

Maple Syrup Urine Disease (MSUD)

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Dietetic Intern

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Maple Syrup Urine Disease, defined:

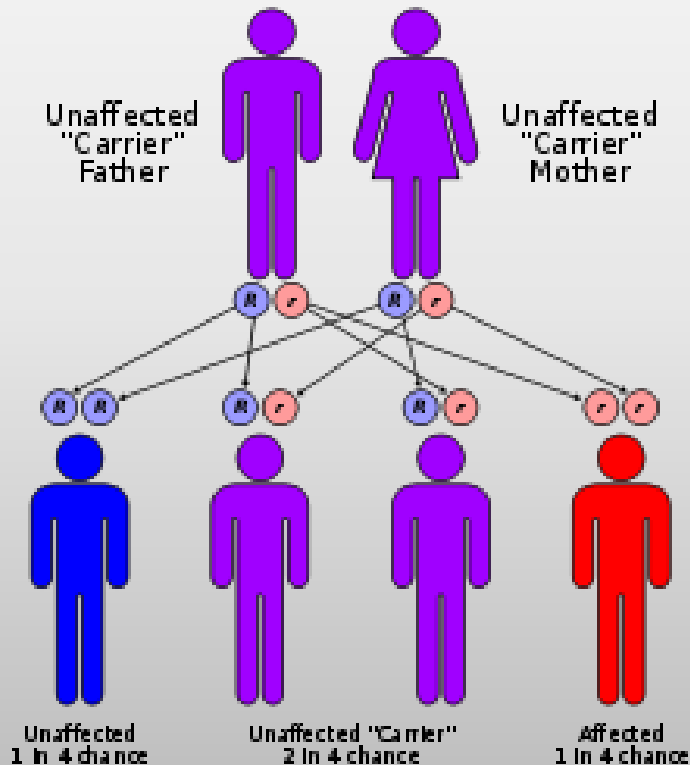
- A metabolic disorder characterized by a deficiency of branched-chain α -ketoacid dehydrogenase (BCKD), resulting in elevated levels of the BCAA leucine (LUE) in the plasma and urine
- Untreated, MSUD will result in:
 - Severe mental and physical disabilities
 - Death within weeks or months of life

History and Overview

- Landmark case studies and research
 - Menkes, Hurst, and Craig in 1954
 - First to observe and describe MSUD
 - Dancis et al. and Pettit et al. in 1960
 - Identified BCKA as the missing enzyme
 - Snyderman et al in 1964
 - Laid the foundation of nutritional intervention and management

History and Overview

MSUD- An autosomal recessive metabolic disorder

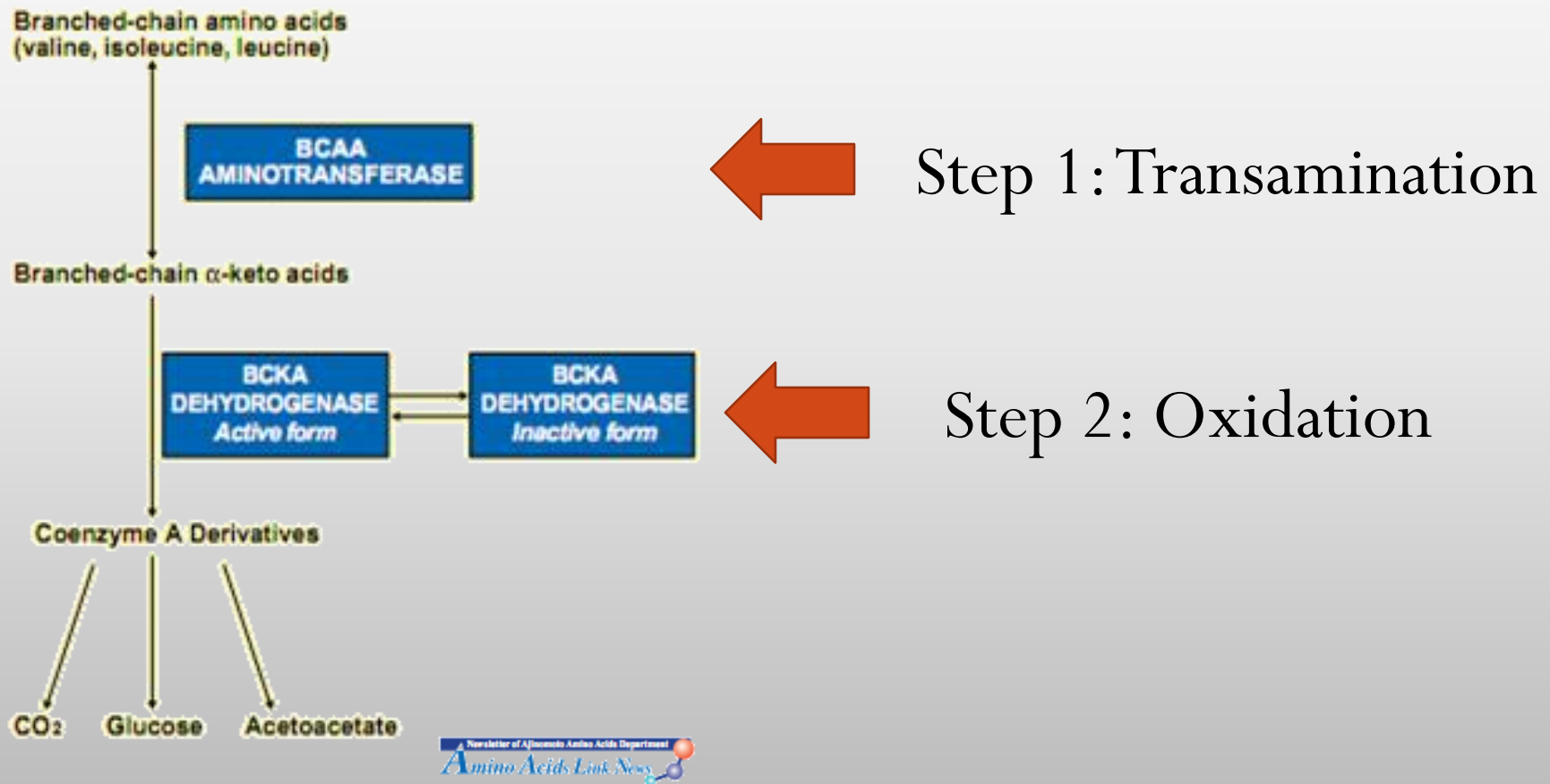


- 1 in 176 live births in Mennonite population
- 1 in 185,000 live births world wide
- 1 in 560,000 live births in Japan



The Clinic for Special Children

BCAA Metabolism



In MSUD the BCKA enzyme complex is missing or deficient

Clinical Phenotypes

1. Classic
2. Intermediate
3. Intermittent
4. Thiamine-Responsive
5. Dihydrolipol Dehydrogenase (E3)-Deficient
MSUD

Infant Screening

Identifies infants with blood LEU levels above normal
> 61-168 umol/L



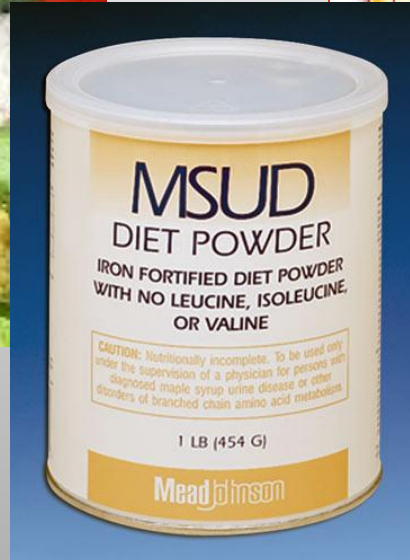
STATE	Core ¹ Conditions - Metabolic																			
	Fatty Acid Disorders					Organic Acid Disorders									Amino Acid Disorders					
	CUD	LCIAD	MCAD	TPP	VLCAD	GA-I	HMG	IVA	3-MCC	Chl-A,B	BKT	MUT	PROP	MCD	ASA	CIT	HCY	MSUD	PKU	TYR-I
Alabama	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Alaska	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Arizona	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Arkansas	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
California	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Colorado	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Connecticut	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
D. of Columbia	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Delaware	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Florida	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Georgia	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Hawaii	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Idaho	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Illinois	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Indiana	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Iowa	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Kansas	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Kentucky	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Louisiana	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Maine	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Maryland	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Massachusetts	●	●	●	D	●	●	●	●	D	●	●	●	●	D	●	●	●	●	●	●
Michigan	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Minnesota	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Mississippi	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Missouri	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Montana	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Nebraska	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Nevada	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
New Hampshire	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
New Jersey	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
New Mexico	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
New York	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
North Carolina	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
North Dakota	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Ohio	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Oklahoma	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Oregon	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Pennsylvania	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Rhode Island	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
South Carolina	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
South Dakota	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Tennessee	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Texas	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Utah	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Vermont	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Virginia	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Washington	●	●	●	●	●	●	●	●	D	●	●	●	●	●	●	●	●	●	●	●
West Virginia	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Wisconsin	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Wyoming	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

Symptoms

- Poor feeding
- Lethargy
- Weight Loss
- Maple sugar/burnt sugar odor in urine
- Neurological deterioration with alternating hypertonia and hypotonia
- Encephalopathic crisis

Symptoms will present within days of life and then again later in childhood during severe illnesses

Nutrition Therapy for MSUD



Acute Nutritional Management:

1. **Discontinue** natural protein.
2. Provide the **large amount of calories** needed
3. Provide **fluids and sodium** to treat dehydration, reestablish normal perfusion and urine output, and **avoid hyponatremia**.
4. **Enteral therapy** with special formula that contains all required amino acids but is free of the branched chain amino acids
5. If neurologically compromised, initiate **PN formula** with no BCAAs
6. **Hemodialysis** (only as a last resort)

Acute Nutritional Management

Energy needs:

Infants	120-140kcal/kg/day
Children	80-100kcal/kg/day
Adults	40-45kcal/kg/day

Acute Nutritional Management

Monitor plasma amino acid concentrations

- When BCAAs reach treatment range

Leucine < 300 $\mu\text{mol/L}$

Isoleucine 300 $\mu\text{mol/L}$

Valine 400 $\mu\text{mol/L}$

1. Add ILE and VAL (100-150 mg/kg/day) to prevent levels from dropping too low
2. Add intact protein source to meet essential LEU requirements

Recovery goal:

Leucine 175 $\mu\text{mol/L}$

Isoleucine 200 $\mu\text{mol/L}$

Valine 300 $\mu\text{mol/L}$

Long Term Nutritional Management

Goal: Achieve near-normal plasma concentrations of BCAAs while providing nutrients necessary for growth

Limit intake of BCAAs

1. Foods low in LEU
2. LEU-free medical food/formulas
3. Supplementation of ILE and VAL as necessary

BCAA requirements for MSUD are about 50-65% of RDIs

Long Term Nutritional Management

Common Deficiencies:

- VAL and ILE
- Other amino acids (specifically alanine, glutamine, glutamate)
- Omega-3 essential fatty acids
- Zinc
- Selenium

Long Term Nutritional Management

Recommended Nutrient Intakes for Infants, Children and Adults with MSUD

Age	Nutrient					
	ILE ^{1,2} (mg/kg)	LEU ¹ (mg/kg)	VAL ^{1,3} (mg/kg)	Protein ⁴ (g/kg)	Energy ⁴ (kcal/kg)	Fluid ⁵ (mL/kg)
Infants						
0 to < 3 mo	36 - 60	60 - 100	42 - 70	3.50 - 3.00	120 (145 - 95)	150 - 125
3 to < 6 mo	30 - 50	50 - 85	35 - 60	3.50 - 3.00	115 (145 - 95)	160 - 130
6 to < 9 mo	25 - 40	40 - 70	28 - 50	3.00 - 2.50	110 (135 - 80)	145 - 125
9 to < 12 mo	18 - 33	30 - 55	21 - 38	3.00 - 2.50	105 (135 - 80)	135 - 120
	(mg/day)	(mg/day)	(mg/day)	(g/day)	(kcal/day)	(mL/day)
Girls and Boys						
1 to < 4 yr	165 - 325	275 - 535	190 - 400	≥ 30.0	1,300 (900 - 1800)	900 - 1,800
4 to < 7 yr	215 - 420	360 - 695	250 - 490	≥ 35.0	1,700 (1300 - 2300)	1,300 - 2,300
7 to < 11 yr	245 - 470	410 - 785	285 - 550	≥ 40.0	2,400 (1650 - 3300)	1,650 - 3,300
Women						
11 to < 15 yr	330 - 445	550 - 740	385 - 520	≥ 50.0	2,200 (1500 - 3000)	1,500 - 3,000
15 to < 19 yr	330 - 445	550 - 740	385 - 520	≥ 55.0	2,100 (1200 - 3000)	1,200 - 3,000
≥ 19 yr	300 - 450	400 - 620	420 - 650	≥ 60.0	2,100 (1400 - 2500)	1,400 - 2,500
Men						
11 to < 15 yr	325 - 435	540 - 720	375 - 505	≥ 55.0	2,700 (2000 - 3700)	2,000 - 3,700
15 to < 19 yr	425 - 570	705 - 945	495 - 665	≥ 65.0	2,800 (2100 - 3900)	2,100 - 3,900
≥ 19 yr	575 - 700	800 - 1100	560 - 800	≥ 70.0	2,900 (2000 - 3300)	2,000 - 3,300

Source: Abbott Laboratories

Long Term Nutritional Management

Resources:

- Food Lists
- USDA website and nutrient database
- MSUD-Family Support Group

Table 6.3 *Estimation of the LEU Content of Foods*

Food	Approx LEU (mg/g protein)	Example
Fruits	40	1 cup raspberries = 1.5 g protein $1.48 \times 40 = \mathbf{60 \text{ mg LEU}}$
Vegetables	50	$\frac{1}{2}$ cup sweet pepper = 0.8 g protein $0.8 \times 50 = \mathbf{40 \text{ mg LEU}}$
Bread, crackers, and other starches	70	2 sq graham crackers = 1.0 g protein $1 \times 70 = \mathbf{70 \text{ mg LEU}}$ 1 slice white bread = 2.3 g protein $2.3 \times 70 = \mathbf{161 \text{ mg LEU}}$
Meat, poultry, and fish	80	1 oz ham = 5.0 g protein $5 \times 80 = \mathbf{400 \text{ mg LEU}}$
Dairy products	100	$\frac{1}{2}$ cup milk = 4.0 g protein $4 \times 100 = \mathbf{400 \text{ mg LEU}}$

Source: USDA Agricultural Research Service, Nutrient Data Laboratory. Available at: <http://www.nal.usda.gov/fnic/foodcomp/search/>. Accessed July 8, 2008.

Note: The quick calculation method in Table 6.3 may be used to estimate the LEU content of food when specific LEU information is not available; this provides an estimate only.

Source: Acosta, Phyllis. *Nutrition Management of Patients with Inherited Metabolic Disorders*

LEU-free Medical Supplements

Maple Syrup Urine Disease (MSUD)	MSUD 1 Ⓢ?	Milupa	infants	valine-, leucine-, and isoleucine-free powdered medical food enriched w/ vitamins and minerals
	MSUD Analog Ⓢ*	NUTRICIA	infants	valine-, leucine-, and isoleucine-free powdered medical food
	MSUD Diet Powder Ⓢ††	Mead Johnson	infants and children	valine-, leucine-, and isoleucine-free diet powdered medical food
	Ketonex Ⓢ-1 ‡	Ross	infants and toddlers	valine-, leucine-, and isoleucine-free powdered medical food
	BCAD1 Ⓢ††	Mead Johnson	infants and toddlers	valine-, leucine-, and isoleucine-free iron fortified powdered medical food
	MSUD 2 Ⓢ?	Milupa	children	valine-, leucine-, and isoleucine-free powdered medical food enriched w/ vitamins and minerals
	MSUD Maxamaid Ⓢ (orange)*	NUTRICIA	children 1-8 yrs	valine-, leucine-, and isoleucine-free powdered medical food
	BCAD 2 Ⓢ (vanilla)††	Mead Johnson	children and adults	valine-, leucine-, and isoleucine-free powdered medical food
	Ketonex Ⓢ-2 ‡	Ross	children and adults	valine-, leucine-, and isoleucine-free, powdered medical food
	MSUD Gel Ⓢ≠	VitaFlo	children 1-10 yrs	valine-, leucine-, and isoleucine-free drink
	MSUD Express Ⓢ≠	VitaFlo	children >8 yrs	valine-, leucine-, and isoleucine-free protein supplement
	MSUD Maxamum Ⓢ (orange)*	NUTRICIA	individuals >8 yrs	valine-, leucine-, and isoleucine-free powdered medical food
	Complex Ⓢ MSUD (vanilla) ^b	Applied Nutrition	children and adults	valine-, leucine-, and isoleucine-free powdered medical food
	Acerflex Ⓢ (pineapple)*	NUTRICIA	individuals >1 yrs	valine-, leucine-, and isoleucine-free powdered medical food
	Complex Ⓢ MSUD Amino Acid Bar (chocolate) ^b	Applied Nutrition	individuals >1 yrs	valine-, leucine-, and isoleucine-free medical food bar
	Complex Ⓢ MSUD Amino Acid Blend ^b	Applied Nutrition	children and adults	valine-, leucine-, and isoleucine-free amino acid-derived medical powder used to fortify food

†† Source: Mead Johnson Nutritionals Metabolics Guide. Product Information for Health Care Professionals. www.meadjohnson.com/metabolics. Accessed on 7/1/02.

‡ Source: Ready Reference: Composition of Medical Foods for Infants, Children, and Adults With Metabolic Disorders. Columbus, OH: Ross Products Division, April, 2001.

* Source: Nutricia North America, Rockville, MD. 2007

^a Source: A Comprehensive Guide to PhenylAde. Randolph, NJ: Applied Nutrition Corp., 2000.

^b Source: A Comprehensive Guide to Complex MSUD. Randolph, NJ: Applied Nutrition Corp., 2000.

? Source: Milupa Product Guide, 2004.

× Source: Blend of 20 Pure Form Amino Acids. Jo Mar Labs, 2003.

LEU-free Medical Supplements- Infants

Nutrition Information:

Nutrients	Per 100 g	Per 10 g Protein Equivalent	Vitamins	Per 100 g	Per 10 g Protein Equivalent
Calories	475	365	Vitamin A, IU (mcg R.E.)	1760 (528)	1355 (406)
Protein Equivalent, g	13	10	Vitamin D, IU (mcg)	340 (8.5)	263 (6.5)
Fat, g	20.9	16	Vitamin E, IU (mg α T.E.)	4.9 (3.3)	3.7 (2.5)
Saturated, g	6.8	5.2	Vitamin K, mcg	21	16
Monounsaturated, g	9.5	7.3	Thiamine, mcg	500	385
Polyunsaturated, g	3.6	2.8	Riboflavin, mcg	600	462
Carbohydrate, g	59	45	Vitamin B ₆ , mcg	520	400
Linoleic Acid, mg	3025	2330	Vitamin B ₁₂ , mcg	1.25	0.96
Amino Acids, g			Niacin, mcg	4500	3462
L-Alanine	0.76	0.58	Folic Acid, mcg	38	29
L-Arginine	1.34	1.03	Pantothenic Acid, mcg	2600	2000
L-Aspartic Acid	1.11	0.85	Biotin, mcg	26	20
L-Cystine	0.49	0.38	Vitamin C, mg	40	31
L-Glutamic Acid	1.49	1.15	Choline, mg	50	38
Glycine	1.19	0.92	Inositol, mg	100	77
L-Histidine	0.76	0.58	Minerals		
L-Isoleucine	None	None	Calcium, mg	600	462
L-Leucine	None	None	Phosphorus, mg	500	385
L-Lysine	1.38	1.06	Magnesium, mg	40	31
L-Methionine	0.32	0.25	Iron, mg	10	8
L-Phenylalanine	0.90	0.69	Zinc, mg	8	6
L-Proline	1.44	1.11	Manganese, mcg	600	462
L-Serine	0.89	0.68	Copper, mcg	450	346
L-Threonine	1.00	0.77	Iodine, mcg	47	36
L-Tryptophan	0.40	0.31	Molybdenum, mcg	15	12
L-Tyrosine	0.90	0.69	Chromium, mcg	15	12
L-Valine	None	None	Selenium, mcg	15	12
L-Carnitine	0.01	0.01	Sodium, mg (mEq)	120 (5.2)	92 (4.0)
Taurine	0.02	0.02	Potassium, mg (mEq)	420 (10.8)	323 (8.3)
L-Glutamine	0.1	0.08	Chloride, mg (mEq)	290 (8.2)	223 (6.3)

Ingredients:

Corn Syrup Solids, High Oleic Safflower Oil, Refined Vegetable Oil (Coconut, Soy), L-Lysine L-Glutamate, Calcium Phosphate Dibasic, L-Proline, L-Arginine, Glycine, L-Aspartic Acid, L-Threonine, L-Phenylalanine, L-Tyrosine, Galactose, L-Serine, Tripotassium Citrate, L-Histidine, L-Alanine, Calcium Phosphate Monobasic, Mono and Diglycerides, L-Cystine, L-Tryptophan, L-Methionine, Sodium Chloride, Magnesium Acetate, Potassium Chloride, Diacetyl Tartaric Acid Esters of Monoglycerides, Tricalcium Citrate, L-Glutamine, Choline Bitartrate, M-Inositol, L-Ascorbic Acid, L-Glutamic Acid, Soy Lecithin, Calcium Phosphate Tribasic, Ferrous Sulfate, Zinc Sulfate, Taurine, L-Carnitine, Nicotinamide, DL-Alpha Tocopheryl Acetate, Calcium Pantothenate, Manganese Sulfate, Cupric Sulfate, Vitamin A Acetate, Pyridoxine Hydrochloride, Riboflavin, Thiamine Chloride Hydrochloride, Chromium Sulfate, Potassium Iodide, Folic Acid, Sodium Molybdate, Phylloquinone, D-Biotin, Sodium Hydrogen Selenite, Vitamin D₃, Cyanocobalamin.



LEU-free Medical Supplements- Older Children

Nutrition Information:

Nutrients	Per 100 g	Per 10 g Protein Equivalent	Vitamins	Per 100 g	Per 10 g Protein Equivalent
Calories	300	56	Vitamin A, IU (mcg R.E.)	5200 (1562)	963 (288)
Protein Equivalent, g	54	10	Vitamin D, IU (mcg)	1310 (32.8)	243 (6)
Fat, g	None	None	Vitamin E, IU (mg α T.E.)	18 (12)	3.3 (2.2)
Carbohydrate, g	21	3.9	Vitamin K, mcg	167	31
Amino Acids, g			Thiamine, mg	1.4	0.3
L-Alanine	3.1	0.57	Riboflavin, mg	2	0.4
L-Arginine	2.7	0.50	Vitamin B ₆ , mg	1.5	0.3
L-Aspartic Acid	7.6	1.41	Vitamin B ₁₂ , mcg	3	0.6
Cystine	1.8	0.33	Niacin, mg	24	4
L-Glutamic Acid	16.0	2.96	Folic Acid, mcg	400	74
Glycine	1.8	0.33	Pantothenic Acid, mg	11	2
L-Histidine	1.8	0.33	Biotin, mcg	300	56
L-Isoleucine	None	None	Vitamin C, mg	80	15
L-Leucine	None	None	Choline, mg	260	48
L-Lysine	5.4	1	Inositol, mg	300	56
L-Methionine	1.8	0.33	Minerals		
L-Phenylalanine	3.2	0.59	Calcium, mg	1310	243
L-Proline	7.1	1.31	Phosphorus, mg	1010	187
L-Serine	4.0	0.74	Magnesium, mg	156	29
L-Threonine	3.6	0.67	Iron, mg	15	2.8
L-Tryptophan	1.4	0.26	Zinc, mg	7.8	1.4
L-Tyrosine	3.9	0.72	Manganese, mg	0.7	0.1
L-Valine	0	0	Copper, mcg	2000	370
			Iodine, mcg	120	22
			Molybdenum, mcg	32	6
			Sodium, mg	640	119
			Potassium, mg	1330	246
			Chloride, mg	990	183

Ingredients:

L-Amino Acids (L-Lysine-L-Glutamate, L-Glutamic Acid, L-Proline, L-Aspartic Acid, L-Serine, L-Tyrosine, L-Threonine, L-Phenylalanine, L-Alanine, L-Arginine, Magnesium-L-Aspartate, L-Histidine, L-Methionine, L-Cystine, Glycine, L-Tryptophan), Sugar, Potassium Phosphate, Calcium Phosphate, Calcium Carbonate, Salt, Choline Bitartrate, M-Inositol, Ascorbic Acid, Ferrous Sulfate, Vanillin, Niacinamide, Vitamin E Acetate, Zinc Sulfate, Calcium-D-Pantothenate, Copper Acetate, Pyridoxine Hydrochloride, Thiamine Hydrochloride, Riboflavin, Manganese Sulfate, Vitamin A Acetate, Biotin, Folic Acid, Potassium Iodide, Vitamin K₁, Ammonium Heptamolybdate, Vitamin D₃, Vitamin B₁₂.



Monitoring

- Plasma amino acid concentrations:
 - Daily in initial stages
 - Weekly in first year of life
 - Monthly during childhood
- Home monitoring
 - Measure level of ketones in urine



Outcomes

- With life-long adherence to diet, children with MSUD can enjoy a normal, high quality life.



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