Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 1/1/25**
(See policy history boxes for previous effective dates)

Title: Medical Formula for Inborn Errors of Metabolism

Description/Background

Inborn errors of metabolism (IEM) are a large group of rare, inherited biochemical disorders. The broadest definition of inborn errors of metabolism describes endogenous processes, such as biosynthesis, as well as the exogenous process of ineffective metabolism of food substances. The focus of this policy is medical treatment of individuals who are unable to metabolize typical food sources.

Most metabolic disorders are caused by the absence or deficiency of an enzyme, its cofactor or its transport protein which are essential in the metabolism of protein, carbohydrate or fatty acid. This disruption may lead to an accumulation of metabolites preceding the interrupted step, or the inability to make certain intermediates or end products of a specific metabolic pathway. The majority of these disorders are inherited as autosomal recessive, although there are some which are autosomal dominant or X-linked.[1]

Individual inborn errors of metabolism are rare disorders, most are found in fewer than 1 in 100,000 births. Collectively, the incidence of inborn errors of metabolism may approach 1 in 800 to 1 in 2,500 births. However, incidence rates vary among ethnicities, populations and geography. Some of the major classes of inborn errors of metabolism include disorders of amino acid metabolism, urea cycle disorders, disorders of fatty acid oxidation, disorders of carbohydrate metabolism, disorders of organic acid metabolism, etc.[1,2]

Phenylketonuria (PKU) and medium-chain acyl-CoA dehydrogenase (MCAD) are the most prevalent inborn error of metabolism conditions in the U.S. As an example of the complexity of these conditions, ACOG states that more than 600 variants of the PAH gene, responsible for PKU, have been described. Furthermore, new IEM conditions continue to be identified when research of rare conditions finds IEM to be the causative process.[1,3]

An inborn error of metabolism has an individualized expression, with a spectrum of severity that is dependent both on the defect and the individual's response to the resulting deficiency. These metabolic disturbances can lead to a host of medical and developmental consequences ranging from gastrointestinal or neurologic findings to intellectual disability, severe cognitive impairment and even death. Early identification and initiation of treatment may mitigate or prevent many of the adverse outcomes.[1,3]

Treatment
For many inborn errors of metabolism, treatment strategies rely on exclusion or restriction of foods that contain the offending substance. As an adjunct to restriction, there is also a need to substitute food that is specially formulated to provide none, or negligible amounts, of the offending substance. Complex dietary calculations by experienced dieticians are necessary to balance the nutrition needs for healthy growth and development. Additionally, single amino acids, amino acid mixtures, vitamins and other compounds may be necessary to replace essential nutrients or enhance enzyme activity.

Medical Foods – Medical Formulas
A medical food is formulated to be consumed under the supervision of a physician. A medical food is intended for the specific dietary management of a disease or condition which has distinctive nutritional requirements that are based on a medical evaluation. These food items are not generally available at retail stores. Medical foods include metabolic formulas, also called medical formulas (liquids), as well as solid foods that are specially formulated and processed. Medical formulas contain nutrients required for growth and development that are modified to exclude the offending nutrient. The formulas are either powdered and reconstituted with water or juice, or they may be liquid products that are ready to consume. The medical formulas are part of the diet for a lifetime. Inborn errors of metabolism that require medical formulas include disorders of amino acid, organic acid or fatty acid metabolism.[4,5]

Novel drug therapies for inborn errors of metabolism are limited. Alfadhel et al (2013) identified 83 medications used in various inborn errors of metabolism.[6] These include medications used in the treatment of lysosomal storage disorders, disorders of organic acids and amino acid metabolism or transport, and vitamins and co-factors used in the treatment of inborn errors of metabolism.[7] The FDA relaxed their role in the approval of new drugs used for the treatment of specific inborn errors of metabolism and considers them as orphan drugs, to be prescribed under compassionate use.[8]

Regulatory Status

The U.S. Food and Drug Administration defined a medical food in the 1988 amendment to the Orphan Drug Act of 1983 as "a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation." Medical foods are distinguished from the broader category of foods for special dietary use 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.

In 2007 the FDA approved 2007 Kuvan® (sapropterin dihydrochloride) (BioMarin Corporation, Tiburon, CA), a synthetic form of the naturally occurring cofactor tetrahydrobiopterin (BH4), to reduce blood Phe levels in patients 4 years of age and older who have tetrahydrobiopterin-responsive PKU. On April 23, 2014, Kuvan® was approved for use in patients 1 month to 4 years of age. A trial of the drug is required to determine if the patient is responsive.[7]

On May 24, 2018 BioMarin received standard approval from the FDA for Palynziq™ (pegvaliase-pqpz) Injection. Palynziq reduces Phe levels in adult patients who have Phe blood concentrations greater than 600 micromol/L on existing management. Palynziq is a PEGylated recombinant phenylalanine ammonia lyase enzyme, and is the first approved enzyme substitution therapy to target the underlying cause of PKU.[8]

Medical Policy Statement

The safety and effectiveness of oral medical formula for individuals with inborn errors of metabolism have been established. Oral medical formula is considered an established treatment option when policy criteria are met.

Inclusionary and Exclusionary Guidelines

Inclusions:
Oral medical formula (metabolic formula for consumption by mouth), for individuals of any age, is considered established when all of the following are met:

- The individual has a diagnosis of an inborn error of metabolism (IEM)* that requires oral medical formula; OR
  The individual has an inherited condition that is proven to be treated by oral medical formula; AND,
- The oral medical formula is labeled and used for nutritional management of an inborn error of metabolism that interferes with the metabolism of specific nutrients (eg, Phenylketonuria, Homocystinuria, Maple Syrup Urine Disease, etc.); AND,
- The oral medical formula nutrition is ordered by a clinical or medical biochemical geneticist or by other qualified medical professionals in consultation with a clinical or medical biochemical geneticist

*See Appendix A for a list of inborn errors of metabolism

Exclusions:

- Formula for any condition **other than** an inborn error of metabolism (eg, diabetes, hypercholesterolemia, etc.)
- Formula not specifically used for the nutrition of an individual with an inborn error of metabolism
- Medical food product that is not formula (eg, food modified to be low in protein [meat or cheese substitutes, pasta, etc.])
- Nutrition by tube feeding (refer to the Enteral Nutrition policy for guidelines)

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

B4157 B4162

Other codes (investigational, not medically necessary, etc.):

NA

Note: Code(s) B4157, B4162 may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage. Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

Phenylketonuria is the most prevalent IEM, and as such is the most researched. Initiation of treatment for PKU should begin within the first week of life with a goal of serum phenylalanine (Phe) in the treatment range within the first 2 weeks of life. The initial Phe level determines whether there is complete exclusion of Phe until levels approach treatment range.[3]

Dietary therapy involving the restriction of Phe and supplementation with Phe-free amino acid formulas is effective in preventing severe mental retardation associated with untreated classical PAH deficiency. Over time, subtle intellectual and neuropsychiatric issues may manifest even with treatment. In addition, patients treated from the early weeks of life with initial good metabolic control but who lose that control in later childhood or adult life may experience both reversible and irreversible neuropsychiatric consequences.[3]

Koch et al (2012) reported on a follow-up study to 211 children diagnosed with PKU, who were originally followed from 1967 to 1983.[9] In 1998, 70 of the original subjects were located. Only 9 remained on the diet. The adults who had stopped the diet reported more problems than those who remained on the diet; and, problems were more common among those who stopped the diet before 6 1/2 years of age. The most notable symptoms include a higher incidence of eczema among those off the diet (28% vs. 11% on-diet); hyperactivity (14% vs. none on-diet); lethargy and lack of energy (19% versus none on- diet); recurrent headaches (31% vs. none on-diet); and neurological signs (24% versus none on-diet) which were mainly increased or decreased muscle tone and deep tendon reflex changes. A variety of mental disorders including phobias, panic attacks, and depression afflicted 41% of those off-diet. Only 2 in the on-diet group reported transient depression not requiring psychiatric care. A large percent (54%) of the off-diet group had a variety of other problems not reported by the on-diet group. Of 16 adults with classical PKU who resumed diet treatment, 9 were still taking the medical food and showed an increase in adult IQ compared to childhood. In contrast, 7 who did not continue the diet experienced a drop in adult IQ compared to childhood. Interestingly, individuals with classical PKU currently taking the medical food had significantly higher adult IQ scores than those on a regular diet, even when the blood Phe levels were far from optimal. Twenty-two adults were selected for a pilot substudy of Magnetic Resonance Imaging (MRI).

Ten adults were on the diet from infancy until at least age 10 (7 had never discontinued) and were currently taking the medical food as their primary source of protein. Twelve adults stopped the diet by age 10 years. A MRI scoring system of 1 to 3 was used. Zero indicates completely normal, where 3 indicates abnormalities of 3 regions of the brain. Seven adults in the on-diet group had a code 0 or 1 (70%) compared to only 6 in the off-diet group (56%). Patients with MRI code 0 or 1 had significantly lower brain Phe concentrations than those with codes 2 or 3.

SUPPLEMENTAL INFORMATION

National Institutes of Health Consensus Development Conference Statement: Phenylketonuria: Screening and Management, October 16–18, 2000
National Institutes of Health Consensus Development Panel[10]
Conclusions:

> "…Metabolic control is necessary across the lifespan of individuals with PKU … Uniform policies must be established to remove financial barriers to the acquisition of medical foods and modified low-protein foods and to provide access to support services needed to maintain metabolic control in individuals with PKU. Research on nondietary alternative treatments for PKU is strongly encouraged …"

American College of Medical Genetic and Genomics (ACGM) and Genetic Metabolic Dietician's International (GMDI), Medical and Dietary Guidelines for the Treatment of PKU, 2014[11]

> "The treatment of PKU should be initiated as early as possible. Treatment 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."
>
> "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."

The American College of Obstetricians and Gynecologists Committee Opinion Number 802 (Replaces Committee Opinion No. 363, June 2015), April 2020; Management of Women with Phenylalanine Hydroxylase Deficiency (Phenylketonuria)[12]

- Lifelong dietary restriction and therapy improve quality of life in patients with phenylalanine hydroxylase (PAH) deficiency and should be encouraged …
- It is recommended that phenylalanine levels less than 6 mg/dL be achieved for at least 3 months before conception and maintained at 2-6 mg/dL during pregnancy.

Government Regulations

National:

There is no NCD related to inborn errors of metabolism or metabolic formula.

Local:

There is no LCD related to inborn errors of metabolism or metabolic formula.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Enteral Nutrition
Metabolic Foods (Blue Cross Blue Shield of Michigan Policy)
Elemental Formula

References

1. Sutton, VR. Inborn errors of metabolism: Epidemiology, pathogenesis, and clinical features. UpToDate, Last Updated July 2024. https://www.uptodate.com/contents/inborn-errors-of-metabolism-epidemiology-pathogenesis-and-clinical-features Accessed 8/7/24.
2. Advisory Committee on Heritable Disorders in Newborns and Children, Recommended Uniform Screening Panel, 2016.
3. Vockley J et al. Phenylalanine hydroxylase deficiency: diagnosis and management guideline, ACMG Practice Guidelines. Genetics in Medicine. August 2013.
4. Camp KM et al. Nutritional Treatment for Inborn Errors of Metabolism: Indications, Regulations, and Availability of Medical Foods and Dietary Supplements Using Phenylketonuria as an Example, Mol Genet Metab. 2012 Sep; 107(1-2): 3-9. PMID: 22854513.
5. Camp KM et al. Expanding research to provide an evidence base for nutritional interventions for the management of inborn errors of metabolism, Mol Genet Metab. 2013 Aug; 109(4):319-328. PMID: 23806236.
6. Alfadhel, M et al, Drug Treatment of inborn errors of metabolism: a systematic review. Archives of Disease in Childhood, 98(6), 454-461.
7. Kuvan® (sapropterin dihydrochloride) prescribing information. BioMarin Pharmaceutical, Novato, CA. Revised November 2019. FDA label (fda.gov) Accessed 8/7/24
8. U.S. Food and Drug Administration, Medical Foods Guidance Documents & Regulatory Information 5/24/2018. FDA approves a new treatment for PKU, a rare and serious genetic disease | FDA Accessed 8/7/24
9. Koch R, et al. Phenylketonuria in adulthood: A collaborative study, J Inherit Metab Dis (2002) 25: 333-346 https://doi.org/10.1023/A:1020158631102 Phenylketonuria in adulthood: A collaborative study - Koch - 2002 - Journal of Inherited Metabolic Disease - Wiley Online Library Accessed 8/7/24.

10. National Institutes of Health Consensus Development Conference Statement: Phenylketonuria: Screening and Management, October 16–18, 2000, National Institutes of Health Consensus Development Panel. National Institutes of Health Consensus Development Conference Statement: Phenylketonuria: Screening and Management, October 16–18, 2000 | Pediatrics | American Academy of Pediatrics (aap.org) Accessed 8/7/24
11. American College of Medical Genetics and Genomics (ACMG) and Genetic Metabolic Dietician's International (GMDI), Medical and Dietary Guidelines for the Treatment of PKU, 2014. Phenylalanine hydroxylase deficiency: diagnosis and management guideline (acmg.net) Accessed 8/7/24
12. American College of Obstetricians and Gynecologists, Committee Opinion No. 802 (Replaces Committee Opinion No. 636, June 2015), Management of women with phynylalanine hydroxylase deficiency (Phenylketonuria). Obstet Gynecol 2015;125:1548-50.2020 https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2020/04/management-of-women-with-phenylalanine-hydroxylase-deficiency-phenylketonuria Accessed 8/7/24.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 8/7/24, the date the research was completed.

Appendix A
ICD-10-CM Codes – Inborn Errors of Metabolism
(Codes are listed only to the Subcategory level)

Note: Not all Inborn Errors of Metabolism require medical formula supplementation. Most disorders that require medical formula are found in categories E70, E71, E72; rarely, a disorder that requires medical formula may be found in a category not listed in this appendix. All medical policy criteria must be met.

E70 Disorders of aromatic amino-acid metabolism
E70.0 Classical phenylketonuria
E70.1 Other hyperphenylalaninemias
E70.2 Disorders of tyrosine metabolism
Includes codes E70.20 – E70.29
E70.3 Albinism
Includes codes E70.30 – E70.39
E70.4 Disorders of histidine metabolism
E70.5 Disorders of tryptophan metabolism
E70.8 Other disorders of aromatic amino-acid metabolism
E70.9 Disorder of aromatic amino-acid metabolism, unspecified
E71 Disorders of branched-chain amino-acid metabolism and fatty-acid metabolism
E71.0 Maple-syrup-urine disease
E71.1 Other disorders of branched-chain amino-acid metabolism
Includes codes E71.11 – E71.19
E71.2 Disorder of branched-chain amino-acid metabolism, unspecified
E71.3 Disorders of fatty-acid metabolism
Includes codes E71.30 – E71.39
E71.4 Disorders of carnitine metabolism
Includes codes E71.40 – E71.44
E71.5 Peroxisomal disorders
Includes codes E71.50 – E71.54
E72 Other disorders of amino-acid metabolism
E72.0 Disorders of amino-acid transport
Includes codes E72.00 – E72.09
E72.1 Disorders of sulfur-bearing amino-acid metabolism
Includes codes E72.10 – E72.19
E72.2 Disorders of urea cycle metabolism
Includes codes E72.20 – E72.29
E72.3 Disorders of lysine and hydroxylysine metabolism
E72.4 Disorders of ornithine metabolism
E72.5 Disorders of glycine metabolism
Includes codes E72.50 – E72.59
E72.8 Other specified disorders of amino-acid metabolism
Includes codes E72.80 – E72.89
E72.9 Disorder of amino-acid metabolism, unspecified

Appendix B

As of this policy creation, October 2018, the following ICD-10-CM Categories under Metabolic Disorders do NOT require medical formula.
Therefore, codes are listed only to Category level.

E73 Lactose intolerance
E74 Other disorders of carbohydrate metabolism
E75 Disorders of sphingolipid metabolism and other lipid storage disorders
E76 Disorders of glycosaminoglycan metabolism
E77 Disorders of glycoprotein metabolism
E78 Disorders of lipoprotein metabolism and other lipidemias
E79 Disorders of purine and pyrimidine metabolism
E80 Disorders of porphyrin and bilirubin metabolism
E83 Disorders of mineral metabolism
E84 Cystic fibrosis
E85 Amyloidosis
E86 Volume depletion
E87 Other disorders of fluid, electrolyte and acid-base balance
E88 Other and unspecified metabolic disorders

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
1/1/19	1/10/19		Joint policy established
1/1/20	10/15/19		Routine maintenance
1/1/21	10/20/20		Routine maintenance References re-formatted
1/1/22	10/19/21		Routine maintenance
1/1/23	10/18/22		Routine maintenance (ls) Edits to inclusions/exclusions
1/1/24	10/17/23		Routine maintenance (jf) Vendor Managed: NA Added: Ref 7
1/1/25	10/15/24		Routine maintenance (jf) Vendor Managed: NA

Next Review Date: 4th Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: MEDICAL FORMULA FOR INBORN ERRORS OF METABOLISM

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered, medical policy criteria apply.
BCNA (Medicare Advantage)	See Government Regulations section.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.