Medical Foods for Inborn Errors of Metabolism

I. Description

Inborn errors of metabolism are genetic disorders that are characterized by deficient metabolism (breakdown) of protein, carbohydrate or fat. These defects may be congenital or manifest shortly after birth, resulting in the build-up of toxic chemicals in the body, causing severe malnutrition, nerve damage, mental retardation or death. In the past 50 years, more than 500 types of inborn errors of metabolism have been identified in the world; however, fewer than 200 cases have been described in detail. Because they share common biochemical features, many of the disorders have been grouped together, even though each condition is unique in its diagnostic criteria and methods of treatment. A standardized therapeutic diet is highly unusual. Each case is usually supervised by specially trained nutritionists.

A medical food is a food that is formulated to be consumed or administered enterally under the supervision of a physician and intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by a medical evaluation.

II. Criteria/Guidelines

A. Medical foods, formulas and low-protein modified food products are covered (subject to Limitations and Administrative Guidelines) only when they are prescribed by a physician for the therapeutic treatment of diagnosed inborn errors of metabolism. Examples of inborn errors of metabolism are:

1. Phenylketonuria (PKU)
2. Tyrosinemia type I and type II
3. Homocystinuria
4. Maple syrup urine disease (MSUD)
5. Propionic acidemia
6. Methylmalonic academia
III. Limitations
The following are not covered:
A. Over-the-counter nutritional products.
B. Special medical formulas/formulations or nonprescription enteral formulas that do not require tube feeding for conditions other than inborn errors of metabolism, (e.g., malabsorption syndromes, celiac disease, food allergies or lactose intolerance).
C. Blended baby food or regular store-bought food products for use with an enteral feeding system.
D. Prescription foods when store-bought food products meet the nutritional needs of the patient (e.g., ketogenic diet which uses regularly available foods).
E. Treatment of conditions or services that are not supported or established by current medical evaluation and scientific literature.

IV. Administrative Guidelines
Precertification is not required. Documentation supporting the medical necessity should be legible, maintained in the patient's medical record and must be made available to HMSA upon request. HMSA reserves the right to perform retrospective review using the above criteria to validate if services rendered met payment determination criteria.
1. A confirmed diagnosis (by clinical and laboratory tests) of the inborn error of metabolism.
2. A medical and nutritional treatment plan for the inborn error of metabolism, including information about the type and amount of medical foods required, as well as information about the expected duration of treatment.

V. Scientific Background
Phenylketonuria (PKU)
Phenylketonuria is an inherited metabolic disease usually caused by a defect in the enzyme phenylalanine hydroxylase, which converts the essential amino acid phenylalanine to another amino acid, tyrosine. Failure of the conversion results in a buildup of phenylalanine in the blood and body tissues which is toxic to the central nervous system. Parents are healthy "carriers", but have a one in four (25 percent) chance for an affected child with each pregnancy. The individual with PKU lacks an enzyme to properly convert the amino acid phenylalanine to tyrosine.

Untreated individuals with PKU may have behavior disorders, musty odor, eczema, seizures and severe mental retardation. Screening criteria include a serum phenylalanine assay after 24 hours after breast or formula feeding. Infants confirmed to have elevated phenylalanine levels of 4 mg/100 dL or greater will need a diagnostic work-up.

Phenylketonuria treatment guidelines:
A. Therapy should begin within three weeks after birth.
B. Infants with blood phenylalanine levels over 10 mg/dL measured while eating a normal protein diet (two to three grams protein/kg/day), and in whom other amino acids levels, such as tyrosine, are low or normal.
C. The PKU formula should be enriched with tyrosine, and provide two to three grams protein/kg/day. It should be taken as evenly as possible throughout the day.
D. 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 one to two times per month. The ideal time for this blood test is two hours after eating.

E. Diet, including special formula intake, is modified to achieve optimal blood levels.

F. Optimal blood phenylalanine levels:
   1. Younger than 10 years old - 2-6 mg/dL
   2. Older than 10 years old - 2-10 mg/dL
   3. Women trying to conceive - 2-6 mg/dL
   4. Pregnant women - 2-6 mg/dL

G. Women who wish to have children should optimize their levels two to three months before conception, and continue close nutritional monitoring during pregnancy.

Tyrosinemia
Type I tyrosinemia is a severe neonatal disorder resulting in an accumulation of tyrosine and phenylalanine from fumarylacetoacetate hydroxylase deficiency. Clinical features of type 1 tyrosinemia include failure to thrive, hepatomegaly, rickets, thrombocytopenia and hepatocellular damage leading to cirrhosis and liver failure.

Type 2 tyrosinemia may present with corneal ulceration and unusual red, discrete raised hyperkeratotic pustules on the palms and soles, mental retardation.

Diagnosis is aided by detection of elevated serum tyrosine levels of greater than 4 mg/dL and a metabolite, succinylacetone, in the urine. Individuals with tyrosinemia respond rapidly to a tyrosine-restricted diet.

Homocystinuria
Homocystinuria is a metabolic disorder caused by a deficiency of the enzyme cystathionine B synthase that is needed for homocystine metabolism, resulting in an accumulation of methionine, homocysteine and various metabolites of homocystine.

Clinical manifestations vary in degree, type and age of onset. They include thromboembolism, seizures, behavior disorders, dislocation of the optic lens, osteoporosis, tall and lanky stature, psychiatric disturbances and mental retardation. Diagnosis is aided by the detection of elevated methionine greater than 2 mg/100 dL.

Homocystinuria may be treated with a methionine restricted diet with cystine supplementation. Vitamin pyridoxine (B6) supplement is given if responsive.

Maple Syrup Urine Disease (MSUD)
Inherited metabolic disorder associated with an absent or low activity of the enzyme needed to metabolize the three branched chain amino acids, leucine, isoleucine and valine found in all natural protein. These amino acids accumulate in the blood causing toxic effects that interfere with brain functions.

The earliest symptoms of MSUD are usually observed in the first few days of life with an increase of plasma leucine, ketoacids and a characteristic sweet maple syrup odor in the urine, poor appetite and irritability. Affected infants gradually lose their sucking reflex, have a high-pitched cry, become
listless and limp with episodes of rigidity. Without diagnosis and treatment, symptoms progress to seizures, coma and death usually by two to four weeks of age.

MSUD in newborn should be tested within 24 hours of birth and the test results available by two to three days of age. Diagnosis is aided by the detection of elevated leucine of greater than 4 mg/100dL.

Treatment of MSUD is complex and death can occur rapidly. A strict diet low in leucine, isoleucine and valine must be continued for life. Thiamine supplement is given if responsive.

**Propionic Acidemia**
Inherited disorder of branch-chain amino acid metabolism characterized by the build-up of propionic acid resulting in episodes of vomiting, dehydration and severe metabolic acidosis. Onset within the first few weeks of life with recurrent episodes triggered by recurrent infections, constipation, and/or a high-protein diet.

Clinical features include apneas, hypoglycemia, poor feeding, vomiting, infantile hypotonia, lethargy, frequent infections, transient purpura, neonatal seizures, mental retardation, coma and death. The diagnosis is aided by elevated serum glycine, propionic and methylcitric acids, and urinary ketoacids.

Treatment includes a diet restricted in protein (1 to 1.5 g/kg/day) consisting of 50 percent to 75 percent natural protein to prevent deficiency of essential amino acids and chronic alkaline therapy to correct acidosis.

**Methylmalonic Acidemia**
Methylmalonic acidemia is an inherited disease resulting in a deficiency in the metabolism of an amino acid, causing severe acidosis and ketosis. Infection or high protein intake may precede episodes of acidosis. Untreated acidosis progresses to coma and can be fatal.

Symptoms include failure to thrive, irritability, restlessness, decreased muscle tone (hypotonia) and delayed development. Physical examination and laboratory testing show signs of acidosis, ketosis and elevated serum ammonia, methylmalonic acid levels. Enzyme assay in cultured amniotic cells shows methylmalonyl CoA mutase activity.

Treatment includes long-term administration of alkalinizing agents to prevent episodes of acidosis. Large doses of vitamin B-12 may be given during acute attacks. A low-protein diet must be maintained and the patient should be careful to avoid infection to reduce recurrent attacks of acidosis.

**Urea Cycle Disorder**
Genetic disorder caused by a deficiency of one of the enzymes responsible for removing ammonia from the blood stream. Nitrogen, a waste product of protein metabolism, is converted to urea, which is usually excreted in the urine. In urea cycle disorders, the nitrogen accumulates in the form of ammonia, which is highly toxic and causes brain damage and death.

Symptoms during the neonatal period in severe patients occur within the first 24 hours of life and include irritability, vomiting, increasing lethargy, seizures, hypotonia (poor muscle tone), respiratory distress and coma. In childhood, symptoms include hyperactive behavior, screaming, self-inflicting behavior, refusal to eat meat or other high-protein foods, vomiting, lethargy, delirium and
coma. Adults exhibit stroke-like symptoms, episodes of lethargy and delirium. Children and adults with these symptoms are likely to be referred to neurologists or psychiatrists. If the condition is undiagnosed and untreated, the prognosis is permanent brain damage, coma and death.

Treatment consists of balancing dietary protein intake in conduction with medications, essential amino acid therapy, multiple vitamins and calcium supplements. Frequent blood tests are required to monitor and control the disorders.

Urea cycle disorders include ornithine transcarbamylase deficiency, citrullinemia, argininemia, argininosuccinate aciduria, carbamylphosphate synthetase deficiency, N-acetylglutamate synthetase deficiency.

**Other Inborn Errors of Metabolism**

Other inborn errors of metabolism which require treatment with low protein modified food and/or medical foods products include (but not limited to) the following:

A. Alcaptonuria
B. Beta ketothialase deficiency
C. Glutaric acidemia
D. Glycogen storage diseases
E. Gyrate atrophy
F. Hypermethionemia
G. 3-Hydroxyisobutyric aciduria
H. Isovaleric acidemia
I. Mitochondrial fatty acid oxidation defects
J. Pyruvate dehydrogenase complex deficiency
K. Pyruvate carboxylase deficiency

**VI. Important Reminder**

The purpose of this Medical Policy is to provide a guide to coverage. This Medical Policy is not intended to dictate to providers how to practice medicine. Nothing in this Medical Policy is intended to discourage or prohibit providing other medical advice or treatment deemed appropriate by the treating physician.

Benefit determinations are subject to applicable member contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

**VII. References**