Abbott

Information for the U.S. products. Please refer to the Canadian product label for the list of ingredients and nutritional information for products available in Canada.

METABOLIC BACKGROUNDER

Abbott Metabolic Formulas for Meeting Special Nutrition Needs

Abbott Metabolic Formulas

21 products to meet a wide range of nutrition needs in more than 40 inborn errors of metabolism.

Phenylketonuria

Maple Syrup Urine Disease

Urea Cycle Disorders

Propionic and Methylmalonic Acidemia

Glutaric Aciduria Type I

Tyrosinemia

Disorders of Leucine Metabolism

Homocystinuria

Dietary Modification of Protein

Hypercalcemia

Dietary Modification of Carbohydrate and Fat

Ketogenic Diet Management Carbohydrate Disorders

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Introduction to Metabolics

Many hereditary biochemical disorders, called inborn errors of metabolism or inherited metabolic disorders, have been discovered over the past 60 years. Approximately 3,000 inborn errors of metabolism are known, and although individually they are rare, since newborn screening started, the incidence is estimated to be greater than 1 in 3,000 births.

Metabolic disorders may affect the function of any tissue in the body and may present at any age—from infancy to adulthood.

Screening for inborn errors of metabolism has expanded greatly since the first newborn screening for phenylketonuria in the 1960s. Tandem mass spectrometry (MS/MS) is now being used in most states in the US and in developed countries as this technology increases the number of metabolic disorders that can be detected from a single dried-blood spot sample. Current newborn screening (NBS) conditions in the United States are published by the National Newborn Screening and Genetics Resource Center (available at http://genes-r-us.uthscsa.edu).

Early identification of selected inborn errors will lead to a significant reduction in morbidity, mortality, and associated disabilities in affected individuals. Nutrition therapy, including the use of medical foods, is frequently the only treatment available. Proper nutrition management is essential in these disorders amenable to diet treatment and may prevent mental handicap and, possibly, death.

Abbott Metabolic Formulas (AMF) Product Information

OVERALL DESCRIPTION OF AMF MEDICAL FOODS

The formulation and nutrient composition of AMF medical foods are based on clinical research findings and recognized nutrient needs for growth and maintenance of nutrition status of infants, toddlers, children and adults.

The AMF medical foods are complete foods except for the removal or modification of disease-specific nutrients. The medical foods are intended for two broad age groups: infant/toddler and child/adult. The amino acid-modified medical foods for each age group contain a different base powder that provides carbohydrate, fat, minerals, and vitamins. The appropriate base powder is blended with specific free L-amino acids. The amount of amino acids added or removed depends on the metabolic disorder and the age of the intended patient. The base powders for the infant/toddler products and the child/adult products differ to meet the specific nutrient requirements for each age group. Therefore, they contain age-appropriate amounts of minerals and vitamins. The total amount of protein equivalents (amino acids) added is designed to meet the needs of the two broad age groups.

When used as directed, these medical foods provide adequate amounts of all nutrients essential for growth, and meet or exceed current Dietary Reference Intakes (DRIs) for minerals and vitamins.

All Abbott Metabolic Formulas medical foods must be used under medical supervision.

Infants, children, and adults dependent on medical foods to meet the majority of their nutrient requirements must be closely supervised and frequently monitored to ensure the adequacy of the prescribed diet. Frequent monitoring is especially important during infancy and early

childhood because of the child's rapid growth and changing nutrient needs. Monitoring provides both the clinician and the family with valuable information on the adequacy of the diet prescription, diet compliance, and the effectiveness of the treatment plan.

The base powders used in all the medical foods contain carbohydrate (hydrolyzed cornstarch), fat (high-oleic safflower, coconut, and soy oil, DHA and ARA in level 1, and DHA only in level 2 medical foods), minerals, and vitamins. Cyclinex®-1 and Cyclinex®-2 contain a slightly different nutrient profile from other medical foods in the -1 (infant/toddler) and -2 (child/adult) groups because of the reduced amounts of amino acids added. Pro-Phree®, which is the base powder used in the infant/toddler medical foods, is sold separately.

FAT

AMF medical foods contain more fat than many competitive products. Fat is important to supply energy requirements and to decrease the osmolality of the medical food. A decreased osmolality may help improve patient tolerance of the medical food. AMF medical foods are all formulated with essential fatty acids including linoleic acid (C18:2n-6), alpha-linolenic acid (C18:3n-3), docosahexaenoic acid (DHA), and arachidonic acid (ARA). Linolenic acid (C18:3n-3) is present at 0.7% of energy. Medical foods fed with adequate amounts of normal infant formula or breast milk supply required linoleic and linolenic acids.

DHA AND ARA

Docosahexaenoic acid (DHA) and arachidonic acid (ARA) are two fatty acids that are important for mental and visual development in infants. They can be obtained directly from the diet or made naturally by the baby from two precursor essential fatty acids—alpha linolenic acid (precursor of DHA) and linoleic acid (precursor of ARA). DHA and ARA function as nutritional building blocks in brain and eye development, which occurs most rapidly during the first two years of life. DHA and ARA have been added to the level 1 AMF medical foods. Those with inborn errors of metabolism are unable to have high protein foods, such as fish (which is a main source), so they are at risk for low DHA intake. DHA has been added to all level 2 AMF medical foods.

CARNITINE

Carnitine deficiency has been found in children with inborn errors of metabolism. Carnitine has several functions in the body, the most important of which is helping the body utilize fat for energy. AMF medical foods are either supplemented or fortified with carnitine, depending on the specific disorder. Carnitine fortification is important for individuals with glutaric aciduria type I, isovaleric acidemia, propionic acidemia, and methylmalonic acidemia. Plasma carnitine is abnormally low in these conditions because it binds with the toxic compounds formed in these disorders and is excreted in the urine. Fortification may eliminate the need for separate carnitine administration and helps prevent deficiency. The major sources of carnitine in normal diets are human milk, infant formulas, and foods of animal origin. Because patients with metabolic disorders consume only limited amounts of infant formula and animal protein, the major source of dietary carnitine is supplied by AMF medical foods.

TAURINE

Taurine, a nutrient found in human milk and foods of animal origin, is supplemented in AMF medical foods at a concentration of 50 mg/100 g in Pro-Phree, 40 mg/100 g in all level 1 metabolic products. Cyclinex®-2 contains 140 mg/100 g powder, while the remainder of the child/adult medical foods contain 125 mg/100 g powder. Most individuals with a metabolic disorder must restrict the amount of animal protein in their diet. Consequently, they would receive limited taurine in their diet. AMF medical foods are the primary sources of daily taurine.

MINERALS

Calcium, phosphorus, and zinc are added to the

AMF in amounts that should supply nutrient needs consistent with the current DRIs. These nutrients have many functions, but are most recognized for enhancing bone development. The major source of calcium in normal diets is dairy products; the major source of phosphorus and zinc is meat products. Because dairy products and animal proteins are fed in small, prescribed amounts, AMF medical foods become the major source of calcium, phosphorus, and zinc in the diets of patients with inborn errors of metabolism.

Infants and children with phenylketonuria (PKU) have increased iron requirements to maintain normal iron status. Iron is supplemented in all AMF medical foods to help prevent deficiency and meet increased needs. Increased needs may be related to poor bioavailability of iron and frequent blood draws to monitor the patient.

Selenium deficiency has been reported internationally in children with metabolic disorders who consume medical foods with no added selenium. The limited amounts of intact protein prescribed in the nutrition support of patients with metabolic disorders provides minimal amounts of selenium. AMF medical foods are supplemented with selenium in amounts consistent with current DRIs to help prevent deficiencies. Chromium and molybdenum are also added to AMF medical foods to prevent deficiencies.

TABLE 1: AMF PRODUCT GUIDE USE

PRODUCT	PRODUCT CODE	PRODUCT DESCRIPTION
INFANT/TODDLER PRODUCTS		
Cyclinex®-1	67032	Amino Acid-Modified Medical Food With Iron • Nonessential amino acid-free • For nutrition support of infants and toddlers with a urea cycle disorder, gyrate atrophy, or HHH syndrome.
Glutarex®-1	67036	Amino Acid-Modified Medical Food With Iron • Lysine- and tryptophan-free. • For nutrition support of infants and toddlers with glutaric aciduria type I.
Hominex®-1	67040	Amino Acid-Modified Medical Food With Iron • Methionine-free. • For nutrition support of infants and toddlers with vitamin B_6-nonresponsive homocystinuria or hypermethioninemia.
I-Valex®-1	67044	Amino Acid-Modified Medical Food With Iron • Leucine-free. • For nutrition support of infants and toddlers with a disorder of leucine catabolism.
Ketonex®-1	67048	Amino Acid-Modified Medical Food With Iron • Isoleucine-, leucine-, and valine-free. • For nutrition support of infants and toddlers with maple syrup urine disease.
Phenex™-1	67052	Amino Acid-Modified Medical Food With Iron • Phenylalanine-free. • For nutrition support of infants and toddlers with phenylketonuria or hyperphenylalaninemia.
Propimex®-1	67058	Amino Acid-Modified Medical Food With Iron • Methionine- and valine-free. • Low in isoleucine and threonine. • For nutrition support of infants and toddlers with propionic or methylmalonic acidemia.
Tyrex®-1	67062	Amino Acid-Modified Medical Food With Iron • Phenylalanine- and tyrosine-free. • For nutrition support of infants and toddlers with tyrosinemias type I, II, or III.

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PRODUCT	PRODUCT CODE	PRODUCT DESCRIPTION
CHILD/ADULT		
Cyclinex®-2	67034	Amino Acid-Modified Medical Food • Nonessential amino acid-free. • For nutrition support of children and adults with a urea cycle disorder, gyrate atrophy, or HHH syndrome.
Glutarex®-2	67038	Amino Acid-Modified Medical Food • Lysine- and tryptophan-free. • For nutrition support of children and adults with glutaric aciduria type I.
Hominex®-2	67042	Amino Acid-Modified Medical Food • Methionine-free. • For nutrition support of children and adults with vitamin B_6-nonresponsive homocystinuria or hypermethioninemia.
I-Valex®-2	67046	Amino Acid-Modified Medical Food • Leucine-free. • For nutrition support of children and adults with a disorder of leucine catabolism.
Ketonex®-2	67050	Amino Acid-Modified Medical Food • Isoleucine-, leucine-, and valine-free. • For nutrition support of children and adults with maple syrup urine disease.
Phenex™-2, Vanilla	67056	Amino Acid-Modified Medical Food, Vanilla Flavored • Phenylalanine-free. • For nutrition support of children and adults with phenylketonuria or hyperphenylalaninemia.
Phenex™-2, Unflavored	67054	Amino Acid-Modified Medical Food, Unflavored • Phenylalanine-free. • For nutrition support of children and adults with phenylketonuria or hyperphenylalaninemia.
Propimex®-2	67060	Amino Acid-Modified Medical Food • Methionine- and valine-free. • Low in isoleucine and threonine. • For nutrition support of children and adults with propionic or methylmalonic acidemia.

PRODUCT	PRODUCT CODE	PRODUCT DESCRIPTION
CHILD/ADULT		
Tyrex®-2	67064	Amino Acid-Modified Medical Food • Phenylalanine- and tyrosine-free. • For nutrition support of children and adults with tyrosinemias type I, II, or III.

ADDITIONAL SPECIALTY PRODUCTS		
Calcilo XD®	53328	Low-Calcium/Vitamin D-Free Infant Formula With Iron • For nutrition support of infants with hypercalcemia when a low-calcium, vitamin D-free formula is needed.
Pro-Phree®	67030	Protein-Free Energy Module With Iron, Vitamins & Minerals • For nutrition support of infants and toddlers who require extra calories, minerals, vitamins, and/or protein restriction. • Nutrient profile designed for infants and toddlers. May be used by children and adults.
ProViMin®	50260	Protein-Vitamin-Mineral Formula Component With Iron • For use in management of patients who require a formula modified in carbohydrate, fat, and/or increased protein.
RCF®	00108	No Added Carbohydrate Soy Infant Formula Base With Iron • For persons who are unable to tolerate the type or amount of carbohydrate in milk or infant formulas. • This product contains no added carbohydrate.

Phenylketonuria

INTRODUCTION

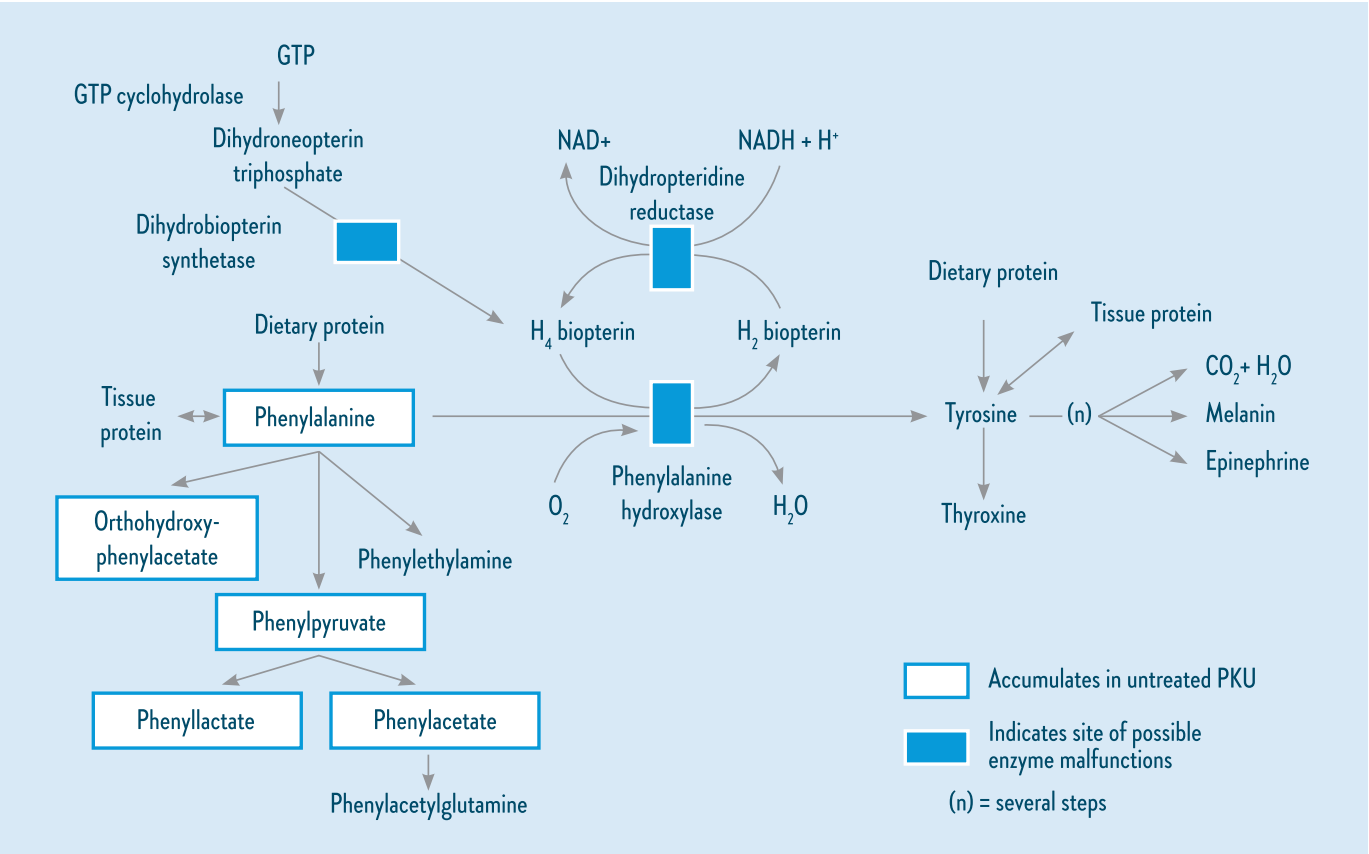
Phenylketonuria (PKU) results from a defect in the enzyme phenylalanine (PHE) hydroxylase, which is responsible for changing PHE, an essential amino acid, to tyrosine (TYR), normally a nonessential amino acid (Fig 1). A defect in the activity of PHE hydroxylase results in the accumulation of PHE in blood and body tissues, which produces toxic PHE metabolites. Another consequence is that blood and tissue concentrations of TYR may be deficient because TYR cannot be synthesized and is an essential amino acid for patients with PKU. Hyperphenylal-aninemia may also result from a deficiency of tetrahydrobiopterin (BH_4), a coenzyme for phenylalanine hydroxylase. Therapy for BH_4 deficiency may require L-dopamine, carbidopa, and BH_4 in addition to a PHE-restricted diet. Kuvan® (sapropterin dihydrochloride) prescription medicines are used to lower blood PHE levels in adults and children over one month of age with a certain type of PKU. Kuvan is used along with a PHE-restricted diet. Palynziq® (pegvaliase-pqpz) Injection that lowers blood PHE levels by substituting for the PAH enzyme. Treatment with Palynziq does not require a PHE-restricted diet.

SCREENING FOR PKU

Newborn screening for PKU started in the mid-1960s. The PHE concentration in blood is measured. An elevated blood PHE level found on a newborn screen suggests the need for a diagnostic workup. A positive newborn screen for elevated blood PHE is NOT a positive diagnosis.

The prevalence of PKU shows considerable geographic variation. It is estimated to be 1/10,000 live births in Europe with a higher rate in some countries (Ireland, Iran, Italy). Prevalence is particularly high in Turkey: 1/4,000 live births. PKU is far rarer in the Finnish, African, and Japanese populations.

FIGURE 1: PHE METABOLISM IN PKU



OUTCOME AND CONCERNS

If untreated, individuals with PKU may have irreversible mental retardation and one or more of the following: neurologic abnormalities, abnormal electroencephalograms (EEG) (brain waves), seizures, hyperactivity, musty odor, and eczema. Newborn screening, early diagnosis, and prompt nutrition intervention have resulted in children with normal intelligence.

Years ago, children with PKU were removed from a PHE-restricted diet at school age or younger. It was believed that brain growth was complete and, therefore, these children need not continue on a PHE-restricted diet. But, data have shown that children removed from a PHE-restricted diet have decreased IQ and poorer school performance compared to the same age-matched children with PKU who remained on the diet. Neurologic deterioration, mental aberrations, physical changes in the brain, and psychiatric problems have been reported in individuals either removed from the PHE-restricted diet or in poor metabolic control. For these reasons, it is now recommended that individuals with PKU remain on diet for life and remain in good metabolic control.

Offspring of mothers with untreated PKU or hyperphenylalaninemia (increased blood PHE without phenylketones in the urine) suffer from permanent mental retardation and have microcephaly (small head), congenital heart defects, and other anomalies. Although these offspring usually do not have PKU, they are exposed in utero to toxic levels of PHE. Research has shown that women who are in good metabolic control at the time of conception and maintain good metabolic control throughout pregnancy usually have successful outcomes. Consequently, all women of childbearing age should stay on diet and maintain near-normal blood PHE concentrations.

RATIONALE FOR NUTRITION SUPPORT

Correction of the primary biochemical imbalance is achieved through restriction of essential dietary PHE and supplementation with TYR.

GOALS OF NUTRITION SUPPORT

1. Maintenance of normal plasma concentrations of PHE and TYR.
2. Maintenance of normal growth and development.
3. Maintenance of normal nutrition status.
4. Prevention of body protein breakdown.

METHODS OF NUTRITION SUPPORT

The primary treatment for PKU is strict dietary control of essential PHE intake. Nutrition support requires the use of prescribed amounts of intact protein to provide essential PHE, which is required for body protein synthesis, and a medical food free of PHE, but supplemented with TYR (Phenex™-1 Amino Acid-Modified Medical Food With Iron, and Phenex™-2 Amino Acid-Modified Medical Food, Unflavored and Vanilla). High-protein foods, such as dairy products, eggs, fish, legumes, meat, and poultry, are prohibited. Low-protein breads, cereals, fats, fruits, and vegetables are prescribed to supply PHE. Protein-free foods are used to supply energy. In infants, dietary PHE is supplied by infant formula or breast milk until about 4 to 6 months of age, when solid foods are gradually introduced.

Marked protein malnutrition and failure to thrive can occur if only low-protein foods and/or proprietary infant formula are used to reduce plasma PHE concentrations to treatment range. For this reason, Phenex-1 and Phenex-2, which are free of PHE but contain all other essential and nonessential amino acids, minerals, and vitamins, are required. Medical foods often provide 50 to 80% of the patient's protein requirements. The nutrient compositions of the Phenex products are found in Table 2. Recommended daily nutrient intakes (ranges) for infants, children, and adults with PKU are given in Table 2, and a sample diet calculation is illustrated in Appendix IV.

MONITORING

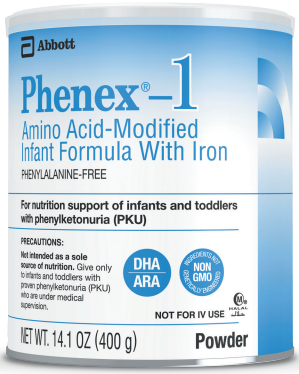
The frequency of monitoring depends on the age and clinical status of the patient. Minimum assessment should include blood PHE, TYR,

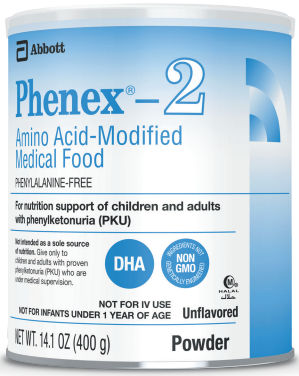
and other amino acids, as well as indices of protein and iron status, growth rate, and nutrient intake. Additional tests, including developmental assessment, may be warranted.

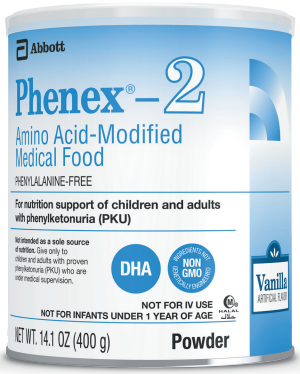
Genetic Metabolic Dietitians International (GMDI) and the Southeast Regional Genetics Network (SERN) have partnered to develop nutrition guidelines for metabolic disorders. Please go to www.gmdi.org to learn more on nutrition management guidelines for PKU.

TABLE 2: NUTRIENT COMPOSITION OF PHENEX™-1 AND PHENEX™-2

NUTRIENT	PHENEX-1* Per 100 g powder	PHENEX-2* Unflavored & Vanilla Per 100 g powder
Energy, kcal	480	410
Protein equiv, g	15	30
Fat, g	21.7	14
Carbohydrate, g	53	35
Linoleic Acid, mg	3650	2200
Linolenic Acid, mg	360	225
L-Carnitine, mg	20	40
Minerals		
Calcium, mg	575	975
Phosphorus, mg	400	760
Magnesium, mg	50	225
Iron, mg	7.6	13
Zinc, mg	5.2	13
Manganese, mg	0.385	0.8
Copper, mg	0.408	1.5
Iodine, µg	65	100
Selenium, µg	21	35
Chromium, µg	12	27
Molybdenum, µg	13.8	30
Sodium, mg (mEq)	190 (8.3)	880 (38.3)
Potassium, mg (mEq)	675 (17.3)	1370 (35)
Chloride, mg (mEq)	325 (9.2)	940 (26.5)
Vitamins		
A, IU (µg RE)	1300 (390)	1500 (450)
D, IU (µg)	450 (11.3)	900 (22.5)
E, IU (mg α-TE)	12.5 (6.4)	12 (5.9)
K, µg	60	60
Thiamin (Vit B_1), mg	1.12	3.3
Riboflavin (Vit B_2), mg	0.65	1.6
B_6, mg	0.56	1.1
B_{12}, µg	0.85	5
Niacin, mg (mg NE)†	4.45 (7.7)	16 (21.7)
Folic Acid (Folacin), µg	88	425
Pantothenic Acid, mg	4	8
Biotin, µg	23.5	100
Vitamin C (Ascorbic Acid), mg	75	60
Choline, mg	95	100
Inositol, mg	144	82







† 60 mg tryptophan = 1 mg niacin equivalent (NE)

* Approximate **unpacked** weights of Phenex in level, dry US standard household measures:

PHENEX-1, PHENEX-2 (Unflavored and Vanilla)	1 Tbsp =	8 g
	¼ cup =	30 g
	⅓ cup =	40 g
	½ cup =	60 g
	1 cup =	120 g

Tyrosinemias

INTRODUCTION

Tyrosinemia type Ia (TYR-I) results from an inherited defect in the liver enzyme fumarylacetoacetate hydrolyase (FAH), which catalyzes the last step in the breakdown of tyrosine (Fig 2). Succinylacetone, a compound produced because of the defective enzyme, is toxic and interferes with other body processes, including the dysfunction of p-hydroxyphenylpyruvic acid (p-OHPPAD). Since 1992, inhibition of p-OHPPAD using the drug 2(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC) has prevented acute porphyric episodes and decreased rates of progression of cirrhosis.

Tyrosinemia type II (TYR-II) results from a defect in the liver enzyme tyrosine aminotransferase, which catalyzes the first step in the breakdown of TYR (Fig. 3). Diagnosis is made by clinical and laboratory findings. Laboratory findings include elevations in blood PHE and TYR concentrations and increases in specific urinary metabolites not found under normal circumstances.

Two clinical subsets of hereditary tyrosinemia type III (TYR-III) result from dysfunction of p-OHPPAD (Fig. 3). The most severe is type IIIa with no hepatic p-OHPPAD. Hawkinsinuria (Type IIIb) is named for ninhydrin-positive amino acid hawkinsin and later 4-hydroxycyclohexyl acetic acid are formed and excreted.

FIGURE 2: TYROSINE METABOLISM IN TYPES IA AND IB

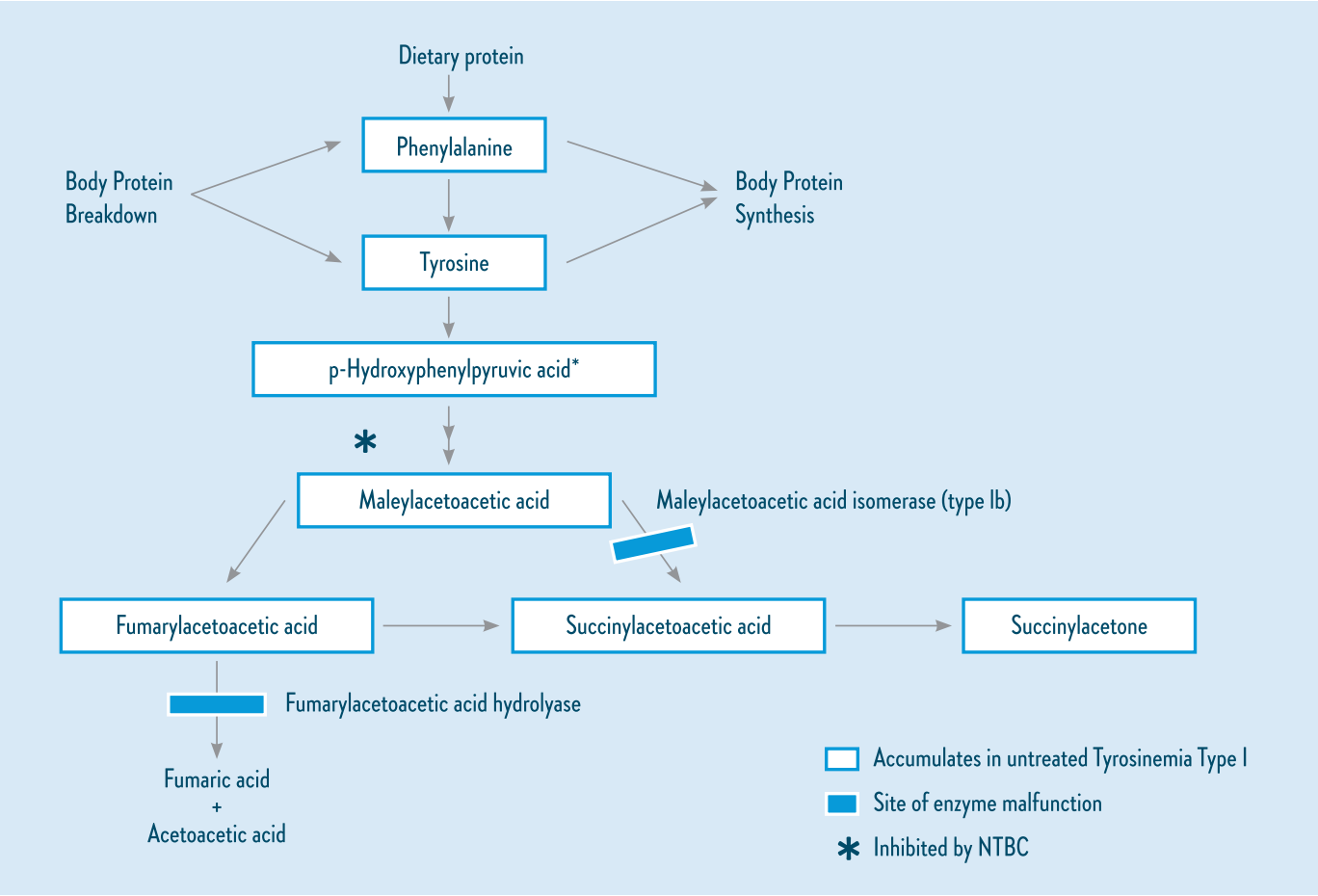
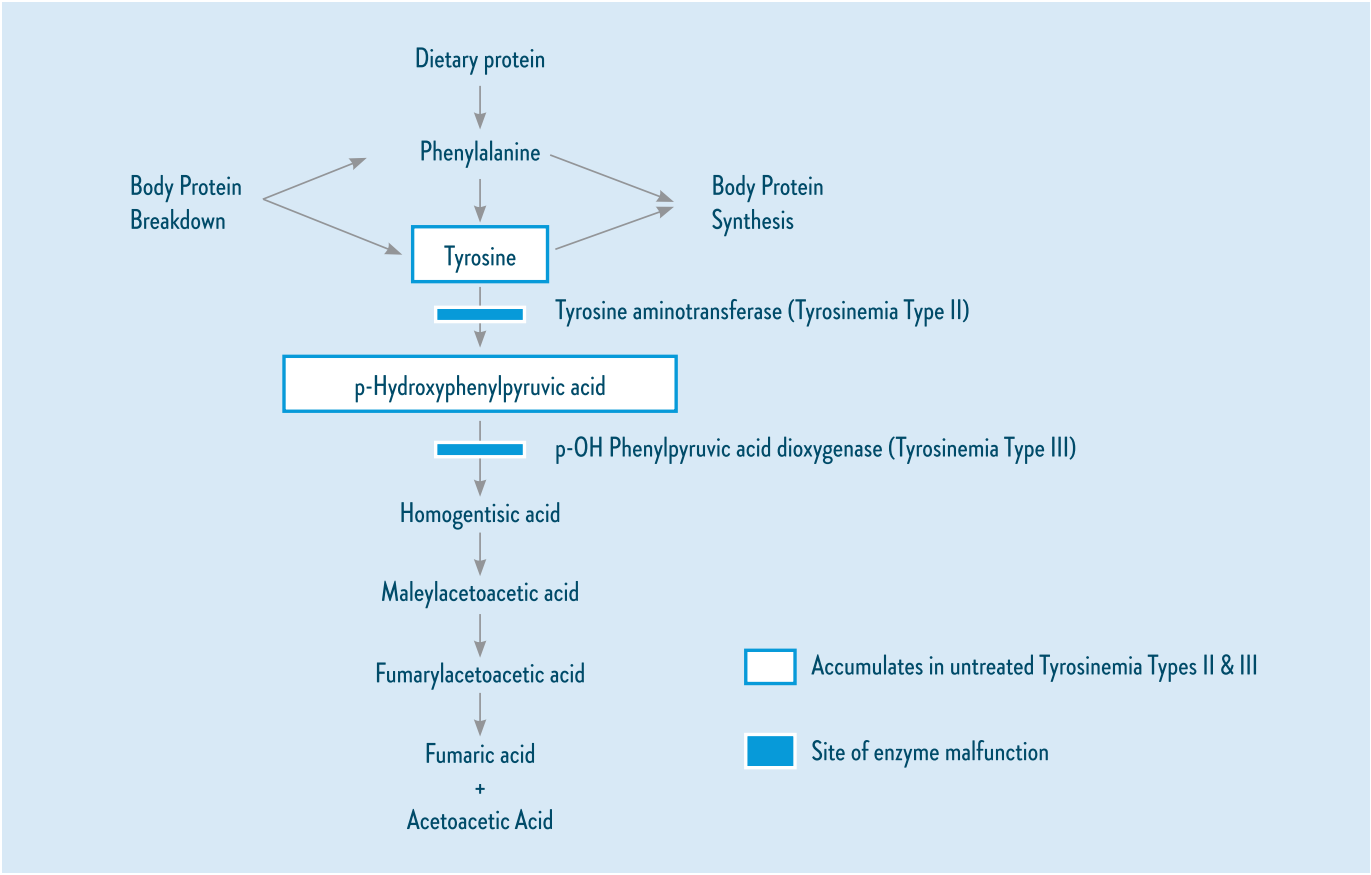


FIGURE 3: TYROSINE METABOLISM IN TYPES II AND III



PRESENTATION

Soon after birth, infants with the acute form of TYR-I develop progressive liver and kidney failure, vomiting, diarrhea, and a "cabbage-like" odor. Because some of these symptoms are similar to other inborn errors of metabolism, accurate diagnosis is essential. Increased concentrations of phenylalanine (PHE), tyrosine (TYR), and frequently methionine (MET) are found in the blood. It is not known whether the elevation in blood MET is related to the progressive liver damage or to the effect of succinylacetone on enzymes that break down MET.

The chronic form of TYR-I is similar to the acute form, but symptoms are usually milder and appear later in infancy. Symptoms include rickets, liver and kidney dysfunction, high blood pressure, and nervous system dysfunction. The incidence of TYR-I is estimated at 1/100,000 live births. A high frequency of 1/12,500 has been reported in Quebec, Canada.

Major symptoms of TYR-II include skin and eye lesions due to the deposition of TYR crystals in these areas. Typical skin lesions include blisters and hyperkeratosis (growth similar to a callus) on the fingers and palms of the hand and the soles of the feet. A positive diagnosis for TYR-II is essential because the rationale for and goals of nutrition support differ for types I and II. Fewer than 150 cases of TYR-II have been reported. The actual incidence is not documented.

Presentation of Type III may include neurologic abnormalities, seizures, and/or ataxia. Mental retardation has been reported in untreated patients with Type IIIa. Metabolic acidosis, failure to thrive, and a "swimming pool-like" odor are described in Type IIIb.

OUTCOME

NTBC has dramatically improved the course of patients with tyrosinemia type I. It is not yet known whether hepatomas will develop in patients treated with NTBC. Liver transplantation has significantly improved the outcome in patients with TYR-I. Without liver transplantation, patients develop hepatomas, usually within the first or second decade of life. Medical and nutrition support are essential to maintain optimal health and nutrition status until a suitable liver is found.

Nutrition support eliminates the skin and eye lesions in patients with TYR-II. Without nutrition support, some patients with TYR-II are mentally impaired. Restriction of PHE and TYR improves the condition of patients with TYR-III.

RATIONALE FOR NUTRITION SUPPORT

Correction of the primary biochemical imbalance and elimination of the physical manifestations are achieved by dietary restriction of PHE and TYR in all types of tyrosinemia. Correction of the abnormal changes in the nervous system which result from elevated α-aminolevulinic acid (α-ALA) is by restricting PHE and TYR and by prescribing NTBC in Type I.

GOALS OF NUTRITION SUPPORT

1. Maintenance of normal blood concentrations of PHE and TYR.
2. Support of normal growth and development.
3. Maintenance of nutrition status.
4. Prevention of body protein breakdown.
5. Prevention of rickets and liver and renal damage in Type I.
6. Prevention of nervous system changes by reducing α-ALA to a normal level.
7. Prevention of eye and skin lesions and mental handicap in Types II and III.

METHODS OF NUTRITION SUPPORT

Acute illness in TYR-I requires rapid medical and nutrition support to limit the breakdown of body protein and reduce α-ALA and succinylacetone concentrations. Intravenous feedings of carbohydrate can be used for short periods of time if oral feedings are not tolerated. Oral feedings using medical food free of PHE and TYR (Tyrex®-1 Amino Acid-Modified Medical Food With Iron and Tyrex®-2 Amino Acid-Modified Medical Food) and containing adequate intact protein to supply essential PHE, TYR, and extra energy should be given as tolerated. Prescribed amounts of standard infant formula or breast milk should be added to the diet to provide PHE and TYR. Long-term nutrition support requires the use of prescribed amounts of intact protein to provide PHE and TYR and a medical food free of PHE and TYR (Tyrex-1) for management of tyrosinemia. High-protein foods, such as dairy products, eggs, fish, legumes, meat, and poultry cannot be used. Low-protein breads, cereals, fats, fruits, and vegetables to supply PHE and TYR are prescribed. Protein-free foods are used to supply additional energy. In infants, the restricted amino acids are supplied by infant formula or breast milk until about 4 to 6 months of age, when solid foods are gradually introduced. Nutrient composition of the Tyrex formulas is found in Table 5.

Low-protein diets alone, without the use of medical foods, over-restrict protein, minerals, and vitamins causing growth failure and nutrient deficiencies. Medical foods should provide most of the required protein needed for growth and are the major sources of minerals and vitamins. Because L-amino acids, rather than whole protein, are the principle source of protein equivalent, the recommended intakes are higher than for a normal infant or toddler.

MONITORING

Monitoring is essential to meet the goals of nutrition support. The frequency of monitoring depends on the age and clinical status of the patient. Minimum assessment should include blood PHE, TYR, and other amino acids; protein and iron status; growth rate; and nutrient intake.

Additional tests related to liver and kidney function are usually required for managing patients with TYR-I.

TABLE 5: NUTRIENT COMPOSITION OF TYREX®-1 AND TYREX®-2

NUTRIENT	TYREX-1* Per 100 g powder	TYREX-2* Per 100 g powder
Energy, kcal	480	410
Protein equiv, g	15	30
Fat, g	21.7	14
Carbohydrate, g	53	35
Linoleic Acid, mg	3650	2200
Linolenic Acid, mg	360	225
L-Carnitine, mg	20	40
Minerals		
Calcium, mg	575	975
Phosphorus, mg	400	760
Magnesium, mg	50	225
Iron, mg	7.6	13
Zinc, mg	5.2	13
Manganese, mg	0.385	0.8
Copper, mg	0.408	1.5
Iodine, µg	65	100
Selenium, µg	21	35
Chromium, µg	12	27
Molybdenum, µg	13.8	30
Sodium, mg (mEq)	190 (8.3)	880 (38.3)
Potassium, mg (mEq)	675 (17.3)	1370 (35)
Chloride, mg (mEq)	325 (9.2)	940 (26.5)
Vitamins		
A, IU (µg RE)	1300 (390)	1500 (450)
D, IU (µg)	450 (11.3)	900 (22.5)
E, IU (mg α-TE)	12.5 (6.4)	12 (5.9)
K, µg	60	60
Thiamin (Vit B_1), µg	1.12	3.3
Riboflavin (Vit B_2), mg	0.65	1.6
B_6, mg	0.56	1.1
B_{12}, µg	0.85	5
Niacin, mg (mg NE)†	4.45 (7.7)	16 (21.7)
Folic Acid (Folacin), µg	88	425
Pantothenic Acid, mg	4	8
Biotin, µg	23.5	100
Vitamin C (Ascorbic Acid), mg	75	60
Choline, mg	95	100
Inositol, mg	144	82

† 60 mg tryptophan = 1 mg niacin equivalent (NE)

* Approximate **unpacked** weights of Tyrex in level, dry US standard household measures:

TYREX-1, TYREX-2	1 Tbsp =	8 g
	¼ cup =	30 g
	⅓ cup =	40 g
	½ cup =	60 g
	1 cup =	120 g

Propionic Acidemia and Methylmalonic Acidemia

INTRODUCTION

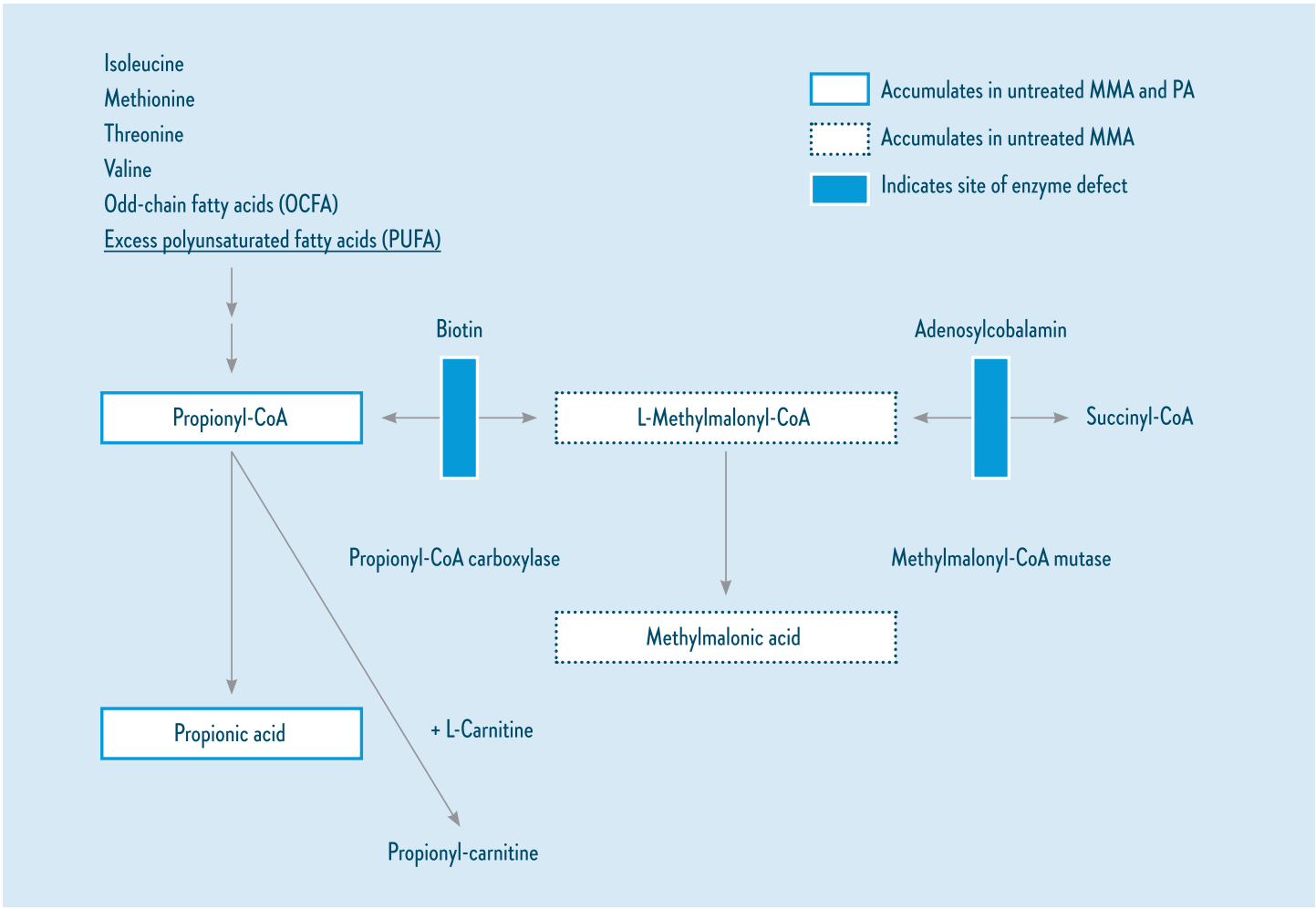
Propionic acidemia (PA) is an inherited disorder caused by a defect in the enzyme propionyl-CoA carboxylase, which breaks down the essential amino acids isoleucine (ILE), methionine (MET), threonine (THR), and valine (VAL), as well as odd-chain fatty acids (Fig. 4).

Methylmalonic acidemia (MMA) is caused by a defect in the enzyme methylmalonyl-CoA mutase, which requires a form of vitamin B_{12} to help process ILE, MET, THR, VAL, and odd-chain fatty acids (Fig 4). Those patients with MMA who improve with large doses of vitamin B_{12} usually do not require additional nutrition support.

PRESENTATION

Symptoms in patients with PA or MMA usually appear within the first few days of life and include vomiting, loss of appetite, drowsiness, failure to thrive, dehydration, and severe acidosis. Low blood sugar concentrations and high blood levels of ammonia and glycine may be found in PA. Symptoms in some patients with PA or MMA appear late in infancy, usually accompanying an illness or after ingestion of a large amount of protein. Symptoms in late-presenting patients are usually milder, and these patients may tolerate more intact protein than patients who present in the neonatal period.

FIGURE 4: METHYLMALONIC AND PROPIONIC ACIDEMIA



Laboratory findings for PA and MMA are increased amounts of toxic compounds characteristic of each disorder. Identification of these toxic compounds is usually diagnostic for these disorders.

PA has an incidence of about 1/100,000 live births. The incidence is greater in patients of Arabic or Spanish descent. Incidence of MMA (mutase deficiency) is approximately 1/50,000 live births.

OUTCOME

Patients without treatment who survive the acute neonatal illness may suffer mental retardation, frequent infections, and "cerebral palsy-like" symptoms. Many patients die from overwhelming acidosis, usually associated with infection. Progressive kidney damage may occur with MMA and is often associated with untreated or inadequately treated patients.

RATIONALE FOR NUTRITION SUPPORT

Correction of the major biochemical imbalances is achieved by restricting ILE, MET, THR, VAL, odd-chain fatty acids, and excess polyunsaturated fatty acids and preventing the breakdown of body protein and fat. Accumulated toxic compounds are removed by supplementation with L-carnitine. Any defective enzyme present in MMA is stabilized by administering large doses of vitamin B_{12}. The breakdown of body protein and fat is prevented by a generous energy allowance and by frequent feeding, even during infection.

GOALS OF NUTRITION SUPPORT

1. Maintenance of normal blood ILE, MET, THR, VAL, and carnitine.
2. Avoidance of long-term fasting to prevent the breakdown of body protein and fat.
3. Maintenance of normal growth, development, and nutrition status.
4. Prevention of carnitine deficiency.

METHODS OF NUTRITION SUPPORT

Acute illness requires immediate medical care to reduce the accumulation of toxic compounds and limit the breakdown of body protein and fat. Intravenous feedings of carbohydrate can be used for a short time if oral feedings are not tolerated. Feedings of medical foods free of MET and VAL, low in ILE and THR, with adequate intact protein, and high in energy should be introduced to promote the building of body protein.

Long-term nutrition support requires the use of prescribed amounts of intact protein as a source of ILE, MET, THR, and VAL; medical foods free of MET and VAL and low in ILE and THR (Propimex®-1 Amino Acid-Modified Medical Food With Iron and Propimex®-2 Amino Acid-Modified Medical Food); energy; fluid; vitamin B_{12} (MMA); and L-carnitine. Medical foods may be given to supply up to 50% of the total protein prescribed. The majority of minerals and vitamins required for maintaining nutrition status are provided by the medical food. Low-protein diets alone, without medical foods, do not supply adequate amounts of nutrients and result in protein, mineral, and vitamin deficiencies and in growth failure. Nutrient composition of the Propimex formulas is found in Table 6, next page.

L-carnitine administration is recommended to remove accumulated toxins and to prevent carnitine deficiency. Propimex is fortified with 60 mg carnitine per gram of protein. Additional carnitine administration may not be required when Propimex is the primary source of protein.

Foods are limited to prescribed amounts of low-protein breads, cereals, fats, fruits, vegetables, and protein-free foods. High-protein foods, such as dairy products, eggs, fish, legumes, meat, and poultry, are prohibited in the diet. Milk fats, lard, and olive oil may be limited because they contain odd-chain fatty acids. For infants, the restricted ILE, MET, THR, and VAL are supplied by infant formula. At about 4 to 6 months of age, solid

foods are introduced and gradually displace infant formula as the source of the restricted amino acids. Children with PA or MMA frequently lose their appetite and must depend on nasogastric or gastrostomy feeding to ensure adequate provision of nutrients. The loss of appetite has been related to excess serotonin (a brain chemical). The production of serotonin can increase with too much dietary tryptophan or carbohydrate. Propimex is low in tryptophan (11 mg per g of protein) and supplies approximately 30% (Propimex-2) to 40% (Propimex-1) of energy from fat to help prevent excess serotonin synthesis.

MONITORING

Frequent monitoring is essential to ensure adequate nutrition support. Evaluation should include assessment of nutrient intake, plasma amino acids and free carnitine, protein and iron status, and growth rates.

GMDI and SERN have partnered to develop nutrition guidelines for metabolic disorders. Please go to www.gmdi.org to learn more on nutrition guidelines for PA.

TABLE 6: NUTRIENT COMPOSITION OF PROPIMEX®-1 AND PROPIMEX®-2

NUTRIENT	PROPIMEX-1* Per 100 g powder	PROPIMEX-2* Per 100 g powder
Energy, kcal	480	410
Protein equiv, g	15	30
Fat, g	21.7	13
Carbohydrate, g	53	35
Linoleic Acid, mg	3650	2200
Linolenic Acid, mg	360	225
L-Carnitine, mg	900	1800
Minerals		
Calcium, mg	575	975
Phosphorus, mg	400	760
Magnesium, mg	50	225
Iron, mg	7.6	13
Zinc, mg	5.2	13
Manganese, mg	0.385	0.8
Copper, mg	0.408	1.5
Iodine, µg	65	100
Selenium, µg	21	35
Chromium, µg	12	27
Molybdenum, µg	13.8	30
Sodium, mg (mEq)	190 (8.3)	880 (38.3)
Potassium, mg (mEq)	675 (17.3)	1370 (35)
Chloride, mg (mEq)	410 (11.6)	1160 (32.7)
Vitamins		
A, IU (µg RE)	1300 (390)	1500 (450)
D, IU (µg)	450 (11.3)	900 (22.5)
E, IU (mg α-TE)	12.5 (6.4)	12 (5.9)
K, µg	60	60
Thiamin (Vit B_1), mg	1.12	3.3
Riboflavin (Vit B_2), mg	0.65	1.6
B_6, mg	0.56	1.1
B_{12}, µg	0.85	5
Niacin, mg (mg NE)†	4.45 (7.7)	16 (21.7)
Folic Acid (Folacin), µg	88	425
Pantothenic Acid, mg	4	8
Biotin, µg	23.5	100
Vitamin C (Ascorbic Acid), mg	75	60
Choline, mg	95	100
Inositol, mg	144	82

† 60 mg tryptophan = 1 mg niacin equivalent (NE)

* Approximate **unpacked** weights of Propimex in level, dry US standard household measures:

PROPIMEX-1, PROPIMEX-2	1 Tbsp =	8 g
	¼ cup =	30 g
	⅓ cup =	40 g
	½ cup =	60 g
	1 cup =	120 g

Maple Syrup Urine Disease

INTRODUCTION

Maple syrup urine disease (MSUD), also called branched-chain ketoaciduria, results from a defect in the enzyme complex, branched-chain ketoacid dehydrogenase (BCKD). This enzyme complex is responsible for the breakdown of the ketoacids of the branched essential amino acids, isoleucine (ILE), leucine (LEU), and valine (VAL) (Fig 5).

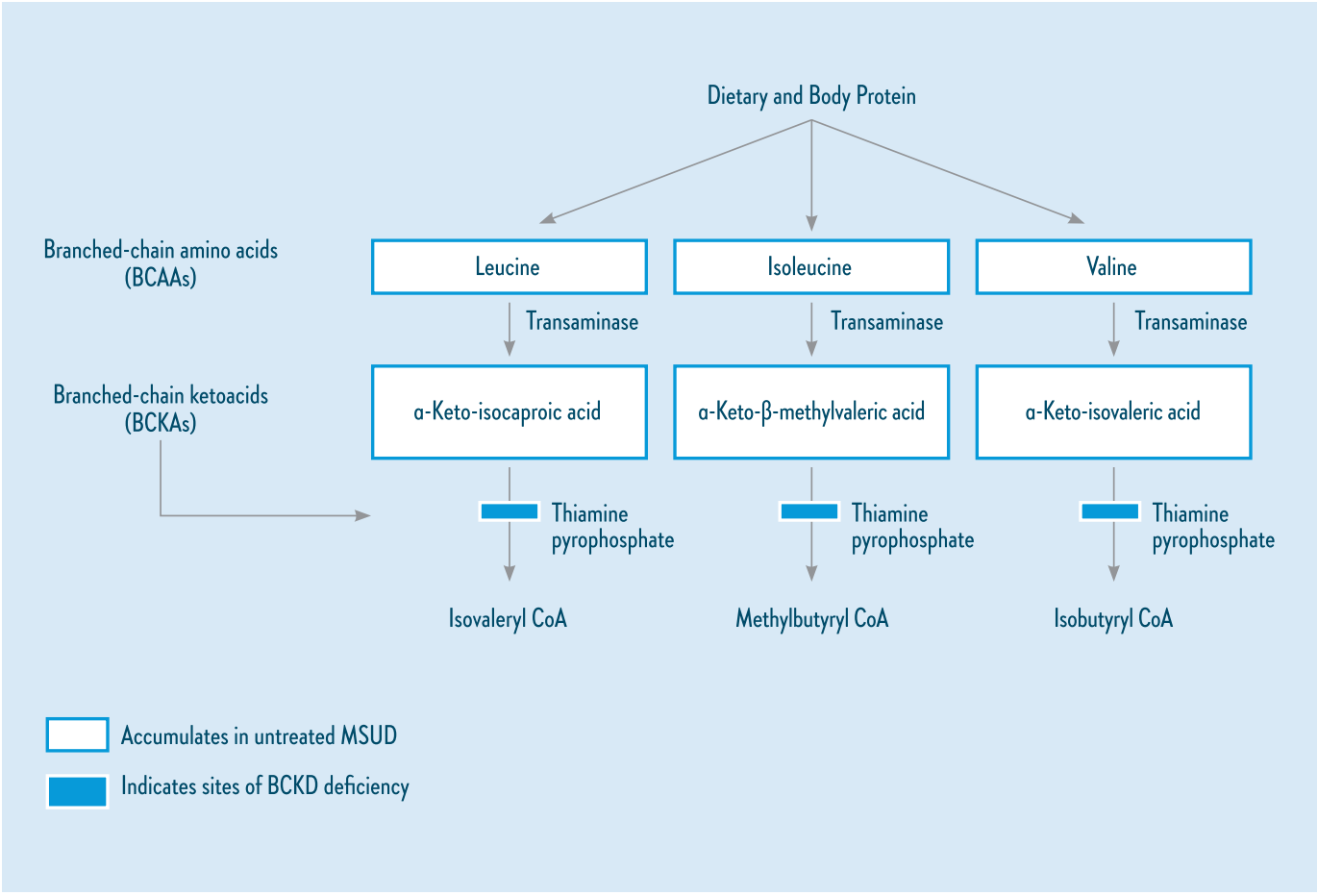
A defect in the BCKD complex results in accumulation of ILE, LEU, and VAL and their respective toxic ketoacids in blood and body fluids. Several forms of MSUD, including classical, intermittent, intermediate, and thiamine-responsive, are known. These four forms differ in their clinical picture and outcome, with the classical form being the most severe.

Many patients with a variant (not classical) form of MSUD who have some BCKD activity may be biochemically responsive to pharmacologic doses of thiamine (vitamin B_1). Thiamine is a coenzyme for the BCKD complex and is needed for its activation in body cells. In patients with some activity of BCKD complex, thiamine may help by increasing the life of the enzyme, thereby increasing its effectiveness.

PRESENTATION

The incidence of MSUD is approximately 1/100,000 to 1/300,000 live births in the general population, and 1/760 live births in the Mennonite population. The incidence is greater in people of African, Arabic, or Spanish descent. Infants with MSUD may appear normal at birth,

FIGURE 5: BRANCHED-CHAIN AMINO ACID METABOLISM IN MSUD



but those with the severe form soon develop serious complications, including lethargy, vomiting, neurologic deterioration, loss of consciousness, and coma. These symptoms occur in response to significant elevations in plasma ILE, LEU, and VAL, and their ketoacids. Because of the chance of serious and rapid clinical deterioration, an elevated blood LEU requires rapid diagnosis followed by prompt medical intervention.

OUTCOME

Children who survive the neonatal period without treatment may have permanent neurologic impairment and mental retardation. Early medical and nutrition intervention (<1 week of age) with maintenance of good metabolic control significantly improves the patient's outcome. Improved medical and nutrition management has allowed patients to live longer and improved lives. Women with MSUD who are treated prior to and during pregnancy have been reported to have normal, healthy children.

RATIONALE FOR NUTRITION SUPPORT

Correction of the primary biochemical imbalance is achieved by restriction of essential dietary ILE, LEU, and VAL to amounts required to maintain normal plasma concentrations. Thiamine may stabilize the BCKD complex, if any activity is present.

GOALS OF NUTRITION SUPPORT

1. Maintenance of normal plasma concentrations of ILE, LEU, and VAL.
2. Prevention of muscle protein breakdown during acute illness.
3. Maintenance of normal nutrition status.
4. Maintenance of normal growth and development.

METHODS OF NUTRITION SUPPORT

The primary treatment for MSUD is strict dietary control of essential ILE, LEU, and VAL intake. Nutrition support requires the use of prescribed amounts of intact protein to provide essential ILE, LEU, and VAL needed for growth and development. Medical foods (Ketonex®-1 Amino Acid-Modified Medical Food With Iron and Ketonex®-2 Amino Acid-Modified Medical Food) free of ILE, LEU, and VAL provide the majority of protein, minerals, and vitamins in the diet. High-protein foods, such as dairy products, eggs, fish, legumes, meat, and poultry, are strictly prohibited. Low-protein breads, cereals, fats, fruits, and vegetables are prescribed to supply ILE, LEU, and VAL. Protein-free foods are used to supply energy. In infants, dietary ILE, LEU, and VAL are supplied by infant formula until about 4 to 6 months of age, when solid foods are gradually introduced. Nutrient composition of the Ketonex formulas is found in Table 7.

Marked protein deficiency and failure to thrive can occur if only low-protein foods and/or infant formula are used to reduce plasma ILE, LEU, and VAL concentrations to treatment range. For this reason, Ketonex-1 and Ketonex-2, which are free of ILE, LEU, and VAL, but contain all other essential and nonessential amino acids, minerals, and vitamins, are required. Medical foods often provide >75% of the patient's protein requirement. Additional supplements of ILE and VAL are required in some cases.

MONITORING

The frequency of monitoring depends on the age and clinical status of the patient. Minimum assessment should include plasma ILE, LEU, and VAL; indices of protein and iron status; growth rate; and nutrient intake. Additional tests, including developmental assessment, may be warranted.

GMDI and SERN have partnered to develop nutrition guidelines for metabolic disorders. Please go to www.gmdi.org to learn more on nutrition guidelines for MSUD.

TABLE 7: NUTRIENT COMPOSITION OF KETONEX®-1 AND KETONEX®-2

NUTRIENT	KETONEX-1* Per 100 g powder	KETONEX-2* Per 100 g powder
Energy, kcal	480	410
Protein equiv, g	15	30
Fat, g	21.7	14
Carbohydrate, g	53	35
Linoleic Acid, mg	3650	2200
Linolenic Acid, mg	360	225
L-Carnitine, mg	100	200
Minerals		
Calcium, mg	575	975
Phosphorus, mg	400	760
Magnesium, mg	50	225
Iron, mg	7.6	13
Zinc, mg	5.2	13
Manganese, mg	0.385	0.8
Copper, mg	0.408	1.5
Iodine, µg	65	100
Selenium, µg	21	35
Chromium, µg	12	27
Molybdenum, µg	13.8	30
Sodium, mg (mEq)	190 (8.3)	880 (38.3)
Potassium, mg (mEq)	675 (17.3)	1370 (35)
Chloride, mg (mEq)	325 (9.2)	940 (26.5)
Vitamins		
A, IU (µg RE)	1300 (390)	1500 (450)
D, IU (µg)	450 (11.3)	900 (22.5)
E, IU (mg α-TE)	12.5 (6.4)	12 (5.9)
K, µg	60	60
Thiamin (Vit B_1), mg	1.12	3.3
Riboflavin (Vit B_2), mg	0.65	1.6
B_6, mg	0.56	1.1
B_{12}, µg	0.85	5
Niacin, mg (mg NE)†	4.45 (7.7)	16 (21.7)
Folic Acid (Folacin), µg	88	425
Pantothenic Acid, mg	4	8
Biotin, µg	23.5	100
Vitamin C (Ascorbic Acid), mg	75	60
Choline, mg	95	100
Inositol, mg	144	82

† 60 mg tryptophan = 1 mg niacin equivalent (NE)

* Approximate **unpacked** weights of Ketonex in level, dry US standard household measures:

KETONEX-1, KETONEX-2	1 Tbsp =	8 g
	¼ cup =	30 g
	⅓ cup =	40 g
	½ cup =	60 g
	1 cup =	120 g

Urea Cycle Enzyme Defects

INTRODUCTION

Urea cycle disorders (UCDs) result from any one of six enzyme defects in urea synthesis. Urea is the body's major compound for the excretion of waste nitrogen from dietary protein that is not used for making body protein and from the breakdown of body protein (Fig 6). A defect in any of the enzymes of the urea cycle results in elevated blood ammonia, which may damage the brain and nervous system. Rapid medical intervention is essential for the patient with coma, secondary to elevated blood ammonia, to prevent permanent brain damage and possibly death.

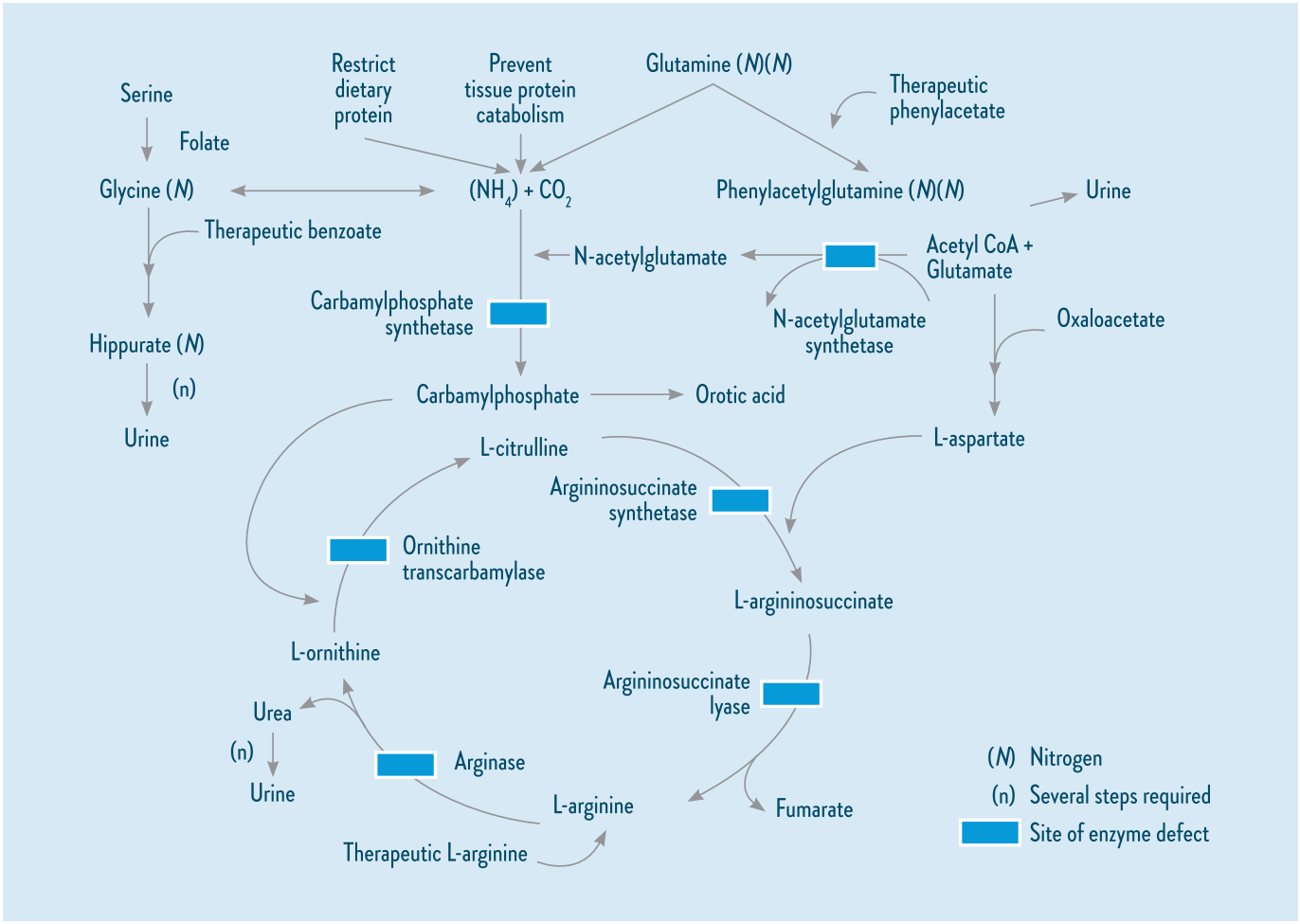
UREA CYCLE ENZYME DEFECTS

- N-acetylglutamate synthetase (NAG)
- Carbamyl-phosphate synthetase (CPS)
- Ornithine transcarbamylase (OTC)
- Argininosuccinate synthetase (AS) (also called citrullinemia)
- Argininosuccinate lyase (AL)
- Arginase

PRESENTATION

Clinical features in the newborn suggestive of urea cycle enzyme defects occur with protein ingestion (breastfeeding or infant formula intake), infection, or body protein catabolism. In increasing order of severity, these defects may result in poor feeding, vomiting, lethargy, hypotonia, stupor, bleeding diatheses, convulsions, coma, shock, and death.

FIGURE 6: NITROGEN METABOLISM IN UREA CYCLE ENZYME DEFECTS



OUTCOME

Although the outcome for patients with a disorder of the urea cycle is variable and depends on the specific enzyme defect, early diagnosis and prospective treatment affect the quality of life and long-term prognosis.

Results of therapy in infants with complete or near complete enzyme deficiencies have been less than optimal with delayed death and below normal development. If serious brain swelling and coma are prevented in the neonatal period or if onset of disease expression is delayed, physical growth and mental development are nearly normal with nutrition and pharmacologic support.

RATIONALE AND GOALS OF NUTRITION SUPPORT

Correction of the primary biochemical imbalance associated with high blood ammonia is achieved by severely restricting dietary protein and preventing the breakdown of body protein. Reduction of the accumulated nitrogen is achieved by using specific drugs that enhance its excretion. Supplementation of essential products of the urea cycle that are not made when there is a block in the cycle is required. Supplements of L-carnitine, L-arginine (except in arginase deficiency), and L-citrulline are required to prevent a possible deficiency. The goals of nutrition support are normal physical and mental development and maintenance of nutrition status.

METHODS OF NUTRITION SUPPORT

Nutrition support during acute episodes of high blood ammonia involves removing all dietary protein for a very short period of time (2 to 3 days) and providing increased energy from fat and carbohydrate to limit the breakdown of body protein. In cases of extremely elevated blood ammonia concentrations, more extensive medical care is necessary. When the patient is clinically stable, protein is slowly added back into the diet.

Nutrition support of UCDs uses a combination of intact protein that contains both essential and nonessential amino acids, and the medical food (Cyclinex®-1 Amino Acid-Modified Medical Food With Iron and Cyclinex®-2 Amino Acid-Modified Medical Food) that contains only essential amino acids. This combination is necessary when intact protein is severely restricted. Use of excess dietary protein above that required for growth and maintenance increases waste nitrogen and consequently increases the production of ammonia. Dietary protein is limited to prescribed amounts of low-protein breads, cereals, fats, fruits, and vegetables. Protein-free foods are used to supply additional energy, if needed. High-protein foods, such as dairy products, eggs, fish, legumes, meat, and poultry, are prohibited. The amount of dietary protein prescribed is dependent on age, gender, and enzyme activity. For infants, intact protein is supplied by infant formula or breast milk until about 4 to 6 months of age, when solid foods are added to the diet. Solid foods gradually replace infant formula as the source of intact protein.

Low-protein diets alone, without the addition of Cyclinex, may not be sufficient to provide adequate essential amino acids. Consequently, over-restriction of dietary protein results in protein, mineral, and vitamin deficiencies and in growth failure.

Medical foods consisting of essential L-amino acids, fat, carbohydrate, minerals, and vitamins are used with a prescribed amount of intact protein. Approximately 30 to 70% of the daily protein requirement may be derived from Cyclinex. This regimen provides the necessary essential and nonessential amino acids and nutrients required for growth. Nutrient composition of the Cyclinex formulas is found in Table 8, next page.

A common feature in all urea cycle defects, except arginase deficiency, is a deficiency of arginine. Because arginine is produced in the urea cycle, a defect in this cycle makes arginine an essential amino acid. Deficiencies in blood arginine and citrulline limit the body's ability to excrete unused nitrogen, thereby causing hyperammonemia. Supplementation of L-arginine or L-citrulline can reduce blood ammonia. L-citrulline

supplementation is more effective for OTC and CPS deficiencies because their enzyme defects occur before the production of citrulline. Arginine supplements should NOT be given to children with arginase deficiency because blood arginine is already elevated.

Sodium phenylacetate, sodium benzoate, sodium phenylbutyrate (Buphenyl®), and glycerol phenylbutyrate (Ravicti®) have significantly impacted the treatment of urea cycle disorders and patient outcomes. These drugs bind with unused nitrogen for excretion in the urine. The use of these drugs can also improve the patient's tolerance to protein. Folic acid, niacin, pantothenic acid, vitamin B_6, and vitamin B_{12} are necessary for effective binding of nitrogen with these medications. Cyclinex contains ample amounts of these vitamins. For NAG deficiency, a medication which helps the enzyme work better, such as carglumic acid (Carbaglu®), may be used.

Carnitine deficiency can result from liver damage, the use of very low-protein diets, or from using sodium benzoate or valproic acid. Cyclinex contains carnitine to help prevent deficiencies, but supplemental carnitine may be required during periods of illness with poor appetite.

Liver transplantation is frequently utilized now with excellent long-term survival.

MONITORING

Patients with a UCD require frequent monitoring of blood ammonia and plasma amino acids to prevent over- and under-restriction of essential amino acids. Monitoring of iron and protein status, blood carnitine, and growth, and analysis of nutrient intake are necessary to optimize nutrition support.

TABLE 8: NUTRIENT COMPOSITION OF CYCLINEX®-1 AND CYCLINEX®-2

NUTRIENT	CYCLINEX-1* Per 100 g powder	CYCLINEX-2* Per 100 g powder
Energy, kcal	510	440
Protein equiv, g	7.5	15
Fat, g	24.6	17
Carbohydrate, g	57	45
Linoleic Acid, mg	4000	2800
Linolenic Acid, mg	410	275
L-Carnitine, mg	190	370
Minerals		
Calcium, mg	650	1250
Phosphorus, mg	455	1020
Magnesium, mg	55	300
Iron, mg	8.75	17
Zinc, mg	5.8	17
Manganese, mg	0.425	0.9
Copper, mg	0.450	2
Iodine, µg	70	150
Selenium, µg	23.8	40
Chromium, µg	14	37
Molybdenum, µg	15	40
Sodium, mg (mEq)	215 (9.4)	1175 (51.1)
Potassium, mg (mEq)	760 (19.4)	1800 (46)
Chloride, mg (mEq)	390 (11)	1325 (37.4)
Vitamins		
A, IU (µg RE)	1450 (435)	1650 (495)
D, IU (µg)	510 (12.8)	1100 (27.5)
E, IU (mg α-TE)	14 (7.2)	13 (7)
K, µg	70	70
Thiamin (Vit B_1), mg	1.235	4
Riboflavin (Vit B_2), mg	0.725	1.8
B_6, mg	0.625	1.1
B_{12}, µg	0.92	7.3
Niacin, mg (mg NE)†	4.84 (10.2)	21 (30.3)
Folic Acid (Folacin), µg	97	510
Pantothenic Acid, mg	4.58	10.9
Biotin, µg	26.4	140
Vitamin C (Ascorbic Acid), mg	75	75
Choline, mg	106	130
Inositol, mg	160	100

† 60 mg tryptophan = 1 mg niacin equivalent (NE)

* Approximate **unpacked** weights of Cyclinex in level, dry US standard household measures:

CYCLINEX-1, CYCLINEX-2	1 Tbsp =	8 g
	¼ cup =	30 g
	⅓ cup =	40 g
	½ cup =	60 g
	1 cup =	120 g

Glutaric Aciduria Type I

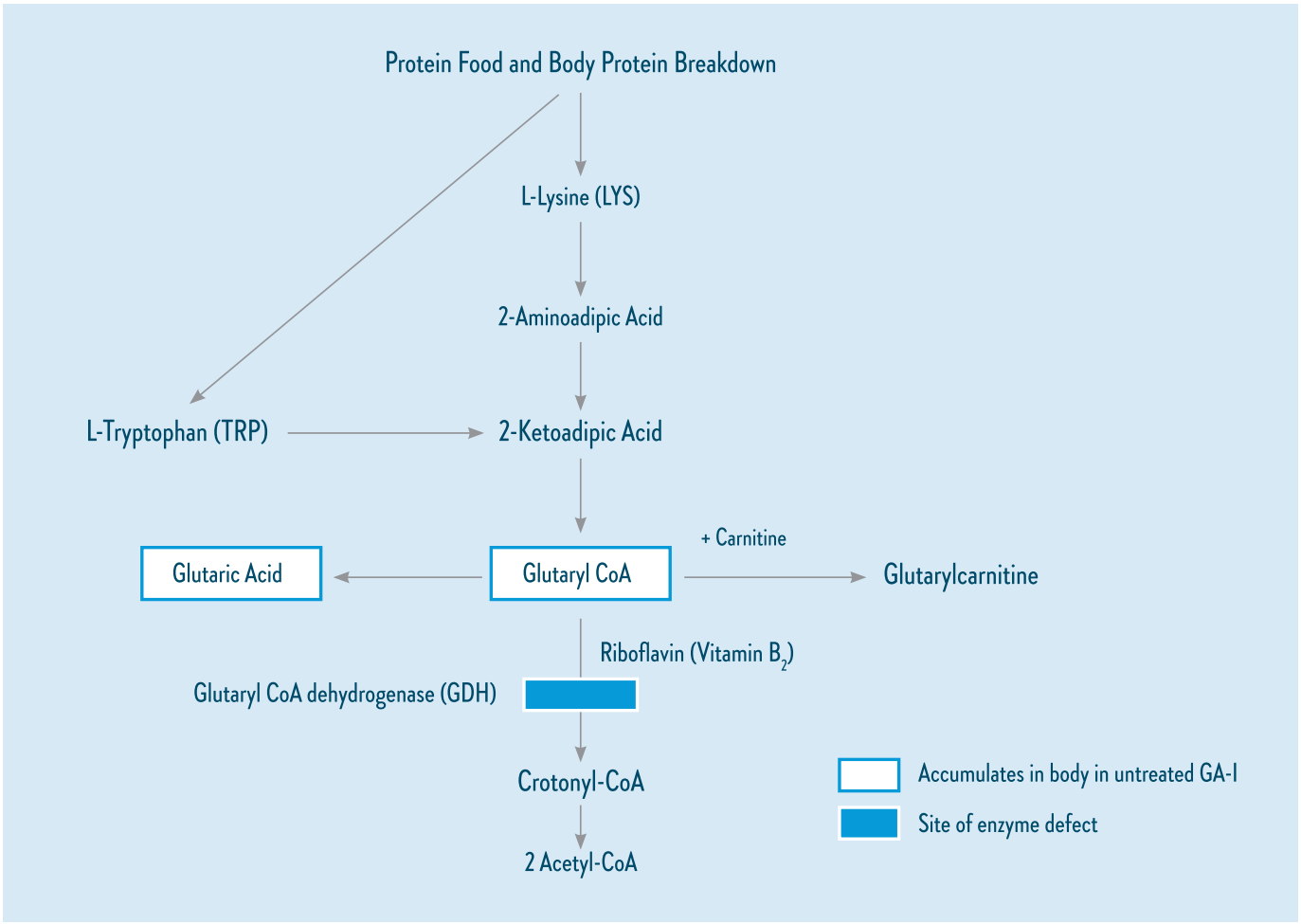
INTRODUCTION

Glutaric aciduria type I (GA-I) results from a defect in the enzyme glutaryl-CoA dehydrogenase (GDH). Because of the enzyme defect, breakdown of essential lysine (LYS) and tryptophan (TRP) does not occur normally, and toxic glutaric acid accumulates in body fluids (Fig 7). The exact cause of the pathophysiology is not known. It is hoped that with early detection, neurological crises will be reduced. The actual incidence of GA-I is not known, but may be as common as 1/30,000 live births with an increased prevalence in certain Amish communities.

PRESENTATION

Patients with GA-I appear normal at birth and develop normally until late infancy or the early toddler years, when an illness, sometimes viral, results in vomiting, acidosis, nervous system damage with a "cerebral palsy-like" disorder, and occasionally, seizures. The cause of the nervous system damage is not known, but a defect in making a specific brain chemical is likely. Elevated blood content of glutaric acid is believed to inhibit the manufacture of this brain chemical.

FIGURE 7: GLUTARIC ACIDURIA TYPE I



OUTCOME

Outcomes in children with GA-I vary from severe physical infirmity to almost-normal development. Many factors, such as time of appearance and severity of symptoms, avoidance of illness, and appropriate medical care during acute episodes, can affect outcome. In theory, if blood glutaric acid concentration can be reduced to and maintained in the normal range during early infancy and throughout life, then the outcome should improve.

RATIONALE FOR NUTRITION SUPPORT

Correction of the primary biochemical imbalance through restriction of essential dietary LYS and TRP may prevent the onset of nervous system damage and/or inhibit further decline if symptoms are already present. Pharmacologic doses of oral riboflavin may help increase the activity of the defective enzyme, but the benefit has not been fully determined. Large doses of L-carnitine are also required to enhance the loss of toxic glutaric acid and to prevent carnitine deficiency.

GOALS OF NUTRITION SUPPORT

1. Maintenance of normal plasma concentrations of LYS, TRP, and urinary glutaric acid.
2. Maintenance of normal growth and development.
3. Maintenance of normal nutrition status.
4. Prevention of body protein breakdown.
5. Prevention of carnitine deficiency.

Acute illness requires rapid therapy in order to maintain fluid balance and to supply additional energy to prevent the breakdown of body protein, which can increase blood concentrations of LYS, TRP, and glutaric acid. If the patient cannot tolerate oral feedings, then parenteral nutrition providing carbohydrate, fat, and amino acids low in or free of LYS and TRP is indicated. Oral feedings should be introduced as tolerated.

METHODS OF NUTRITION SUPPORT

Nutrition support of GA-I requires the use of small, prescribed amounts of intact protein to provide essential LYS and TRP; a medical food (Glutarex®-1 Amino Acid-Modified Medical Food With Iron and Glutarex®-2 Amino Acid-Modified Medical Food) to provide a LYS- and TRP-free protein source; nitrogen-free energy sources (Pro-Phree®, pure fat, sugar); fluid; riboflavin; and L-carnitine. Glutarex-1 and Glutarex-2 are fortified with L-carnitine, therefore, additional supplementation may not be necessary if adequate Glutarex is fed. In infants, infant formula or breast milk is used to supply the prescribed amount of essential LYS and TRP. In children and adults, foods are limited to prescribed amounts of low-protein breads, cereals, fats, fruits, vegetables, and protein-free foods. High-protein foods, such as dairy products, eggs, fish, meat, and poultry, cannot be used in an LYS- and TRP-restricted diet. Low-protein foods alone cannot be used to treat children with GA-I because they result in protein, mineral, and vitamin deficiencies.

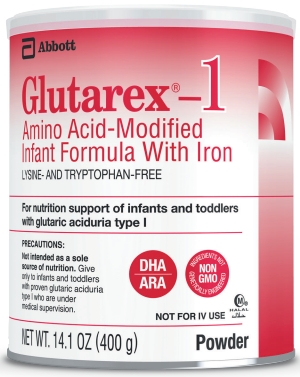
L-carnitine (100 to 300 mg/kg/day) is used to reduce the amount of blood glutaric acid by forming glutarylcarnitine, a nontoxic compound which is excreted in the urine. Nutrient composition of the Glutarex formulas is found in Table 9.

MONITORING

Frequent evaluation of growth; nutrient intake; plasma concentrations of LYS, TRP, and other amino acids; glutaric acid; and protein, iron, and carnitine status is essential in providing optimal nutrition support.

TABLE 9: NUTRIENT COMPOSITION OF GLUTAREX®-1 AND GLUTAREX®-2

NUTRIENT	GLUTAREX-1* Per 100 g powder	GLUTAREX-2* Per 100 g powder
Energy, kcal	480	410
Protein equiv, g	15	30
Fat, g	21.7	13
Carbohydrate, g	53	35
Linoleic Acid, mg	3650	2200
Linolenic Acid, mg	360	225
L-Carnitine, mg	900	1800
Minerals		
Calcium, mg	575	975
Phosphorus, mg	400	760
Magnesium, mg	50	225
Iron, mg	7.6	13
Zinc, mg	5.2	13
Manganese, mg	0.385	0.8
Copper, mg	0.408	1.5
Iodine, µg	65	100
Selenium, µg	21	35
Chromium, µg	12	27
Molybdenum, µg	13.8	30
Sodium, mg (mEq)	190 (8.3)	880 (38.3)
Potassium, mg (mEq)	675 (17.3)	1370 (35)
Chloride, mg (mEq)	325 (9.2)	940 (26.5)
Vitamins		
A, IU (µg RE)	1300 (390)	1500 (450)
D, IU (µg)	450 (11.3)	900 (22.5)
E, IU (mg α-TE)	12.5 (6.4)	12 (5.9)
K, µg	60	60
Thiamin (Vit B_1), mg	1.12	3.3
Riboflavin (Vit B_2), mg	0.65	1.6
B_6, mg	0.56	1.1
B_{12}, µg	0.85	5
Niacin, mg (mg NE)	4.45 (4.5)	16 (16)
Folic Acid (Folacin), µg	88	425
Pantothenic Acid, mg	4	8
Biotin, µg	23.5	100
Vitamin C (Ascorbic Acid), mg	75	60
Choline, mg	95	100
Inositol, mg	144	82



* Approximate **unpacked** weights of Glutarex in level, dry US standard household measures:

GLUTAREX-1, GLUTAREX-2	1 Tbsp =	8 g
	¼ cup =	30 g
	⅓ cup =	40 g
	½ cup =	60 g
	1 cup =	120 g

Leucine Catabolism Disorders

INTRODUCTION

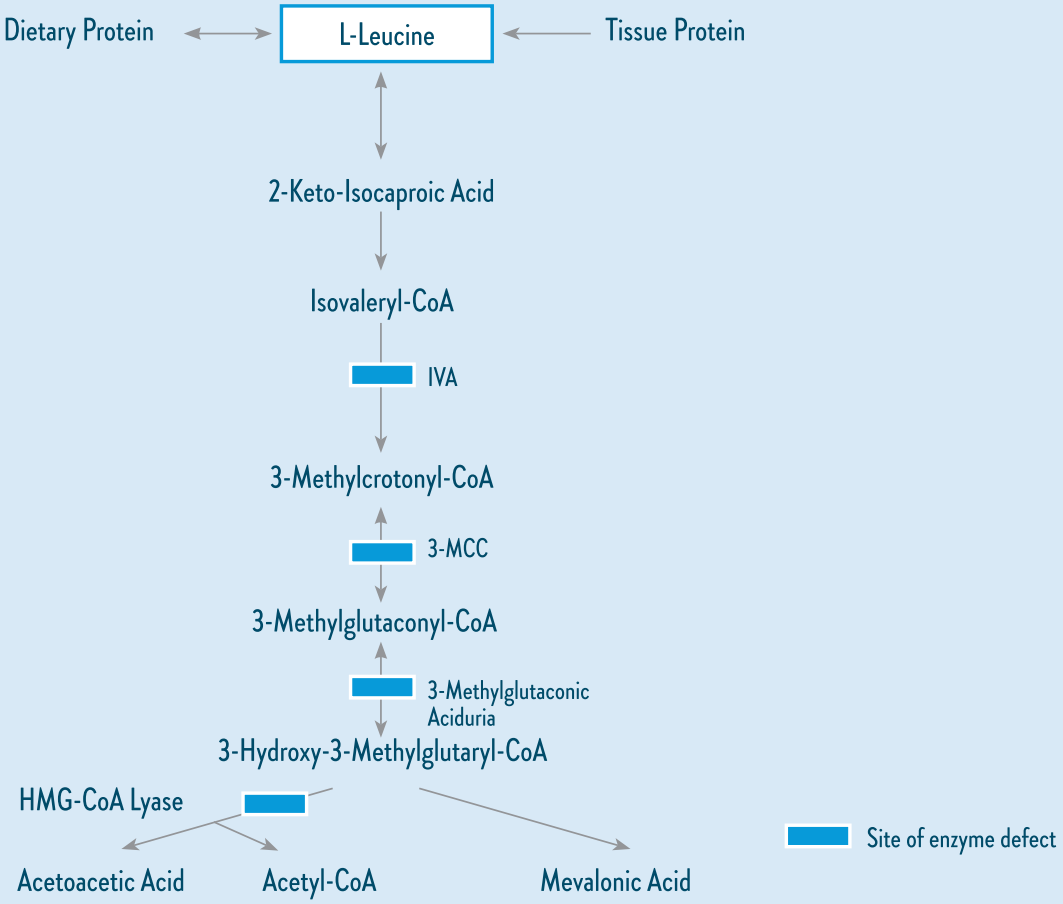
There are four disorders of leucine catabolism considered to be branched-chain organic acidurias. The name of the deficiency generally refers to the enzyme affected. The four disorders have different treatment methods. See Figure 8 for all disorders.

Isovaleric Acidemia, or IVA, is a deficiency of isovaleryl-CoA dehydrogenase (IVD) that prevents LEU from being used in the body. Because LEU cannot be used normally, LEU or the products from its breakdown build up as isovaleric acid and other toxic substances. This excess keeps another important substance, coenzyme A (CoA), from working and causes the symptoms of IVA.

3-Methylcrotonyl-CoA Carboxylase Deficiency, or 3-MCC, is a deficiency in 3-methylcrotonyl CoA, blocking the body's ability to break down LEU (Figure 8).

3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency, also known as HMG-CoA lyase deficiency. This deficiency not only blocks the body's ability to break down LEU, but also prevents the body from making ketones (key-tones), which are used for energy during periods without food (fasting).

FIGURE 8: METABOLIC PATHWAY FOR LEU



3-Methylglutaconic Aciduria Type I is a deficiency of methylglutaconyl-CoA hydratase that results from an increased amount of 3-methylglutaconic acid released and blocks the body's ability to break down LEU (Figure 8).

PRESENTATION

IVA: A characteristic feature of IVA is a distinctive odor of sweaty feet. This odor is caused by the buildup of isovaleric acid in affected individuals. There are two different types of IVA—acute and chronic.

- **"Acute"** IVA infants appear normal at birth but develop poor feeding, vomiting, diarrhea, and drowsiness (lethargy) within the first few weeks of life. A "sweaty-feet" odor of the blood and urine are noted. Some infants also exhibit severe acidosis seizures, high ammonia levels (hyperammonemia), low platelet count in the blood (thrombocytopenia), low number of white blood cells (neutropenia), low number of red and white blood cells and platelets (pancytopenia), and low calcium levels (hypocalcemia).
- **"Chronic Intermittent"** IVA children are normal at birth. During the first few years of life, they may develop episodes of vomiting, metabolic acidosis, and excessive tiredness (lethargy). The characteristic "sweaty-feet" odor is typically present, and temporary hair loss (transient alopecia) is usually seen. Episodes may begin as early as 2 weeks of age, and the frequency of attacks seems to decrease with age. Infections tend to trigger the episodes, as does illness and an excessive intake of protein.

3-MCC Deficiency: Children typically have normal growth and development until they have an acute episode between 6 months and 3 years of age. Symptoms have also been reported in the neonatal period and as late as adulthood. Symptoms typically occur after an infection and may include poor muscle tone (hypotonia) or coordination, poor feeding, vomiting, excessive tiredness (lethargy), developmental delay, or symptoms resembling Reye's syndrome (low blood sugar [hypoglycemia], high ammonia levels in the blood [hyperammonemia], metabolic acidosis, elevated liver enzymes [transaminases], and seizures).

HMG-CoA Lyase Deficiency: Symptoms may include vomiting, excessive tiredness (lethargy), metabolic acidosis, low blood sugar (hypoglycemia), high ammonia levels (hyperammonemia), and an enlarged liver (hepatomegaly), frequently triggered by an illness or fasting. Infection, high protein intake, and prolonged fasting can lead to metabolic decompensation, resulting in low blood sugar with a small amount or no ketones produced (hypoketotic hypoglycemia), and an increase in several organic acids. The inability to produce ketones in response to fasting can cause severe low blood sugar.

Methylglutaconic Aciduria: Symptoms range from isolated speech retardation to slowing down of thought and a reduction in physical movement (psychomotor abnormalities), seizures, and nervous system impairment. Symptoms resembling Reye's syndrome, including low blood sugar (hypoglycemia), acidosis, and high ammonia levels (hyperammonemia), have also been reported.

3-Methylglutaconic Aciduria: The effect of long-term nutrition management of this rare disorder has not been established. Nutrition management may include a LEU-free medical food paired with a low-protein diet (restricting LEU) paired with carnitine supplementation.

OUTCOME

Treating a child as early in life as possible may prevent developmental delay and severe neurological damage. Not following a LEU-restricted diet may cause mental and neurological damage at any age. Lifelong nutrition support must be adapted to each person's needs. Early diagnosis and appropriate treatment promote normal growth and development.

RATIONALE FOR NUTRITION SUPPORT

The rationale for nutrition support includes correction of the primary biochemical imbalance by restriction of essential dietary LEU and provision of adequate glycine and carnitine to bind with toxic metabolites for their removal from body fluids.

GOALS OF NUTRITION SUPPORT

1. Maintenance of normal plasma concentrations of LEU, carnitine, and glycine (in IVA).
2. Maintenance of normal mental and physical growth and development.
3. Prevention of body protein breakdown.
4. Prevention of carnitine deficiency.

METHODS OF NUTRITION SUPPORT

Nutrition support during acute illness must supply adequate energy and protein to prevent the body from breaking down its own protein and releasing LEU into the bloodstream. High-energy foods, free of LEU, should be administered either by mouth or vein. Pharmacologic amounts of L-carnitine and glycine (in IVA and 3-MCC) help remove toxic metabolites. When the patient is clinically stable, dietary LEU can be slowly added back into the diet.

Long-term nutrition support requires a prescription for essential LEU, L-carnitine, glycine (in IVA and 3-MCC), protein, energy, and fluid. The LEU required differs for each patient based on age, gender, and degree of enzyme activity. Glycine administration varies from 100 to 300 mg/kg/day. I-Valex®-1 contains 67 mg glycine per gram of protein, and I-Valex®-2 contains 101 mg glycine per gram of protein. Consequently, additional glycine above that in I-Valex may not be required. Nutrient composition of the I-Valex formulas is found in Table 10, next page.

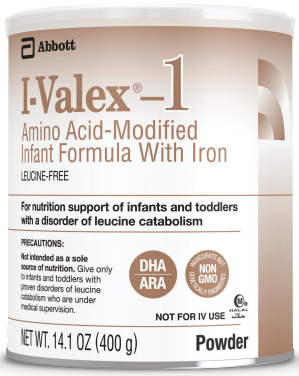
Carnitine also binds isovaleric acid and increases its excretion. Carnitine administration is necessary to prevent secondary L-carnitine deficiency. A deficiency of carnitine can limit the use of fatty acids for energy. Carnitine administration of 100 to 300 mg/kg/day helps normalize plasma-free carnitine concentrations. I-Valex contains 60 mg carnitine per gram of protein. Consequently, additional L-carnitine supplements above that in I-Valex may not be required. High-protein foods, such as dairy products, eggs, fish, legumes, meat, and poultry, cannot be used in a LEU-restricted diet. LEU is provided by infant formula until about 4 to 6 months of age, when solid foods are introduced. As the child grows, solid foods will gradually displace the infant formula as the source of LEU. Prescribed amounts of low-protein breads, cereals, fats, fruits, and vegetables are used to provide LEU, and protein-free foods supply energy in the diet of the child or adult. LEU-free medical foods are used with prescribed amounts of intact protein to supply LEU and other essential amino acids. Medical foods often provide ≥50% of the protein requirement, and thus supply the majority of minerals and vitamins in the diet.

ADDITIONAL THERAPIES

HMG-CoA Lyase Deficiency: Additional therapies include what is listed above paired with decreased fat intake and avoidance of fasting. The goal of long-term nutrition management is to prevent low blood sugar, limit long periods of fasting, and minimize elevations of LEU metabolites. A high-carbohydrate, low-fat diet with LEU restriction results in normal growth and development. A high carbohydrate intake with reduced fat intake is required to prevent the buildup of metabolites arising from the breakdown of stored body fat (fatty acid oxidation). Carnitine helps the body get rid of toxic metabolites that build up in the body as well as help to prevent possible deficiencies.

MONITORING

Nutrition evaluation includes measurement of plasma amino acids; urinary isovaleric acid, isovalerylglycine, and isovalerylcarnitine; indices of protein and iron status; plasma-free and esterified carnitine; growth parameters; and assessment of nutrient intake.



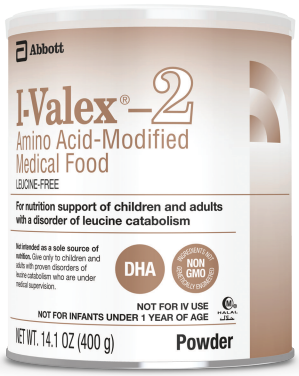


TABLE 10: NUTRIENT COMPOSITION OF I-VALEX®-1 AND I-VALEX®-2

NUTRIENT	I-VALEX-1* Per 100 g powder	I-VALEX-2* Per 100 g powder
Energy, kcal	480	410
Protein equiv, g	15	30
Fat, g	21.7	13
Carbohydrate, g	53	35
Linoleic Acid, mg	3650	2200
Linolenic Acid, mg	360	225
L-Carnitine, mg	900	1800
Minerals		
Calcium, mg	575	975
Phosphorus, mg	400	760
Magnesium, mg	50	225
Iron, mg	7.6	13
Zinc, mg	5.2	13
Manganese, mg	0.385	0.8
Copper, mg	0.408	1.5
Iodine, µg	65	100
Selenium, µg	21	35
Chromium, µg	12	27
Molybdenum, µg	13.8	30
Sodium, mg (mEq)	190 (8.3)	880 (38.3)
Potassium, mg (mEq)	675 (17.3)	1370 (35)
Chloride, mg (mEq)	325 (9.2)	940 (26.5)
Vitamins		
A, IU (µg RE)	1300 (390)	1500 (450)
D, IU (µg)	450 (11.3)	900 (22.5)
E, IU (mg α-TE)	12.5 (6.4)	12 (5.9)
K, µg	60	60
Thiamin (Vit B_1), mg	1.12	3.3
Riboflavin (Vit B_2), mg	0.65	1.6
B_6, mg	0.56	1.1
B_{12}, µg	0.85	5
Niacin, mg (mg NE)†	4.45 (7.7)	16 (21.7)
Folic Acid (Folacin), µg	88	425
Pantothenic Acid, mg	4	8
Biotin, µg	23.5	100
Vitamin C (Ascorbic Acid), mg	75	60
Choline, mg	95	100
Inositol, mg	144	82

† 60 mg tryptophan = 1 mg niacin equivalent (NE)

* Approximate **unpacked** weights of I-Valex in level, dry US standard household measures:

I-VALEX-1, I-VALEX-2	1 Tbsp =	8 g
	¼ cup =	30 g
	⅓ cup =	40 g
	½ cup =	60 g
	1 cup =	120 g

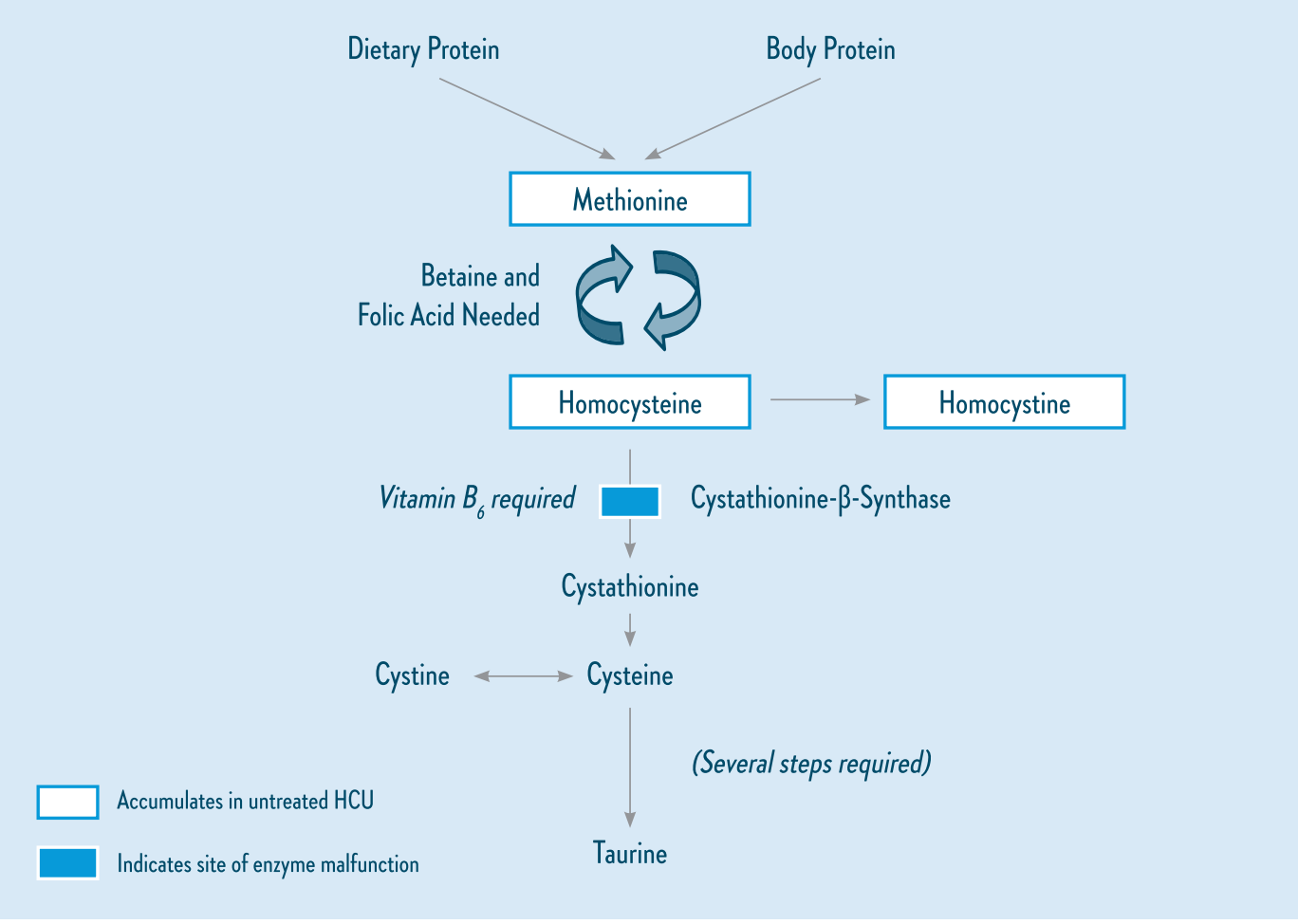
Homocystinuria

INTRODUCTION

Homocystinuria (HCU) results from a defect in the activity of the enzyme cystathionine-ß-synthase, which is responsible for one of the steps in the metabolism of methionine (MET), an essential amino acid. Consequently, there is accumulation of plasma MET and homocysteine and a deficiency of cysteine (CYS) in body cells and fluids (Fig 9).

A small percentage of individuals with HCU respond to pharmacologic doses of pyridoxine (vitamin B_6). In these individuals, pyridoxine, which is normally required for the activation of cystathionine-ß-synthase, can reduce the plasma concentration of MET and homocysteine and ameliorate the symptoms common to HCU. All patients with HCU should be given a trial of pyridoxine. Persons who are pyridoxine-responsive normally do not require an MET-restricted diet. Betaine (a nutrient formed naturally during choline catabolism) and folic acid are helpful in remethylating homocysteine to MET and are used in therapy.

FIGURE 9: METHIONINE METABOLISM IN HOMOCYSTINURIA



PRESENTATION

The incidence of HCU ranges from 1/50,000 to 1/200,000 live births. The incidence is greater in people of Irish descent—1/50,000. Children with HCU appear normal at birth, but without treatment, in time may develop dislocated optic lenses, skeletal changes, and venous and arterial blood clots. Mental retardation, with or without seizures, is variable.

OUTCOME

Infants (pyridoxine-nonresponsive) diagnosed and treated from infancy have had normal IQ, delay or prevention of dislocated lenses, and prevention of seizures. The long-term effects of early diagnosis and treatment on blood clotting and bone formation are not yet known.

RATIONALE FOR NUTRITION SUPPORT

Correction of the primary biochemical imbalance is achieved through a restriction in essential dietary MET and supplementation with betaine, CYS and folic acid. Pyridoxine in the B_6-responsive patient helps to increase the activity of any defective enzyme present.

GOALS OF NUTRITION SUPPORT

1. Maintenance of normal plasma concentrations of MET, CYS and homocysteine.
2. Maintenance of normal growth and development.
3. Maintenance of normal nutrition status.
4. Prevention of dislocated lenses, dystonia, bone problems, and blood clots.
5. Prevention of body protein breakdown.

METHODS OF NUTRITION SUPPORT

Nutrition support of HCU requires the use of prescribed amounts of intact protein to provide essential MET and a special MET-free, CYS-supplemented medical food (Hominex®-1 Amino Acid-Modified Medical Food With Iron and Hominex®-2 Amino Acid-Modified Medical Food) to provide an MET-free protein source. Betaine helps maintain normal plasma MET concentrations after meals. A trial period of pyridoxine is recommended prior to initiation of the MET-restricted diet in newly diagnosed newborns. High-protein foods, such as dairy products, eggs, fish, legumes, meat, and poultry, are prohibited. Foods are limited to prescribed amounts of low-protein breads, cereals, fats, fruits, and vegetables to supply MET. In infants, dietary MET is supplied by infant formula or breast milk until about 4 to 6 months of age, when solid foods are gradually introduced. MET-free foods containing little or no MET are provided for additional energy. Nutrient composition of the Hominex formulas is found in Table 11.

Low-protein diets alone, without medical foods (ie, Hominex-1 and Hominex-2), are not nutritionally adequate and lead to marked protein, mineral, and vitamin deficiencies and failure to thrive. For this reason, Hominex-1 and Hominex-2, which are free of MET, are supplemented with a soluble form of CYS, and contain all other essential and nonessential amino acids, minerals, and vitamins, are required. Medical foods may provide 50-80% of the patient's protein requirement.

MONITORING

Frequent evaluation of plasma concentrations of MET, CYS, homocysteine, and other amino acids; folic acid; and indices of protein and iron status are essential. Assessments of growth and nutrient intake are necessary to ascertain the adequacy of the diet prescription. Pulses, skeletal growth and mineralization, ocular lenses, and neurologic status should be routinely assessed.

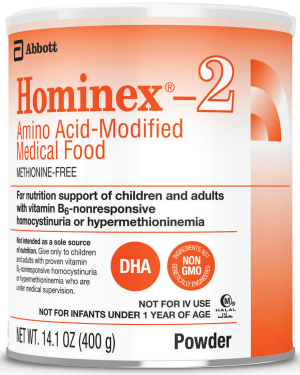
TABLE 11: NUTRIENT COMPOSITION OF HOMINEX®-1 AND HOMINEX®-2

NUTRIENT	HOMINEX-1* Per 100 g powder	HOMINEX-2* Per 100 g powder
Energy, kcal	480	410
Protein equiv, g	15	30
Fat, g	21.7	14
Carbohydrate, g	53	35
Linoleic Acid, mg	3650	2200
Linolenic Acid, mg	360	225
L-Carnitine, mg	20	40
Minerals		
Calcium, mg	575	975
Phosphorus, mg	400	760
Magnesium, mg	50	225
Iron, mg	7.6	13
Zinc, mg	5.2	13
Manganese, mg	0.385	0.8
Copper, mg	0.408	1.5
Iodine, µg	65	100
Selenium, µg	21	35
Chromium, µg	12	27
Molybdenum, µg	13.8	30
Sodium, mg (mEq)	190 (8.3)	880 (38.3)
Potassium, mg (mEq)	675 (17.3)	1370 (35)
Chloride, mg (mEq)	410 (11.6)	1160 (32.7)
Vitamins		
A, IU (µg RE)	1300 (390)	1500 (450)
D, IU (µg)	450 (11.3)	900 (22.5)
E, IU (mg α-TE)	12.5 (6.4)	12 (5.9)
K, µg	60	60
Thiamin (Vit B_1), mg	1.12	3.3
Riboflavin (Vit B_2), mg	0.65	1.6
B_6, mg	0.56	1.1
B_{12}, µg	0.85	5
Niacin, mg (mg NE)†	4.45 (7.7)	16 (21.7)
Folic Acid (Folacin), µg	88	425
Pantothenic Acid, mg	4	8
Biotin, µg	23.5	100
Vitamin C (Ascorbic Acid), mg	75	60
Choline, mg	95	100
Inositol, mg	144	82

† 60 mg tryptophan = 1 mg niacin equivalent (NE)

* Approximate **unpacked** weights of Hominex in level, dry US standard household measures:

HOMINEX-1, HOMINEX-2	1 Tbsp =	8 g
	¼ cup =	30 g
	⅓ cup =	40 g
	½ cup =	60 g
	1 cup =	120 g



Hypercalcemia

Hypercalcemia results from four disorders described below:

WILLIAMS SYNDROME

Williams syndrome (WS) is an autosomal dominant disorder characterized by supravalvular aortic stenosis, which may include peripheral pulmonary stenosis, elfin facies, and psychomotor retardation. Developmental delay is found in approximately 72% of patients. The phenotype of WS may be due to a hemizygous defect in the elastin gene (7q11.3) or genes contiguous to the elastin locus, which may account for some of the vascular problems and dysmorphism associated with WS. Hypercalcemia and central nervous symptoms may result from deletion of adjacent genes.

Infantile hypercalcemia is found in approximately 40% of patients with WS and usually resolves by 4 years of age. A dysfunction of the human calcitonin gene receptor, a transmembrane peptide that acts both as a calcitonin receptor and an extracellular calcium sensor, has been reported in this disorder. Reports of patients with WS also identify defects in vitamin D metabolism and calcitonin secretion. Nephrocalcinosis secondary to hypercalcemia has been reported.

OSTEOPETROSIS

Osteopetrosis is a group of diseases of defective osteoclast function resulting in reduced resorption of calcified cartilage. Consequently, patients exhibit increased skeletal mass and bone density and abnormal bone remodeling. Inheritance is either autosomal recessive or autosomal dominant. The milder dominant form exhibits in adult life. Autosomal recessive malignant infantile osteopetrosis is a rare disease affecting approximately 1/200,000 live births with increased incidence in Saudi Arabia and Costa Rica. The cause of osteopetrosis is unknown except for a small number of patients with a carbonic anhydrase II deficiency.

The accumulation of bone in osteopetrotic patients results in narrowing of the cranial nerve foramina and reduction in the bone marrow cavity. Immunodeficiency results from reduced leukocyte superoxide generation. These defects can lead to hearing loss, blindness, and/or sepsis.

PRIMARY NEONATAL HYPERPARATHYROIDISM

Primary neonatal hyperparathyroidism (PNH) is a rare disorder resulting in excessive production of parathyroid hormone (PTH) due to parathyroid hyperplasia. A defect in the gene that expresses the calcium-sensing receptor protein in parathyroid, thyroid, and renal cells may be responsible for PNH.

Patients with PNH present early in infancy with failure to grow, anorexia, irritability, lethargy, respiratory distress, bone demineralization, and fractures. Severe hypercalcemia (>15 to 20 mg/dL [3.75 to 5.00 mmol/L]) and increased plasma PTH concentrations are found.

IDIOPATHIC HYPERCALCEMIA

Idiopathic hypercalcemia may be due, in part, to disorders that result in excessive intestinal calcium absorption, increased resorption of bone calcium, or enhanced renal resorption. Additionally, disturbances of vitamin D and calcium-phosphate metabolism may be evident. Phenotypes may be benign or malignant. Any infant or child with hypercalcemia must have a thorough clinical evaluation for diagnosis.

These disorders are all treated with Calcilo XD®, a vitamin D-free, low-calcium powdered formula. No other company manufactures a similar formula. Nutrient composition of Calcilo XD formula is found in Table 12.

TABLE 12: NUTRIENT COMPOSITION OF CALCILO XD®

NUTRIENT	CALCILO XD Per 100 g powder
Energy, kcal	513
Protein, g	11.4
Carbohydrate, g	52.3
Fat, g	28.7
Linoleic acid, mg	6660
Minerals	
Calcium, mg	15
Chloride, mg/mEq	292 (8.2)
Copper, µg	460
Iodine, µg	31
Iron, mg	9.2
Magnesium, mg	31
Manganese, µg	26
Phosphorus, mg	128
Potassium, mg (mEq)	420 (10.7)
Selenium, µg	10
Sodium, mg (mEq)	125 (5.4)
Zinc, mg	3.8
Vitamins	
A, IU	1540
D, IU	0
E, IU	10
K, µg	41
Vitamin C (Ascorbic Acid), mg	46
Biotin, µg	23
B_6, µg	310
B_{12}, µg	1.3
Choline, mg	62
Folic Acid (Folacin), µg	77
Inositol, mg	123
Niacin, µg	5400
Pantothenic Acid, µg	2300
Riboflavin (Vit B_2), µg	770
Thiamine (Vit B_1), µg	513
Other	
Potential Renal Solute Load, mOsm/100 g	94

Approximate **unpacked** weights of Calcilo XD in level, dry US standard household measures:

CALCILO XD	1 scoop =	8.6 g
	1 Tbsp =	7 g
	¼ cup =	26 g
	⅓ cup =	35 g
	½ cup =	53 g
	1 cup =	105 g

Galactosemia

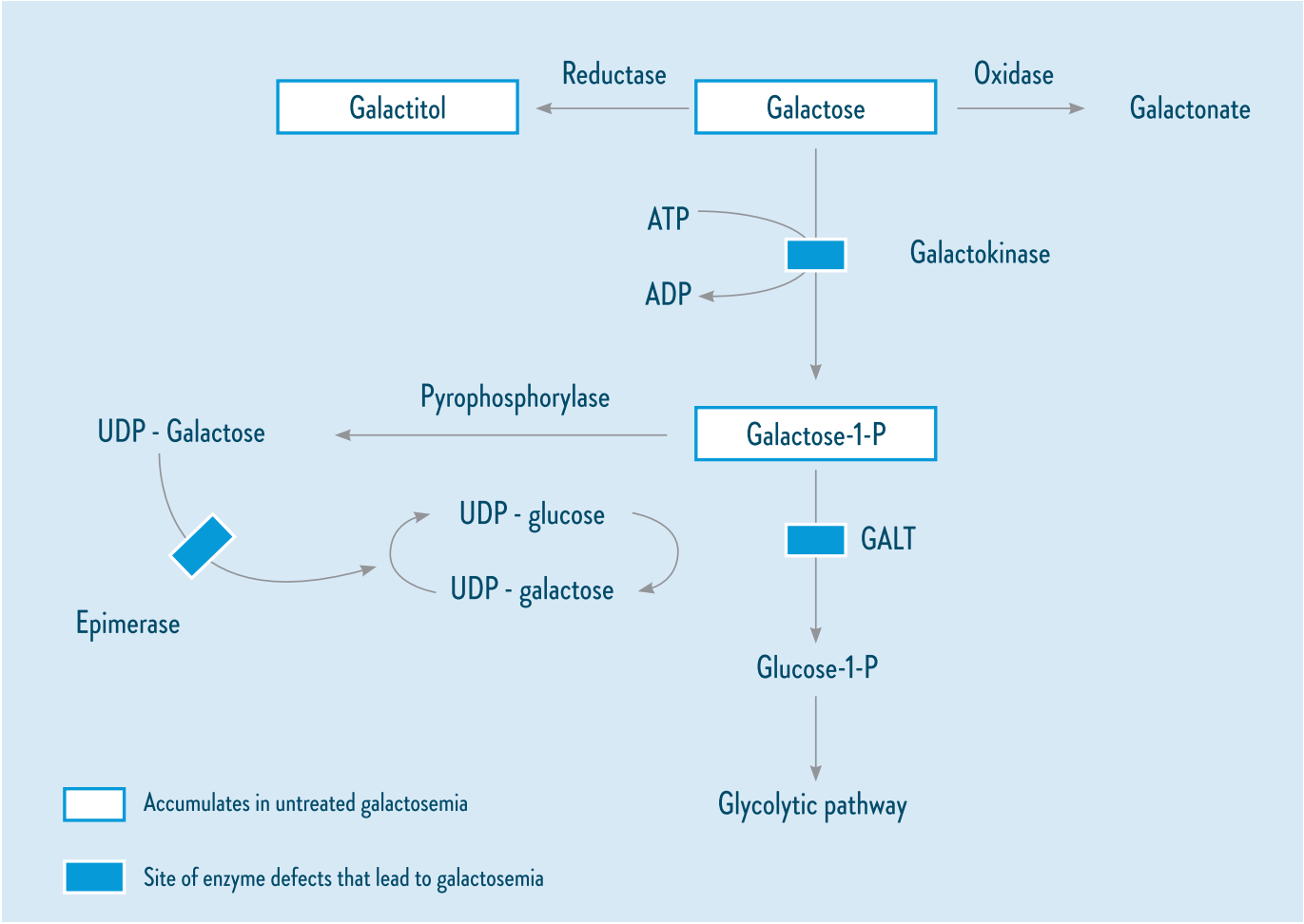
Galactosemia is an inherited disorder of galactose (GAL) metabolism that results from a defect in one of three enzymes: galactokinase, GAL-1-phosphate uridyltransferase (GALT), and uridine diphosphate (UDP)-GAL-4-epimerase (Fig 10). The most common form of galactosemia results from a defect in GALT activity. It's estimated incidence is 1/40,000 to 1/80,000 live births. A milder variant, called Duarte galactosemia, in which one gene is the galactosemic gene and one is the Duarte variant, is approximately 1/4,000 births. Patients with GALT deficiency appear normal at birth, but soon develop severe hepatic, renal, and gastrointestinal manifestations that, if not treated, lead to death. Symptoms may include cataracts, diarrhea, *E coli* sepsis, failure to thrive, jaundice, vomiting, and increased intracranial pressure. Patients with galactokinase deficiency present with cataracts secondary to accumulation of galactitol in eye lenses.

Galactonate accumulates in erythrocytes of patients with GALT deficiency and may contribute to GAL toxicity. Removal of dietary lactose and GAL is essential to prevent further metabolic crises in patients with GALT deficiency. Rapid screening, retrieval, diagnosis, and treatment are essential to prevent clinical manifestations.

Treatment of Duarte galactosemia is controversial. Some clinicians treat with a galactose-restricted diet in the first year of life, whereas others regard it as a benign condition.

Galactosemia due to a deficiency of GALT

FIGURE 10: METABOLISM OF GAL IN GALACTOSEMIA



leads to an accumulation of GAL-1-phosphate (GAL-1-P) and galactitol in erythrocytes, liver, kidney, brain, and other tissues. Additional laboratory findings include albuminuria, hypophosphatemia, hypokalemia, and hyperaminoacidiuria. Reasons for symptoms associated with GALT deficiency are not well defined but hypotheses include the involvement of GAL-1-P in a futile phosphorylation cycle and defective GAL incorporation into galactosylated compounds.

Soy protein isolate infant formulas, including Similac® Soy Isomil® Powder, Concentrated Liquid (CL), and Ready To Feed (RTF) have been used for years in the nutrition support of patients with galactosemia. However, Similac Soy Isomil CL and RTF formulas contain carrageenan, a natural gum, which contains approximately 27% bound galactose by weight. Similac Soy Isomil Powder is NOT manufactured with carrageenan and contains an average 14 mg bound galactose/L (reconstituted). Similac Soy Isomil CL has approximately 31 mg total bound galactose/L (reconstituted), and Isomil RTF contains approximately 97 mg total bound galactose/L.

The digestion and absorption of bound galactose from dietary carrageenan is not known. Moreover, the type and processing of carrageenan may affect the quantity of bound galactose in liquid forms of Similac Soy Isomil. The effect of consumption of carrageenan from either Similac Soy Isomil or other soy protein isolate liquid formulas on clinical outcomes in patients with galactosemia is not known.

Individuals must remove all foods and medications from the diet that contain GAL, including milk and all milk products and some fruits and vegetables.

RCF® No Carbohydrate Added Soy Infant Formula Base With Iron

INTRODUCTION

RCF can be used in a number of different diseases and disorders. Among these are carbohydrate intolerance, some glycogen storage diseases, pyruvate dehydrogenase complex deficiency, glucose transport defects, and seizure disorders requiring a ketogenic diet. RCF is the only no carbohydrate formula available for infants.

CARBOHYDRATE INTOLERANCE

Carbohydrate intolerance results from deficiencies of enzymes that split sugars to their smallest parts in the small intestine or from a deficiency of a compound that carries glucose and galactose from the small intestine into the blood. Symptoms of carbohydrate intolerance are similar, whatever the cause, and include watery diarrhea, gas, and bloating. Abdominal cramping may occur. If diarrhea persists, dehydration and acidosis may be severe. Loss of skin on the buttocks may occur. RCF can be used to manage the diets of infants and children when the amount and/or type of carbohydrate may need to be carefully regulated, such as in sucrase-isomaltase deficiency and glucose-galactose malabsorption.

PROTRACTED DIARRHEA IN INFANCY

Carbohydrate malabsorption is a constant feature of this syndrome, which typically occurs in early infancy. Infants with this condition experience diarrhea, dehydration, and malnutrition. The etiology includes infection, allergy, and inborn errors of gastrointestinal development. Some clinicians choose to use RCF with gradually increasing amounts of carbohydrate or use a specific carbohydrate (eg, fructose) in the treatment of these infants.

GLYCOGEN STORAGE DISEASES (GSD)

Several different inherited enzyme defects interfere with the breakdown of glycogen (a storage form of carbohydrate in the body) and raise the glycogen content of the organ in which the enzyme is located. Because stored glycogen is a between-meal and nighttime source of blood sugar, when enzymes that break down glycogen do not function, blood glucose concentrations often drop to dangerously low levels.

When the enzyme defect is in the liver, the excess glycogen stored in the liver causes a protruding abdomen due to an enormously enlarged liver, retarded growth, elevated blood uric acid that can cause gout, elevated blood lipids, and problems with blood clotting due to liver damage. Hepatoma (cancer) of the liver may also occur.

Treatment during infancy consists of frequent feeds around the clock with continuous gastric drip feeding of RCF with glucose powder at night. Raw cornstarch, because of its slow release of glucose, may gradually be introduced at 6 to 9 months of age and may supply 50% to 60% of the energy in the diet. Raw cornstarch may be added to RCF as the carbohydrate source during all daytime and bedtime feedings.

Because polyunsaturated fats (PUFAs) help prevent hyperlipidemia, they are the fat of choice in GSD. The fat blend in RCF contains soy oil which is high in PUFAs.

PYRUVATE DEHYDROGENASE COMPLEX DEFICIENCY

Pyruvate dehydrogenase complex (PDHC) is a group of enzymes that is required for the use of carbohydrate as a fuel by the body. This enzyme complex is not required for use of fat as a fuel. Consequently, when PDHC is deficient, the body must get the majority of its fuel from fat.

Symptoms of this inherited, rare disorder include psychomotor retardation, hypotonia, ataxia, severe acidosis, failure to thrive, seizures, and dysmorphic features. Few patients with enzyme complex activity <10% of normal survive beyond 4 to 5 years of age.

Therapy consists of administering a ketogenic diet (ie, a diet very high in fat and low in

carbohydrate), the drug dichloroacetate, L-carnitine, and thiamine. The high-fat ketogenic diet bypasses the PDHC to provide fuel to the body. Dichloroacetate increases the half-life of any active PDHC that is made. L-carnitine enhances the use of fat as fuel and thiamine is a coenzyme (helper) for one of the enzymes in PDHC.

GLUCOSE TRANSPORT PROTEIN (GLUT1) DEFICIENCY

Glucose is the major fuel for cellular metabolism. Absorption and cellular uptake of glucose are regulated by a system of tissue-specific glycoproteins that maintain body glucose homeostasis.

GLUT1 is a facilitative glucose transport protein found in erythrocytes, fibroblasts, and the blood-brain barrier. GLUT1 functions effectively in glucose uptake by tissue in the absence of insulin.

Patients have presented with depressed cerebrospinal fluid (CSF) glucose concentrations, normal concentrations of blood glucose, and normal to low CSF lactate, suggesting a defect in GLUT1 transport. Clinical features include seizures, delayed mental and motor development, hypotonia, and impaired language skills and behavior. Onset of symptoms range from 2 to 27 months of age.

The ketogenic diet has reduced or eliminated seizures and improved psychomotor development within several days of diet onset. Mild cognitive impairment, and speech and motor delay may persist. Early diagnosis and diet intervention may lessen the pathophysiology associated with the GLUT1 defect.

INTRACTABLE SEIZURES

The ketogenic diet for the treatment of intractable seizures has experienced a resurgence in use in the last 10 years. The efficacy of the ketogenic diet in treating children with refractory epilepsy has been systematically reviewed in many individual studies and estimates of improvement were complete cessation of seizures in 16% of children, greater than 90% reduction of seizures in 32%, and greater than 50% reduction of seizures in 56%.

The two major indications for the ketogenic diet are unacceptable seizure frequency and medication toxicity. The diet is most effective in young children and should be continued for 18 months to 2 years.

The mechanism of action of the ketogenic diet is unknown. Several theories have been advanced but none have been proven.

RCF® has been used as an integral part of a nutritionally complete ketogenic diet for infants and children requiring tube feeding and children consuming solid diets. RCF provides all the vitamins and minerals present in standard infant formulas. Nutrient composition of RCF is found in Table 13.

Some centers use cream as the basis for the ketogenic diet. Cream is deficient in many nutrients requiring that mineral and vitamin supplements, which often contain carbohydrate, must be added.

TABLE 13: NUTRIENT COMPOSITION OF RCF®

NUTRIENT	RCF Per 100 mL unreconstituted	RCF Per 100 Cal (5 fl oz, prepared as directed)*
Energy, kcal	81	100
Protein, g	4	3
Fat, g	7.2	5.3
Carbohydrate, g	0.07	10.1
Water, g	88	133
Linoleic Acid, mg	1352	1000
Minerals		
Choline, mg	15.7	12
Inositol, mg	6.5	5
Calcium, mg	140	105
Phosphorus, mg	100	75
Magnesium, mg	10	7.5
Iron, mg	2.4	1.8
Zinc, mg	1	0.75
Manganese, mcg	34	25
Copper, mcg	100	75
Iodine, mcg	20.3	15
Selenium, mcg	2.7	2
Sodium, mg	59.1	44
Sodium, mEq	2.6	1.9
Potassium, mg	146	108
Potassium, mEq	3.7	2.8
Chloride, mg	83	62
Chloride, mEq	2.3	1.8
Vitamins		
A, IU	405	300
D, IU	81	60
E, IU	2.0	1.5
K, mcg	15	11
Thiamin (Vitamin B_1), mcg	80	60
Riboflavin (Vitamin B_2), mcg	120	90
B_6, mcg	80	60
B_{12}, mcg	0.6	0.4
Niacin, mcg	1800	1350
Folic Acid (Folacin), mcg	20	15
Panthothenic Acid, mcg	1000	750
Vitamin C (Asorbic Acid), mg	12	9

*As prepared: 54 g carbohydrate, 12 fl oz of water and mixed with 13 fl oz of RCF.

Pro-Phree® Protein-Free Energy Module With Iron, Vitamins & Minerals

INTRODUCTION

Pro-Phree is a protein-free energy module with minerals and vitamins that can be used as a base powder for infants and toddlers requiring dietary modification of amino acids, protein, or energy. When used with an appropriate amino acid mixture or prescribed intact protein, Pro-Phree supplies all nutrients, except protein, in adequate amounts. Pro-Phree is the base powder for all level-1 amino acid based products.

INDICATIONS FOR USE

Pro-Phree may be used as a base powder to which protein or amino acids may be added. Two types of protein modification are practiced: alteration in the type of protein and alteration in the amount of protein, either restricted or increased. In these situations, Pro-Phree could be used as the base to which appropriate protein is added. Indications for use of Pro-Phree to which appropriate protein is added are liver disease, increased intestinal loss of nutrients, or hypermetabolism. Pro-Phree is frequently used in metabolic disorders to increase energy without increasing the protein content of the diet. Amino acids may be altered because the patient requires a modification in one or more amino acids due to a disorder of amino acid transport or metabolism. Some examples are cystinuria, 3-hydroxyisobutyric aciduria, ß-ketothiolase deficiency, and hypervalinemia. As new disorders of amino acid metabolism are discovered, Pro-Phree is available as an ideal base for the addition of appropriately designed mixtures of amino acids. See Table 14 on the next page for a list of specific disorders for which Pro-Phree may be beneficial.

FEATURES OF PRO-PHREE COMPOSITION

Pro-Phree contains both fat and carbohydrate for energy. Forty-nine percent of the energy in Pro-Phree is fat, which is comparable to that in human milk. A high-fat content can help maintain an acceptable osmolality, which should improve patient tolerance to the medical food. The emulsified fat in Pro-Phree improves miscibility and significantly reduces the need for non-emulsified fat or oil to meet energy needs.

Linoleic acid is an essential nutrient. Pro-Phree supplies 7.8% of its total energy from linoleic acid. This amount is somewhat greater than the minimum recommended by the American Academy of Pediatrics Committee on Nutrition recommendation for infants (2.7% of energy). Pro-Phree contains 0.8% of energy as linolenic acid. DHA and ARA are fatty acids that function as nutritional building blocks in brain and eye development, which occurs most rapidly during the first two years of life. Those with inborn errors of metabolism are unable to have high protein foods, such as fish, so they may be at risk for low DHA and ARA intake. Pro-Phree is fortified with both DHA and ARA.

Carnitine has several important functions in the body, one of which is helping to use fat for energy. Carnitine is present in diets containing animal protein, such as dairy products, eggs, fish, meat, and poultry, and can also be made in the liver from other amino acids. Infants or children who must avoid protein foods of animal origin, or who have increased loss of carnitine from the body, may have carnitine deficiency. Pro-Phree is supplemented with 25 mg L-carnitine per 100 g powder to help provide adequate intake.

Taurine is important in various metabolic functions in the body. Human milk contains significant amounts of taurine. Taurine insufficiency is a concern for infants and toddlers requiring modification of protein or amino acids. Infants and toddlers on protein-modified diets using commercial protein modules, or L-amino acids, and low-protein cereals, fruits, and vegetables receive virtually no taurine. Pro-Phree is supplemented with taurine to supply amounts normally obtained from human milk and foods of animal origin.

Pro-Phree, when used with an appropriate source of intact protein or amino acids, meets or exceeds current DRIs for vitamins and minerals for infants.

Pro-Phree contains adequate amounts of sodium, potassium, and chloride. Supplementation of these electrolytes is not usually required when Pro-Phree is used. Calcium and phosphorus are added in amounts consistent with the current DRIs for infants and toddlers. Nutrient composition of Pro-Phree is found in Table 15.

Selenium deficiency has been reported in children consuming either L-amino acid mixtures not containing selenium or very-low-protein diets. Selenium is added to Pro-Phree to help prevent deficiency.

TABLE 14: EXAMPLES OF DISORDERS/ DISEASES FOR WHICH PRO-PHREE® MAY BE BENEFICIAL

INDICATIONS FOR USE	DISORDERS
Modification of Amino Acids	Disorders of amino acid transport or metabolism • ß-ketothiolase deficiency • Cystinuria • 3-hydroxyisobutyric aciduria • Hypervalinemia
Modification of Protein	Hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) Liver disease Nonketotic hyperglycinemia Lysinuric protein intolerance Acute treatment of high blood ammonia (urea cycle defects)
Modification of Energy, Vitamins, and Minerals	Failure to thrive • Gastrointestinal problems • Celiac disease • Crohn's disease • Inflammatory bowel disease • Lactose intolerance • Ulcerative colitis Handicapping conditions with underweight
Hypermetabolic States	Burns Cancer Movement disorders (choreic) Sepsis Trauma

TABLE 15: NUTRIENT COMPOSITION OF PRO-PHREE

NUTRIENT	PRO-PHREE* Per 100 g powder
Energy, kcal	510
Protein equiv, g	0
Fat, g	28
Carbohydrate, g	65
Linoleic Acid, mg	4600
Linolenic Acid, mg	470
L-Carnitine, mg	25
Minerals	
Calcium, mg	750
Phosphorus, mg	525
Magnesium, mg	70
Iron, mg	10
Zinc, mg	6.6
Manganese, mg	0.485
Copper, mg	0.51
Iodine, µg	80
Selenium, µg	27
Chromium, µg	16
Molybdenum, µg	17
Sodium, mg (mEq)	250 (10.9)
Potassium, mg (mEq)	875 (22.4)
Chloride, mg (mEq)	350 (9.9)
Vitamins	
A, IU (µg RE)	1700 (510)
D, IU (µg)	575 (14.4)
E, IU (mg α-TE)	16 (8.3)
K, µg	80
Thiamin (Vit B_1), mg	1.4
Riboflavin (Vit B_2), mg	0.825
B_6, mg	0.71
B_{12}, µg	1.1
Niacin, mg (mg NE)†	5.55 (5.6)
Folic Acid (Folacin), µg	110
Pantothenic Acid, mg	5.2
Biotin, µg	30
Vitamin C (Ascorbic Acid), mg	85
Choline, mg	120
Inositol, mg	180

* Approximate **unpacked** weights of Pro-Phree in level, dry US standard household measures:

PRO-PHREE	1 Tbsp =	8 g
	¼ cup =	30 g
	⅓ cup =	40 g
	½ cup =	60 g
	1 cup =	120 g

† Preformed niacin

ProViMin® Protein-Vitamin-Mineral Formula Component With Iron

INTRODUCTION

ProViMin is a carbohydrate- and fat-free formula that provides flexibility in prescribing a formula in which the type of carbohydrate and fat need to be added per an individual infant's need and tolerance. ProViMin contains a high-quality source of protein (casein).

FEATURES OF PROVIMIN

ProViMin does not supply sufficient amounts of energy as carbohydrate and fat. These nutrients should be supplied from other sources under the supervision of a physician. ProViMin meets the current DRI recommendations for vitamins and minerals for infants when fed at a dilution of 3.25 g protein/100 kcal.

ProViMin® is supplemented with L-carnitine (40 mg/100 g) and taurine (100 mg/100 g). The product has been specially processed to enhance product homogeneity.

INDICATIONS FOR USE

ProViMin may be used as a base powder in which carbohydrate and fat may be added. Table 16 lists specific disorders for which ProViMin may be useful. Nutrient composition of ProViMin is found in Table 17, next page.

TABLE 16: INDICATIONS FOR USE

DISORDER	GOAL OF NUTRITION SUPPORT
Abetalipoproteinemia, hypobetalipoproteinemia	Restrict fat intake
Cholestasis, persistent	Restrict fat intake
Chylothorax	Restrict fat intake
Glutaric aciduria type II	Restrict fat intake
Hyperlipoproteinemia type I (fasting chylomicronemia)	Restrict fat intake
Fatty acid oxidation disorders	Restrict fat intake
Lymphangiectasia, intestinal	Restrict fat intake
Supplement for any patient (0 to <18 years old) who requires increased protein, minerals, and vitamins	Provide a carbohydrate-free component that supplies protein, minerals, and vitamins
X-linked adrenoleukodystrophy	Restrict fat intake

TABLE 17: NUTRIENT COMPOSITION OF PROVIMIN

NUTRIENT	PROVIMIN* Per 100 g powder
Energy, kcal	313
Protein, g	73
Other Nitrogen-Containing Compounds	
Carnitine, mg	40
Taurine, mg	110
Carbohydrate, g	2
Fat, g	1.4
Linolenic acid, g	0
Minerals	
Calcium, mg	2400
Chloride, mg (mEq)	2300 (65)
Copper, µg	2100
Iodine, µg	335
Iron, mg	40
Magnesium, mg	200
Manganese, mcg	200
Phosphorus, mg	1700
Potassium, mg (mEq)	3300 (84)
Selenium, µg	46
Sodium, mg (mEq)	1200 (52)
Zinc, mg	17
Vitamins	
A, IU	6740
D, IU	1000
E, IU	67
K, µg	90
Vitamin C (Ascorbic Acid), mg	200
Biotin, µg	100
B_6, µg	1350
B_{12}, µg	5.6
Choline, mg	335
Folic Acid (Folacin), µg	320
Inositol, mg	105
Niacin, µg	24000
Pantothenic Acid	10100
Riboflavin (Vit B_2), mg	2020
Thiamine (Vit B_1), mg	2240
Other Characteristics	
Potential Renal Solute Load, mOsm	673

* Approximate weights per g powder of ProViMin measured in **unpacked** level, dry US standard household measures:

PROVIMIN	1 Tbsp =	2.9 g
	¼ cup =	11 g
	½ cup =	20 g
	⅔ cup =	30 g
	1 cup =	44 g

Appendix I

ABBOTT METABOLIC FORMULA SYSTEM

AMINO ACIDS PER 100 g POWDER								
	Cyclinex®-1	Glutarex®-1	Hominex®-1	I-Valex®-1	Ketonex®-1	Phenex™-1	Propimex®-1	Tyrex®-1
Amino Acids, mg								
Essential								
Cystine	300	150	450	150	150	150	450	150
Histidine	360	420	420	420	420	420	420	420
Isoleucine	1280	1080	1080	430	0	1080	120	1080
Leucine	2170	1680	1680	0	0	1680	1380	1680
Lysine	1110	0	1000	1000	1000	1000	1000	1000
Methionine	340	300	0	300	300	300	0	300
Phenylalanine	750	880	880	880	880	0	880	0
Theonine	750	700	700	700	700	700	100	700
Tryptophan	280	0	170	170	170	170	170	170
Tyrosine	880	890	890	890	890	1500	890	0
Valine	1430	1220	1220	480	0	1220	0	1220
Nonessential								
Alanine	0	1170	1000	2540	2550	1000	2560	1050
Arginine	0	1550	1040	1350	1410	1060	1550	1360
Asparagine	0	0	710	0	720	720	0	750
Aspartic acid	0	1590	120	1590	130	120	1590	300
Glutamic acid	0	2450	200	2450	220	220	2450	220
Glutamine	0	0	1220	0	1230	1260	0	1240
Glycine	0	1000	1000	1000	1000	1000	495	1000
Proline	0	1620	1310	1440	1800	1430	1600	1500
Serine	0	800	750	760	880	760	845	760
Other Nitrogen-Containing Compounds								
Carnitine, mg	190	900	20	900	100	20	900	20
Taurine, mg	40	40	40	40	40	40	40	40

Appendix I (continued)

ABBOTT METABOLIC FORMULA SYSTEM

AMINO ACIDS PER 100 g POWDER								
	Cyclinex®-2	Glutarex®-2	Hominex®-2	I-Valex®-2	Ketonex®-2	Phenex™-2	Propimex®-2	Tyrex®-2
Amino Acids, mg								
Essential								
Cystine	600	300	900	300	300	300	900	300
Histidine	720	840	840	840	840	840	840	840
Isoleucine	2560	2160	2160	860	0	2160	240	2160
Leucine	4340	3360	3360	0	0	3360	2760	3360
Lysine	2220	0	2000	2000	2000	2000	2000	2000
Methionine	680	600	0	600	600	600	0	600
Phenylalanine	1500	1760	1760	1760	1760	0	1760	0
Theonine	1500	1400	1400	1400	1400	1400	200	1400
Tryptophan	560	0	340	340	340	340	340	340
Tyrosine	1760	1780	1780	1780	1780	3000	1780	0
Valine	2860	2440	2440	960	0	2440	0	2440
Nonessential								
Alanine	0	2340	2000	5080	5100	2020	5120	2100
Arginine	0	3100	2080	3100	2820	2120	3100	2720
Asparagine	0	0	1420	0	1440	1420	0	1480
Aspartic acid	0	3180	240	3180	260	250	3180	260
Glutamic acid	0	4900	400	3550	440	430	4900	440
Glutamine	0	0	2440	0	2460	2510	0	2480
Glycine	0	2000	2000	2000	2000	2000	1000	2000
Proline	0	3240	2610	2880	3600	2870	3200	3000
Serine	0	1600	1500	1520	1760	1520	1700	1530
Other Nitrogen-Containing Compounds								
Carnitine, mg	370	1800	40	1800	200	40	1800	40
Taurine, mg	140	125	125	125	125	125	125	125

Appendix II

DISPLACEMENT OF METABOLIC MEDICAL FOODS

PRODUCT	mL/g POWDER
Infant/Toddler	
Calcium XD Low-Calcium Vitamin D-Free Infant Formula with Iron	0.77
Cyclinex -1 Amino Acid Modified Medical Food With Iron	0.75
Hominex-1 Amino Acid Modified Medical Food With Iron	0.75
I-Valex-1 Amino Acid Modified Medical Food With Iron	0.75
Ketonex-1 Amino Acid Modified Medical Food With Iron	0.75
Phenex-1 Amino Acid Modified Medical Food With Iron	0.75
Pro-Phree Protein-Free Energy Module With Iron, Vitamins & Minerals	0.75
Propimex-1 Amino Acid Modified Medical Food With Iron	0.75
ProViMin Protein-Vitamin-Mineral Component With Iron	0.84
RCF Carbohydrate Free Soy Formula Base With Iron	NA[1]
Tyrex-1 Amino Acid Modified Medical Food With Iron	0.75
Child/Adult	
Cyclinex-2 Amino Acid Modified Medical Food	0.75
Glutarex-2 Amino Acid Modified Medical Food	0.75
Hominex-2 Amino Acid Modified Medical Food	0.75
I-Valex-2 Amino Acid Modified Medical Food	0.75
Ketonex·2 Amino Acid Modified Medical Food	0.75
Phenex-2 Amino Acid Modified Medical Food, flavored	0.75
Phenex-2 Amino Acid Modified Medical Food, unflavored	0.75
Propimex -2 Amino Acid Modified Medical Food	0.75
Tyrex -2 Amino Acid Modified Medical Food	0.75

[1] Concentrated liquid.

Appendix III

APPROXIMATE OSMOLALITY OF SELECTED FOODS

FOOD	kcal/fl oz			
	20	24	27	30
	(m0sm/kg H_2O)			
Infant/Toddler				
Cyclinex®-1	275	350	410	450
Calcilo XD®	190	235	275	320
Glutarex®-1	385	475	540	615
Hominex®-1	375	465	525	600
I-Valex®-1	375	470	545	610
Tyrex®-1	380	460	520	595
Ketonex®-1	365	450	515	590
Phenex™-1	370	455	515	590
Pro-Phree®	205	245	275	305
Propimex®-1	370	470	525	605
Child / Adult				
Cyclinex®-2	615	785	895	1,015
Glutarex®-2	830	1,030	1,200	1,360
Hominex®-2	815	1,020	1,160	1,350
I-Valex®-2	845	1,040	1,215	1,390
Ketonex®-2	805	1,000	1,155	1,315
Phenex™-2				
Unflavored	780	965	1,135	1,215
Vanilla	775	940	1,070	1,290
Propimex®-2	835	1,020	1,170	1,355
Tyrex®-2	810	1,000	1,155	1,330

Appendix IV

SAMPLE DIET CALCULATION FOR INFANTS WITH PKU

Assume you have a newborn weighing 3.3 kg who has a plasma PHE of 20 mg/dL (≈1200 µmol/L). Refer to Recommended Daily Nutrient Intakes from the table below and nutrient composition from Table 2.

PRESCRIPTION

PHE	60 mg/kg ≈ 200 mg
Protein	3.5 g/kg ≈ 11.6 g
Energy	120 kcal/kg ≈ 400 kcal
Fluid	160 mL/kg ≈ 530 mL

TYR needs are generally met by infant formula and medical food. Add L-TYR only if plasma TYR concentrations are below normal.

1. Calculate amount of infant formula to meet PHE requirements. For example, Similac® Advance® Ready To Feed has 59 mg PHE/100 mL, so 340 mL of Similac Advance provide the needed 200 mg of PHE.
2. Fill the protein prescription by subtracting the amount of protein provided by the Similac Advance and supply the remaining protein with Phenex™-1. For example, 4.9 g protein is provided by Similac Advance, so 45 g Phenex-1 is needed to complete the protein prescription for total protein of 11.6 g.
3. Assess the energy requirements. Add Pro-Phree® if extra calories are needed.
4. Fill the fluid prescription and assess whether the caloric density is appropriate; eg, to 20 kcal/fl oz.

The diet prescription can be filled as follows:

	Amount	PHE (mg)	TYR (mg)	Protein (g)	Energy (kcal)	Fluid (mL)
Similac Advance Ready To Feed	340 mL	200	197	4.9	230	340
Phenex-1	45 g	0	68	6.8	216	0
Water to make 665 mL (≈22 fl oz)	300 mL					330
Total		200	265	11.7	475	640

RECOMMENDED INTAKES OF PHE, TYR AND PROTEIN FOR PKU

INFANTS TO <4 YR[1]			
Age	PHE (mg/day)	TYR (mg/day)	Protein[2] (g/kg/day)
0 to <3 mo[3]	130-430	1100-1300	2.5-3.0
3 to <6 mo	135-400	1400-2100	2.0-3.0
6 to <9 mo	145-370	2500-3000	2.0-2.5
9 to <12 mo	135-330	2500-3000	2.0-2.5
1 to <4 years[4]	200-320	2800-3500	1.5-2.1

AFTER EARLY CHILDHOOD[5]			
Age	PHE (mg/day)	TYR (mg/day)	Protein[2] (g/kg/day)
>4 yr-adult	200-1100	4000-6000	120-140% DRI for age[6]

Appendix IV (continued)

RECOMMENDED INTAKES OF PHE, TYR AND PROTEIN FOR PKU

PREGNANCY AND LACTATION[7]			
Age	**PHE (mg/day)**	**TYR (mg/day)**	**Protein[2] (g/kg/day)**
Trimester 1	265-770	6000-7600	70
Trimester 2	400-1650	6000-7600	70
Trimester 3	700-2275	6000-7600	70
Lactation[8]	700-2275	6000-7600	70

[1] Adapted from Acosta (G. 102), recommendations for PHE and TYR intake are for infants and children <4 yrs wiht more severe PKU and treated with PHE-restricted diet alone. TYR intake recommencations may require adjustment based on blood TYR monitoring.

[2] Protein recommendations are for individuals consuming medical foods as the major protein source.

[3] PHE recommendations for premature infants may be higher.

[4] PHE tolerance is usually stabilized by 2-5 year of age (F. 2627). Recommendations are based on size (increases with age) and growth rate (decreases with age). Individual PHE intake recommendations should be adjusted based on frequent blood PHE monitoring.

[5] Adapted from Acosta (G. 102). Range of recommended PHE intake applies to spectrum of PKU severity (mild to severe).

[6] Recommended protein intake greater than the DRI is necessary to support normal growth in PKU.

[7] Recommendations are slightly higher for pregnant women <19 years of age.

[8] Recommended nutrient intake during lactation is same as for third trimester of pregnancy for all women.

MEDICAL FOOD NEEDED TO FILL PRESCRIPTION

To calculate the amount of medical food needed per week or per month, remember that the amount of medical food required will increase as the infant/child grows. For example, an infant may gain ≈30 g per day. A 3.5-kg newborn who requires 45 g of Phenex-1 per day at birth may need 55 g Phenex-1 per day at 1 month of age. One can of Phenex-1 contains 400 g. At 50 g Phenex-1 per day, 1 can would last about 8 days. Therefore, approximately four cans of Phenex-1 would be needed each month.

Appendix V

ABBOTT METABOLIC FORMULAS:

NDC, HCPCS CODES, CALORIES, AND PROTEIN											
Stock Code	NDC Code*	HCPCS Code*	Product	Size		Calories		Protein/ Protein Equivalents (g)		Approximate Can Yield kcal/fl oz.	
				Per Can	Per Case[1]	Per 100 g	Per Can	Per 100 g	Per Can	20	30
55328	70074-0533-28	B4162	Calcilo XD®	352 g	2112 g	513	1805	11.4	40.1	90	60
67032	70074-0670-32	B4162	Cyclinex®-1	400 g	2400 g	510	2040	7.5	30.0	102	68
67036	70074-0670-36	B4162	Glutarex®-1	400 g	2400 g	480	1920	15	60	96	64
67040	70074-0670-40	B4162	Hominex®-1	400 g	2400 g	480	1920	15	60	96	64
67044	70074-0670-44	B4162	I-Valex®-1	400 g	2400 g	480	1920	15	60	96	64
67048	70074-0670-48	B4162	Ketonex®-1	400 g	2400 g	480	1920	15	60	96	64
67052	70074-0670-52	B4162	Phenex™-1	400 g	2400 g	480	1920	15	60	96	64
67030	70074-0670-30	B4155	Pro-Phree®	400 g	2400 g	510	2040	--	--	102	68
67058	70074-0670-58	B4162	Propimex®-1	400 g	2400 g	480	1920	15	60	96	64
50260	70074-0502-60	B4155	ProViMin®	150 g	900 g	313	468	73	110	23	15
00108	70074-0401-08	B4155	RCF®	384 mL	2304 mL	100	311	4.0	15.4	26[2]	17
67062	70074-0670-62	B4162	Tyrex®-1	400 g	2400 g	480	1920	15	60	96	64
67034	70074-0670-34	B4157†	Cyclinex®-2	400 g	2400 g	440	1760	15	60	88	59
67038	70074-0670-38	B4157†	Glutarex®-2	400 g	2400 g	410	1640	30	120	82	55
67042	70074-0670-42	B4157†	Hominex®-2	400 g	2400 g	410	1640	30	120	82	55
67046	70074-0670-46	B4157†	I-Valex®-2	400 g	2400 g	410	1640	30	120	82	55
67050	70074-0670-50	B4157†	Ketonex®-2	400 g	2400 g	410	1640	30	120	82	55
67056	70074-0670-56	B4157†	Phenex™-2 Van	400 g	2400 g	410	1640	30	120	82	55
67054	70074-0670-54	B4157†	Phenex™-2 Unfl	400 g	2400 g	410	1640	30	120	82	55
67060	70074-0670-60	B4157†	Propimex®-2	400 g	2400 g	410	1640	30	120	82	55
67064	70074-0670-64	B4157†	Tyrex®-2	400 g	2400 g	410	1640	30	120	82	55

[1] A case contains 6 cans, with the exception of RCF which contains 12 cans per case.

[2] When prepared as directed by the instructions on the label.

* US only.

† These products are used by children and adults. If used by children, code B4162 is utilized.