DIETARY TREATMENT FOR PHENYLKETONURIA (PKU)

Policy Number: 2014M0062A Effective Date: July 1, 2014

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INSTRUCTIONS:

“Medical Policy assists in administering UCare benefits when making coverage determinations for members under our health benefit plans. When deciding coverage, all reviewers must first identify enrollee eligibility, federal and state legislation or regulatory guidance regarding benefit mandates, and the member specific Evidence of Coverage (EOC) document must be referenced prior to using the medical policies. In the event of a conflict, the enrollee’s specific benefit document and federal and state legislation and regulatory guidance supersede this Medical Policy. In the absence of benefit mandates or regulatory guidance that govern the service, procedure or treatment, or when the member’s EOC document is silent or not specific, medical policies help to clarify which healthcare services may or may not be covered. This Medical Policy is provided for informational purposes and does not constitute medical advice. In addition to medical policies, UCare also uses tools developed by third parties, such as the InterQual Guidelines®, to assist us in administering health benefits. The InterQual Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice. Other Policies and Coverage Determination Guidelines may also apply. UCare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary and to provide benefits otherwise excluded by medical policies when necessitated by operational considerations.”
**POLICY DESCRIPTION:**

This policy provides information on dietary treatment for phenylketonuria (PKU), an inborn error of metabolism. While standard food is technically a nutritional product, this document addresses "medical food" and commercially available processed food products, which are not standard food, and are used in the home to meet basic metabolic needs and distinctive nutritional requirements. Medical foods are intended solely to meet routine dietary needs of individuals who have specific metabolic or physiological limitations that restrict their ability to digest regular food.

In PKU there are distinctive nutritional requirements to avert the development of serious physical or mental disabilities and to promote normal development and function. Special medical foods and oral formulas are used under medical supervision and intended for the specific dietary management of the condition, restricting intake of the phenylalanine amino acid.

The use of medical food by individuals who do not meet this definition is not medically necessary.

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**COVERAGE RATIONALE / CLINICAL CONSIDERATIONS:**

1. When prescribed by a physician, specially labeled nutritional supplements (oral formulas and solid food products) intended for use in the dietary management of phenylketonuria (PKU), and regarded as “medical food,” are considered **MEDICALLY NECESSARY** for the lifespan of a patient living with PKU.

   **Note:**
   - These medical food nutrients are not products that can be purchased off the shelf in a drug store. They must be special ordered through a pharmacy or pharmaceutical organization. Examples include, but are not limited to amino acid supplements, bars such as the Phlexy-10, drink mixes, and other basic low-protein food products.
   - The product must be used under the supervision of a physician or nurse practitioner, or ordered by a registered dietician upon referral by a health care provider authorized to prescribe dietary treatments.

2. Enteral or total parenteral nutrition (TPN) formula for the treatment of PKU is considered **MEDICALLY NECESSARY** for individuals who meet the above criteria.

3. The following are considered NOT medical in nature and therefore **NOT MEDICALLY NECESSARY**:
   - Over-the-counter nutritional items, food and food substitutes
   - Usual and customary infant formulas
   - Formulas containing natural foods that are blenderized and packaged by a manufacturer (e.g., Ensure)
   - Self-blenderized formulas and formula additives, including vitamins, minerals, and fibers taken orally (e.g., by mouth)
   - Food thickeners, baby food, and other regular grocery products (cookies, pizza, ice cream, etc.)
   - Low protein meat and cheese substitutes
   - Banked breast milk
   - Oral rehydration therapy fluid does not serve the same purpose as a food
Clinical Considerations:

- The treatment of PKU is lifelong with a goal of maintaining blood PHE levels in the range of 120-360 umol/l (2-6 mg/dl) in patients of all ages for life.
- Treatment of neonates born with PKU should begin 7-10 days after birth. Implementing a Phe-restricted diet early in life can significantly reduce mental deficiencies associated with PKU.
  Note: Patients treated within the early weeks of life with initial good metabolic control, but who lose that control in later childhood or as an adult, may experience both reversible and irreversible neuropsychiatric consequences.
- Dietary supplementation with large neutral amino acids seems to lower the brain Phe in adults with PKU. In addition, these amino acids assist with the protein requirements needed for adolescents and adults.
- Any combination of therapies (medical foods, Kuvan, sapropterin, etc) that improve a patient’s blood PHE levels is appropriate and should be individualized.
- Reduction of blood PHE, increase in PHE tolerance or improvement in clinical symptoms of PKU are all valid indications to continue a particular therapy.
- Due to an increased risk for neurocognitive and psychological issues, regular mental health monitoring is warranted. A number of screening tests are recommended to identify those in need of further assessment.
- Blood phenylalanine levels should be monitored weekly during periods of rapid growth, fluctuating blood levels, or when food intake is unpredictable. In older children and adults, this monitoring can occur 1-2 times per month. The ideal time for this blood test is 2-3 hours after eating.
- All women with PKU or hyperphenylalaninemia who wish to have children should be strongly encouraged to receive family planning and preconception counseling. Appropriate, medically directed dietary phenylalanine (PHE) restriction, should begin 3 months before conception to normalize blood PHE levels, and nutritional monitoring should continue throughout the pregnancy.

BACKGROUND:

Phenylalanine hydroxylase (PAH) deficiency, which has an estimated prevalence of 1 in 10,000 individuals, is an autosomal recessive heritable disorder characterized by an inability to break down the essential amino acid phenylalanine (Phe). The PAH enzyme is encoded by the PAH gene, which is located on chromosome 12 at band q23.2. PAH is responsible for converting Phe to the amino acid tyrosine. An absence of adequate PAH enzyme activity leads to an accumulation of Phe in the blood, a condition known as hyperphenylalaninemia (HPA). A persistent excess of Phe in circulation negatively affects neurological development. PAH deficiency, which is caused by variants in the PAH gene, may be identified by measuring Phe and tyrosine levels in the blood and excluding other causes of HPA. It is typically classified based on Phe levels and daily Phe tolerance, when on an unrestricted diet. Individuals with a PAH deficiency may be diagnosed with classic phenylketonuria (PKU), moderate PKU, mild PKU, or mild HPA.

Symptoms: Phenylalanine plays a role in the body’s production of melanin, the pigment responsible for skin and hair color. Therefore, infants with the condition often have lighter skin, hair, and eyes than brothers or sisters without the disease. Other symptoms may include:
Clinical & Quality Management

MEDICAL POLICY

- Delayed mental and social skills
- Head size significantly below normal
- Hyperactivity
- Jerking movements of the arms or legs
- Intellectual disability
- Seizures
- Skin rashes (eczema)
- Tremors
- Unusual positioning of hands

If the condition is untreated or foods containing phenylalanine are not avoided, a "mousy" or "musty" odor may be detected on the breath and skin and in urine. The unusual odor is due to a buildup of phenylalanine substances in the body.

In addition, pregnant women with PKU are at risk of having a child with multiple congenital anomalies, as a result of the negative effects of excess Phe on embryonic development. Consequently, classic, moderate, and mild PKU require treatment in the form of a Phe-restricted diet and amino acid supplementation with a Phe-free formula. A subset of patients with a PAH deficiency—most frequently those with mild or moderate PKU and a higher level of residual PAH activity—experience a decrease in plasma Phe levels when treated with therapeutic doses of the PAH cofactor tetrahydrobiopterin (BH4). A BH4 response, which is determined by clinical testing, may allow for a less restrictive or even unrestricted diet. Those who are successfully treated (by diet and/or medication) and maintain a low level of Phe avoid the neurological consequences of PKU. The mildest form of PAH deficiency (e.g., mild HPA; also referred to as non-PKU HPA) is not associated with an increased risk of neurological problems and does not require treatment.

**Diagnosis:** The primary alternative to PAH gene testing is biochemical testing. A diagnosis of PAH deficiency may be established by measuring serum amino acids and excluding other causes of HPA, such as a BH4 deficiency. Furthermore, diagnostic algorithms have been published and outline the steps for follow-up in infants with newborn screening results suggestive of a PAH deficiency. BH4-responsive PKU patients are typically identified using a BH4 loading test, a clinical evaluation that assesses changes in Phe levels after a dose of BH4.

Because PKU can be easily detected with a simple blood test and effectively treated, all 50 states in the United States (and many other countries) have adopted newborn screening for this disorder. As a result, affected individuals may be started on a Phe-restricted diet in the first days of life, minimizing the chance of intellectual disability and other neurological dysfunction.

**Treatment:** Treatment involves a diet that is extremely low in phenylalanine, particularly when the child is growing. The diet must be strictly followed. This means the exclusion from the diet of almost all protein such as vegetables and grains containing protein, as well as milk, eggs and meat, fish, poultry, pasta and baked goods made with wheat flour and milk. The artificial sweetener NutraSweet (aspartame) also contains phenylalanine. Any products containing aspartame should be avoided. This requires close supervision by a registered dietitian or doctor, and cooperation of the parent and child. Those who continue the diet into adulthood have better physical and mental health. “Diet for life” has become the standard recommended by most experts. This is especially important before conception and throughout pregnancy.

A special infant formula called Lofenalac is made for infants with PKU. It can be used throughout life as a
protein source that is extremely low in phenylalanine and balanced for the remaining essential amino acids.

Taking supplements such as fish oil to replace the long chain fatty acids missing from a standard phenylalanine-free diet may help improve neurologic development, including fine motor coordination. Other specific supplements, such as iron or carnitine, may be needed.

If untreated or undertreated, PKU can cause severe mental retardation and other serious health problems.

**Outlook (Prognosis):** The outcome is expected to be very good if the diet is closely followed, starting shortly after the child’s birth. If treatment is delayed or the condition remains untreated, brain damage will occur. School functioning may be mildly impaired.

If proteins containing phenylalanine are not avoided, PKU can lead to intellectual disability by the end of the first year of life.

**Possible Complications:** Severe intellectual disability occurs if the disorder is untreated. ADHD (attention-deficit hyperactivity disorder) appears to be a common problem seen in those who do not stick to a very low-phenylalanine diet.

**Prevention:** An enzyme assay can determine if parents carry the gene for PKU. Chorionic villus sampling can be done during pregnancy to screen the unborn baby for PKU.

It is very important that women with PKU closely follow a strict low-phenylalanine diet both before becoming pregnant and throughout the pregnancy, since build-up of this substance will damage the developing baby even if the child has not inherited the defective gene.

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**REGULATORY STATUS:**

1. **U.S. FOOD AND DRUG ADMINISTRATION (FDA):**
   According to the FDA, medical foods are distinguished from the broader category of foods for special dietary use and from foods that make health claims by the requirement that medical foods be intended to meet distinctive nutritional requirements of a disease or condition, used under medical supervision and intended for the specific dietary management of a disease or condition. The term "medical foods" does not pertain to all foods fed to ill individuals. Medical foods are foods that are specially formulated and processed (as opposed to a naturally occurring foodstuff used in a natural state) for the individual who is seriously ill or who requires the product as a major treatment modality. In general, to be considered a medical food, a product must, at a minimum, meet the following criteria:
   a. The product must be a food for oral or tube feeding, and
   b. The product must be labeled for the dietary management of a specific medical disorder, disease, or condition for which there are distinctive nutritional requirements, and
   c. The product must be used under the supervision of a physician.

2. **CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS):**
   There is no Medicare Coverage Determination addressing treatment of phenylketonuria (PKU).

3. **MINNESOTA DEPARTMENT OF HUMAN SERVICES (DHS):**
   Enteral nutrition is covered for eligible MHCP recipients who need nutritional supplementation because solid food or the nutrients in the food cannot be properly absorbed by the body, for treatment of
phenylketonuria (PKU), hyperlysinemia, maple syrup urine disease (MSUD) or a combined allergy to human milk, cow's milk and soy formula. Enteral nutrition may be covered for recipients with other specific medical conditions. Program HH recipients are eligible for up to $100.00 per month toward enteral nutritional supplements without authorization.

**Oral Nutrition for Recipients with Inborn Errors of Metabolism**

Enteral nutritional products are medically necessary for recipients with many inborn errors of metabolism. Oral enteral nutritional products manufactured for the treatment of PKU, hyperlysinemia or MSUD are covered with authorization for recipients under age one and without authorization for recipients over age one if the recipient has the associated diagnosis.

Oral enteral nutritional products manufactured for the treatment of other inborn errors of metabolism are covered with authorization if the recipient has the associated diagnosis.

Solid food products specially manufactured for treatment of amino-acid transport and metabolism including PKU and MSUD are covered up to $525 per calendar month when obtained from an enrolled medical food supplier.

4. **MANDATED BENEFITS UNDER MINNESOTA LAW:**

   [https://www.revisor.mn.gov/statutes/?id=62A.042](https://www.revisor.mn.gov/statutes/?id=62A.042).

Mandated benefits are health care services that state law requires health plans to cover. Current health insurance benefit mandates in Minnesota law, which apply to private, fully-insured group and nongroup policies, requires benefits for special food for persons born with phenylketonuria (PKU).

**CLINICAL EVIDENCE:**

**SUMMARY:**

Phenylketonuria (PKU) is a genetic condition that prevents the body from metabolizing protein foods properly. Treatment consists primarily of restriction of the dietary intake of Phenylalanine, an essential amino acid present in most proteins. This means the exclusion from the diet of almost all protein such as vegetables and grains containing protein, as well as milk, eggs and meat, fish, poultry, pasta and baked goods made with wheat flour and milk. The outcome is expected to be very good if the diet is closely followed, starting shortly after the child's birth. If treatment is delayed or the condition remains untreated, brain damage will occur. School functioning may be mildly impaired. If proteins containing phenylalanine are not avoided, PKU can lead to intellectual disability by the end of the first year of life.

**APPLICABLE CODES:**

*The Current Procedural Terminology (CPT®) codes and HCPCS 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 health service. The inclusion of a code does not imply any right to reimbursement or guarantee claims payment. Other medical policies and coverage determination guidelines may apply.*
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<tr>
<td>S9433</td>
<td>Medical food nutritionally complete, administered orally, providing 100% of nutritional intake</td>
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<tr>
<td>S9434</td>
<td>Modified solid food supplements for inborn errors of metabolism</td>
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### ICD-9 Codes

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### CPT® Codes

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