted diet to reduce blood phenylalanine levels in patients with PKU.

Sapropterin is indicated **in conjunction with** a phenylalanine-restricted diet to reduce blood phenylalanine concentrations in patients with hyperphenylalaninemia due to tetrahydrobiopterin- (BH4-) responsive phenylketonuria (PKU). Sapropterin is a synthetic preparation of naturally occurring tetrahydrobiopterin- (BH4-) and is the first FDA-approved Phenylalanine hydroxylase hydroxylates Phe through an oxidative reaction to form tyrosine. In patients with phenyloketonuria (PKU), Phenylalanine hydroxylase activity is deficient or absent. Treatment with BH4 can activate residual PAH enzyme, improve the normal oxidative metabolism of Phe, and decrease Phe levels in some patients. In patients with PKU who are responsive to treatment, blood Phe levels decrease within 24 hours after administration, although maximal effect on Phe levels may take up to one month. In 8-day and 6-week pivotal trials, response to Kuvan treatment was defined as ≥ 30% decrease in blood Phe concentration from baseline. However, in some cases (e.g., patients

with mild HPA, neonates or children < 4 years of age, or pregnant women), a 20% reduction in blood Phe concentration may be sufficient.

Pivotal Trials

Clinical Efficacy Data

The efficacy of sapropterin was established based on five clinical trials: one open-label trial[11] with a follow-on randomized controlled trial[3] and open-label extension trial[12], as well as two additional Phase 3 trials.[a,4]

- Sapropterin was dosed at 10 to 20 mg/kg/day.
- The study duration ranged from eight days to 22 weeks.
- The primary efficacy endpoint was the change in blood Phe concentration from baseline.
- In clinical trials, patients were considered responders to sapropterin if blood Phe levels decreased at least 30% from baseline. A response was seen as early as eight days after initiating treatment.

❖ Two double blind, placebo controlled studies evaluated the efficacy and safety of saproterin in patients with PKU.[3,4]

- The first randomized clinical trial by Levy et al.[3] was a phase III, multicenter, randomized, double-blind, placebo controlled trial, that included 88 patients who received at least one dose of study drug. There were 41 patients in treatment group received oral doses of saproterin 10mg/kg and 47 patients received placebo once daily for 6 weeks. The patients enrolled in this study were pediatric and adult patients who were screened to show responsiveness, defined as a reduction of 30% or more in blood phenylalanine concentration after 8 days of treatment with saproterin at a dose of 10mg/kg per day. The primary endpoint was mean difference between treatment groups in blood phenylalanine concentration at six weeks. Analysis was on an intention-to-treat basis.

- The second randomized clinical trial conducted by Trefz et al. al[4] was also a phase III, randomized, double blind, placebo controlled study screen for saproterin response among 90 children aged 4 – 12 years of age in part 1. In part 2, 46 responsive subjects were randomized (3:1) to saproterin 20mg/kg/day, or placebo for 10 weeks while continuing on a Phe-restricted diet. After 3 weeks, a dietary Phe supplement was added every 2 weeks if Phe control was adequate. Responders in part 1, were arbitrarily defined as those who achieved at least 30% reduction in blood Phe concentrations between day 1 and day 8, had blood Phe level of ≤ 300 μmol/L on day 8. The primary endpoint was daily Phe supplement tolerated by the saproterin group at week 10 compared with week 0. The Phe supplement tolerated was defined as the cumulative increase or decrease in Phe supplement prescribed in part 2 at the last visit at which the subject had adequate blood Phe control, defined as a blood Phe concentration < 360 μmol/L.

SYSTEMATIC REVIEWS

Based on the clinical trial evidence, two high quality systematic reviews concluded treatment with sapropterin (Kuvan) decreases Phe blood levels.[B,D]

- The systematic review conducted by Lindegren et al. (published by Agency for Healthcare Research and Quality; February 2012) concluded Phe levels were reduced by at least 30% in up to half of sapropterin treated patients (32 to 50%).[D]
- Somaraju et al. (Cochrane database of systematic reviews, 2012) conducted a systematic review to assess the safety and efficacy of saproterin in lowering blood phenylalanine concentration in people with PKU. This review found a decrease in Phe levels versus baseline in sapropterin treated patients. The authors concluded that there is evidence of short-term benefit from using saproterin in some patients with saproterin-responsive forms of phenylketonuria; blood phenylalanine concentration is lowered and protein tolerance increased. There are no serious adverse events associated with using saproterin in the short term. There is no evidence on the long-term effects of saproterin and no clear evidence of effectiveness in severe phenylketonuria.[B]
  - One trial administered 10mg/kg/day saproterin in 89 children and adults with phenylketonuria whose diets were not restricted and who had previously responded to saproterin. This trial measured change in blood phenylalanine concentration.

- The second trial screened 90 children (4 to 12 years) with phenylketonuria whose diet was restricted, for responsiveness to saproterin. Forty-six responders entered the placebo-controlled part of the trial and received 20 mg/kg/day saproterin. This trial measured change in both phenylalanine concentration and protein tolerance. Both trials reported adverse events. The trials showed an overall low risk of bias; but both were BioMarin-sponsored. One trial showed a significant lowering in blood phenylalanine concentration in the saproterin group (10 mg/kg/day), mean difference -238.80 µmol/L (95% confidence interval -343.09 to -134.51); a second trial (20 mg/kg/day saproterin) showed a non-significant difference, mean difference -51.90 µmol/L (95%confidence interval -197.27 to 93.47). The second trial also reported a significant increase in supplemental phenylalanine tolerated, mean difference 18.00 mg/kg/day (95% confidence interval 12.28 to 23.72) in the 20 mg/kg/day saproterin group.

The authors concluded that there is evidence of short-term benefit from using saproterin in some patients with saproterin-responsive forms of phenylketonuria; blood phenylalanine concentration is lowered and protein tolerance increased. There are no serious adverse events associated with using saproterin in the short term. There is no evidence on the long-term effects of saproterin and no clear evidence of effectiveness in severe phenylketonuria.

National Institute of Health (NIH)[A]

In 2000, the National Institute of Health (NIH) convened an expert panel to develop and publish the first national Consensus Statement in the screening and management of NKU.

The 2000 NIH Consensus Statement on PKU includes recommendations such as target blood Phe ranges of 2-6 mg/dL for infants through 12 years of age, 2-15 mg/dL after 12 years of age, and 6 mg/dL three months pre-conception and maintained at 2-6 mg/dL throughout pregnancy. The positive effects of maintaining control of Phe levels lifelong through a restricted-Phe diet are recommended, but not reinforced with outcome data. Questions regarding the potential for subtle suboptimal outcomes of early diet-treated PKU also remained controversial at the time of the 2000 NIH Consensus Statement.

Recommended Maintenance Phenylalanine (Phe) Levels for Classical PKU

The National Institutes of Health (NIH) Consensus Statement[A]

AGE RANGE	MAINTENANCE PHENYLALANINE LEVELS
Neonates through 12 years of age	120-360 µmol/L (2-6 mg/dL)
Greater than 12 years of age	120-600 µmol/L (2-15 mg/dL)
During pregnancy	120-360 µmol/L (2-6 mg/dL)

In 2010, Enns et al. published a review that assessed PKU patient outcomes since the 2000 NIH Consensus Statement publication. The authors concluded that while many of the recommendations within the 2000 NIH Consensus Statement on PKU may still be valid, recent literature coupled with treatment advances such as the availability of sapropterin provides support for a new NIH Consensus Development Conference to revisit PKU management strategies to optimize patient outcomes. In February 2012, the PKU Scientific Review Conference convened to review the 2000 guidelines in light of new advances in PKU treatment.

American College of Medical Genetics and Genomics (ACMG) Practice Guidelines[C]

The ACMG has released policy for the treatment of patients with PKU. The 2014 phenylalanine hydroxylase deficiency diagnosis and management guidelines were developed by a panel of PKU experts from the US and Canada and provide recommendations for diagnosis and treatment of PKU.

- Reclassify PKU as Phenylalanine Hydroxylase (PAH) Deficiency to broaden the definition of the condition and expand treatment options to all patients with PAH deficiency.
- Begin treatment as early as possible, initiating dietary treatment within the first week of life for infants diagnosed at birth, and maintain treatment for life.

- Lower Phe levels with every intervention available, including low-Phe diet and medication for patients who respond to therapy.
- Patients with mild PAH deficiency are most likely to respond because some stable protein is required for sapropterin to function; nonetheless, responsive patients are identified even among those with complete PAH deficiency. Genotype may be predictive of sapropterin response, but genotype-phenotype correlations thus far are imperfect.[3] Sapropterin responsiveness is commonly determined by obtaining a baseline blood Phe level on the day the medication is initiated (baseline) and then starting the patient on a single daily dose of sapropterin at 20 mg/kg. Additional blood Phe levels are then obtained at regular intervals, usually at 24 h, 1 week, 2 weeks, and in some cases, 3 or 4 weeks.
- Treatment of phenylalanine hydroxylase deficiency must be life long, with a goal of maintaining blood phenylalanine in the range of 120–360 µmol/l.

DEFINITIONS

Non-responders: Response to sapropterin treatment is established through treatment (cannot be predetermined by laboratory testing). Patients whose phenylalanine levels do not decrease after treatment at 20 mg/kg/day for 1 month are considered nonresponders.[a]

Phenylketonuria: Monitor and maintain phenylalanine levels within the target range during sapropterin treatment.[a]

- Upon diagnosis, lower blood phenylalanine levels into the desired treatment range (120 to 360 micromol/L) as quickly as possible; infants with levels higher than 600 micromol/L require treatment, although treatment may be initiated at 360 micromol/L or higher.
- If testing is done in early infancy, it is recommended to initially lower blood phenylalanine to 480 to 600 micromol/L.[C]
- Prolonged high levels of phenylalanine can result in severe neurologic damage, including behavioral abnormalities, delayed speech, microcephaly, seizures, and severe mental retardation. Low levels of phenylalanine are associated with catabolism and protein breakdown.
- Dietary management of phenylalanine intake is required to ensure nutritional balance and adequate phenylalanine control.
- Monitor blood phenylalanine levels during treatment (frequently in children).[a]

APPENDIX

Appendix 1: Reference range

- Phenylalanine hydroxylase deficiency, blood phenylalanine goal range: 120 to 360 micromol/L.[C]
- Guideline recommended monitoring for patients with phenylalanine hydroxylase deficiency:
  - Newly diagnosed infants: Monitor phenylalanine and tyrosine frequently until the phenylalanine concentrations stabilize, then monitor phenylalanine weekly until age 1 year (increase frequency during rapid growth or dietary transitions).[C]
  - 1 to 12 years of age: Monitor phenylalanine every 2 to 4 weeks.[C]
  - Adolescents and adults who are stable: Monitor phenylalanine monthly.[C]
  - If formal nutritional assessment suggests suboptimal dietary intake or for over-reliance on nutritionally incomplete medical foods: Consider monitoring plasma amino acids (full panel), transthyretin, albumin,

complete blood cell count, ferritin, 25-OH vitamin D, vitamin B_{12}, red blood cell essential fatty acids, trace minerals (copper, selenium, zinc), vitamin A, comprehensive metabolic panel, and folic acid.[C]

CODING INFORMATION: THE CODES LISTED IN THIS POLICY ARE FOR REFERENCE PURPOSES ONLY. LISTING OF A SERVICE OR DEVICE CODE IN THIS POLICY DOES NOT IMPLY THAT THE SERVICE DESCRIBED BY THIS CODE IS A COVERED OR NON-COVERED. COVERAGE IS DETERMINED BY THE BENEFIT DOCUMENT. THIS LIST OF CODES MAY NOT BE ALL INCLUSIVE.

CPT	Description
84030	Phenylalanine (PKU), blood

HCPCS	Description
J8499	Prescription drug, oral, non-chemotherapeutic, Not Otherwise Specified

ICD-9	Description [For dates of service prior to 10/01/2015]]
270.1	Phenylketonuria (PKU)

ICD-10	Description [For dates of service on or after 10/01/2015]
E70.0	Classical phenylketonuria

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