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Sizer et al.

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(54) **LIQUID NUTRITIONAL FORMULA FOR TYROSINEMIA PATIENTS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(51) **Int. Cl.**

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A61K 31/198	(2006.01)
A61K 31/405	(2006.01)
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A61K 31/20	(2006.01)
A61K 31/70	(2006.01)
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A61K 31/593	(2006.01)
A61K 31/355	(2006.01)
A61K 31/122	(2006.01)
A61K 31/51	(2006.01)
A61K 31/525	(2006.01)
A61K 31/675	(2006.01)
A61K 31/519	(2006.01)
A61K 31/714	(2006.01)
A61K 31/197	(2006.01)
A61K 31/4188	(2006.01)
A23L 2/52	(2006.01)
A23L 2/66	(2006.01)

(52) **U.S. Cl.**

CPC ***A61K 38/1709*** (2013.01); ***A23L 2/52*** (2013.01); ***A23L 2/66*** (2013.01); ***A61K 31/07*** (2013.01); ***A61K 31/122*** (2013.01); ***A61K 31/197*** (2013.01); ***A61K 31/198*** (2013.01); ***A61K 31/20*** (2013.01); ***A61K 31/355*** (2013.01); ***A61K 31/375*** (2013.01); ***A61K 31/405*** (2013.01); ***A61K 31/4172*** (2013.01); ***A61K 31/4188*** (2013.01); ***A61K 31/51*** (2013.01); ***A61K 31/519*** (2013.01); ***A61K 31/525*** (2013.01); ***A61K 31/593*** (2013.01); ***A61K 31/675*** (2013.01); ***A61K 31/70*** (2013.01); ***A61K 31/714*** (2013.01); *A23V 2002/00* (2013.01)

(58) **Field of Classification Search**

CPC A23L 33/17; A23L 33/175; A23L 33/18; A23L 33/185; A23L 33/19; A61K 38/018
See application file for complete search history.

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Primary Examiner — Christina Bradley

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(57) **ABSTRACT**

Liquid metabolic formulas for dietary management of tyrosinemia, including nutritional formulas and hydration beverages (sport drinks).

11 Claims, 6 Drawing Sheets

Figure 1

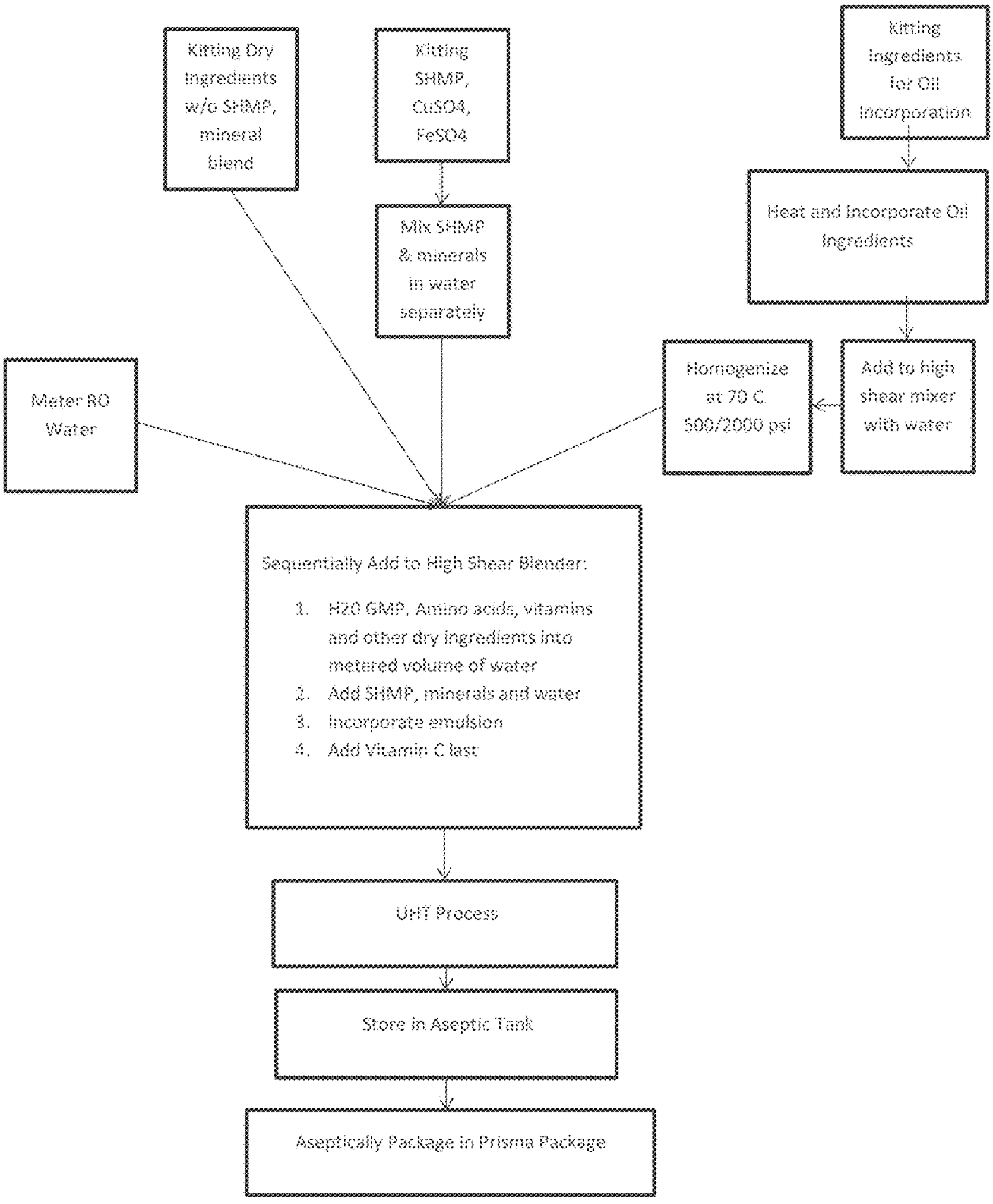
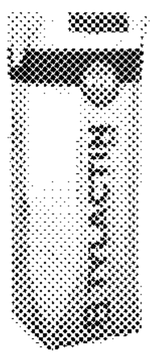

Kitting Dry Ingredients w/o SHMP, mineral blend
Kitting SHMP, CuSO4, FeSO4
Mix SHMP & minerals in water separately
Kitting Ingredients for Oil Incorporation
Heat and Incorporate Oil Ingredients
Meter RO Water
Homogenize at 70 C. 500/2000 psi
Add to high shear mixer with water
Sequentially Add to High Shear Blender:
1. H20 GMP, Amino acids, vitamins and other dry ingredients into metered volume of water
2. Add SHMP, minerals and water
3. Incorporate emulsion
4. Add Vitamin C last
UHT Process
Store in Aseptic Tank
Aseptically Package in Prisma Package

Figure 2

TYLACTIN RTD 15 ORIGINAL

April 07, 2015



SKU 59203

NET WEIGHT 2 GAL (7.5 L)

SERVING SIZE 8.5 fl oz (250mL)

SERVINGS PER PACKAGE 30

REIMBURSEMENT CODE 24039-0592-03
(for USA only)

MEDICAL FOOD PRODUCT
For the dietary management of Tyrosinemia (TYR). Dispensed by prescription.
TYLACTIN RTD - Designed to a ready-to-drink metabolic formula product for TYR patients.
Product comes in a 2Gallon carton.

PRECAUTIONS: Give only to adults and children who are under medical supervision for proven TYR. Protein in prescribed amounts must be supplemented to completely meet tyrosine requirements.

NOT FOR PARENTERAL USE • USE AS DIRECTED BY PHYSICIAN

INGREDIENTS
Water, sucrose, whey protein isolate (glycomacropeptide), vitamin and mineral blend (dicalcium phosphate, calcium lactate, dipotassium phosphate, choline bitartrate, magnesium citrate, sodium ascorbate and ascorbic acid, ferrous sulfate, zinc sulfate, niacinamide, vitamin E dl-alpha tocopheryl acetate, calcium d-pantothenate, manganese sulfate, vitamin A palmitate, vitamin B6 pyridoxine, riboflavin, thiamin hydrochloride, copper gluconate, folic acid, potassium iodide, vitamin K 1 phytonadione, sodium selenite, sodium molybdate, chromium chloride, biotin, vitamin D3 cholecalciferol, vitamin B12 cyanocobalamin), food starch modified, leucine, maltodextrin, cocoa butter, canola oil, arginine, cellulose gel and carboxymethylcellulose sodium, natural flavor (propylene glycol, ethyl alcohol, water, polysorbate 80 potassium sorbate), histidine, sodium hexametaphosphate, tryptophan, cysteine, carrageenan, sodium stearoyl lactylate. Contains corn, milk and soy.

PREPARATION
Ready to drink. Shake well.

STORAGE
Store in cool, dry place. Refrigerate after opening. Do not freeze.

TO REQUEST A SAMPLE
Call 888.888.8888, opt 2 or complete form at www.sample.cambrooke.com

Nutrients	8.5 fl oz (250mL)	per 100mL
Calories	200	80
Calories from Fat	45	18
Protein Equivalent, g	15	6
Free Amino Acids, g		
Tyrosine, mg	3	1
Carbohydrates, g	24	10
Sugar, g	19	8
Sugar Alcohols, g	0	0
Dietary Fiber, g	1	0
Fat, g	5.0	2.0
Saturated Fat, g	2.0	0.8
Trans Fat, g	0.0	0.0
Cholesterol, mg	0	0
Vitamin A, IU	800.0	320.0
Vitamin C, mg	28.0	11.2
Vitamin D, IU	250.0	100.0
Vitamin E, IU	5.0	2.0
Vitamin K1, mcg	20.0	12.0
Thiamin (B1), mg	0.4	0.2
Riboflavin (B2), mg	0.4	0.2
Niacin (B3), mg	5.0	2.0
Vitamin B6, mg	0.4	0.2
Folic acid, mcg	140.0	56.0
Vitamin B12, mcg	0.8	0.3
Pantothenic Acid (B5), mg	1.8	0.7
Biotin, mcg	8.0	3.2
Choline, mg	206.0	82.4
Calcium, mg	350.0	140.0
Chromium, mcg	13.0	5.2
Copper, mg	0.2	0.1
Iodine, mcg	57.0	23.0
Iron, mg	4.5	1.8
Magnesium, mg	120.0	48.0
Manganese, mg	0.8	0.3
Molybdenum, mcg	15.0	6.0
Phosphorus, mg	313.0	125.0
Selenium, mcg	20.0	8.0
Zinc, mg	3.3	1.3
Potassium, mg	340.0	136.0
Sodium, mg	330.0	132.0
Chloride, mg	162.0	64.8
Inositol, mg	0.0	0.0
L-Leucine, mg	700.0	280.0
L-Arginine, mg	1004.0	401.6
L-Isoleucine, mg	700.0	280.0
L-Histidine, mg	382.0	152.8
L-Lysine, mg	1005.0	402.0
L-Methionine, mg	382.0	152.8
L-Phenylalanine, mg	700.0	280.0
L-Proline, mg	1005.0	402.0
L-Serine, mg	700.0	280.0
L-Threonine, mg	700.0	280.0
L-Tryptophan, mg	210.0	84.0
L-Tyrosine, mg	3.0	1.2
L-Valine, mg	900.0	360.0

CAMBROOKE THERAPEUTICS Tel: 555.5555 Fax: 888.888.8888 www.cambrooke.com info@cambrooke.com

Figure 3

TYLACTIN RESTORE 10 CITRUS

SKU 07502

NET WEIGHT 20.3 OZ (601)

SERVING SIZE 16.9 fl oz (500mL)

SERVINGS PER PACKAGE 1.2

REIMBURSEMENT CODE 24359-0575-02
(for USA only)

MEDICAL FOOD PRODUCT

For the dietary management of tyrosinemia (TYR). Dispensed by prescription. TYLACTIN RESTORE is a metabolic formulas for TYR patients, ages one year and older, in the form of a great tasting hydration beverage ("sports drink"). Each 500 mL serving contains 10 grams of Tylactin protein and comes ready to drink in a clear, recyclable bottle.

PRECAUTIONS: Give only to adults and children who are under medical supervision for proven TYR. Protein in prescribed amounts must be supplemented to completely meet tyrosine requirements.

NOT FOR PARENTERAL USE • USE AS DIRECTED BY PHYSICIAN

INGREDIENTS:

Water, sucrose, whey protein isolate (glycomacropeptide), leucine, citric acid, arginine, sodium citrate, natural flavors, (ethyl alcohol, natural flavors, propylene glycol, glycerine, polysorbate 60, citric acid), histidine, tryptophan, potassium sorbate (preservative), cysteine, sodium benzoate (preservative), vitamin/mineral blend (sugar, niacin [vitamin b3], pantothenate [vitamin b5], pyridoxine [vitamin b6], riboflavin [vitamin b2], folic acid, biotin, cyanocobalamin [vitamin b12]), FD&C yellow #5, FD&C red #40.

Contains milk.

PREPARATION

Ready to drink. Shake well.

STORAGE

Store in cool, dry place.

TO REQUEST A SAMPLE

Call 866.456.9776, opt 2 or complete form
www.samples.cambrooke.com

Nutrients	16.9 fl oz (500mL)	per 100mL
Calories	170	34
Calories From Fat	1	0
Protein equivalent, g	10	2
Free Amino Acids, g		
Tyrosine, mg	2	0
Carbohydrates, g	31	6
Sugar, g	28	6
Sugar Alcohol, g		
Dietary Fiber, g	0	0
Fat, g	0.0	0.0
Saturated Fat, g	0.0	0.0
Trans Fat, g	0.0	0.0
Cholesterol, mg	0	0
Vitamin A, IU	0.0	0.0
Vitamin C, mg	0.0	0.0
Vitamin D, IU		
Vitamin E, IU		
Vitamin K, mcg		
Thiamin (B1), mg	0.0	0.0
Riboflavin (B2), mg	0.3	0.1
Niacin (B3), mg	5.0	1.0
Vitamin B6, mg	0.5	0.1
Folic acid, mcg	100.0	20.0
Vitamin B12, mcg	1.5	0.3
Pantothenic Acid (B5), mg	7.5	1.5
Biotin, mcg	70.0	15.0
Choline, mg		
Calcium, mg	160	32
Chromium, mcg		
Copper, mg		
Iodine, mcg		
Iron, mg		
Magnesium, mg	5.4	1.1
Manganese, mg		
Molybdenum, mcg		
Phosphorus, mg	40.2	8.0
Selenium, mcg		
Zinc, mg		
Potassium, mg	200.0	40.0
Sodium, mg	380	76.0
Chloride, mg	8.0	1.6
Inositol, mg		
L-alanine, mg	520.0	104.0
L-arginine, mg	1160.0	232.0
L-aspartate, mg	720.0	144.0
L-cystine, mg	102.7	21.0
L-glutamate, mg	1620.0	324.0
L-glycine, mg	460	92.0
L-histidine, mg	250.0	50.0
L-isoleucine, mg	900.0	180.0
L-leucine, mg	2130.0	422.0
L-lysine, mg	1220.0	244.0
L-methionine, mg	170.0	34.0
L-phenylalanine, mg	150.0	30.0
L-proline, mg	1020.0	204.0
L-serine, mg	640.0	128.0
L-threonine, mg	1000.0	200.0
L-tryptophan, mg	150.0	30.0
L-tyrosine, mg	2.0	0.4
L-valine, mg	960.0	192.0

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Figure 4

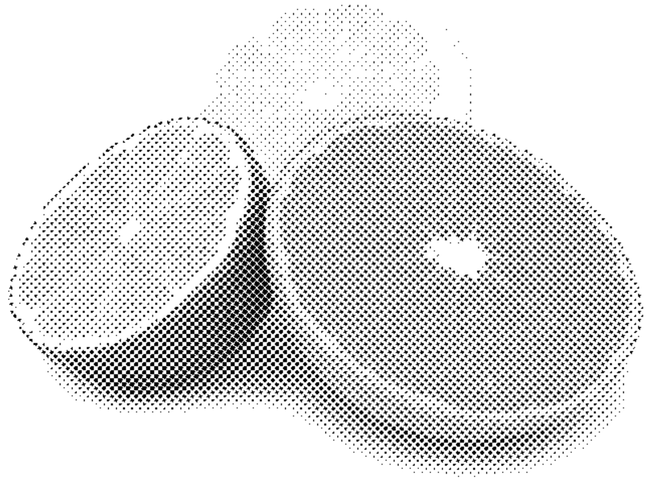
CAMBROOKE THERAPEUTICS™

TYR

10 TYLACTIN RESTORE™

MODIFIED GLYCOMACROPEPTIDE

CITRUS



MEDICAL FOOD PRODUCT
For the dietary management of tyrosinemia (TYR)

DISPENSED BY PRESCRIPTION

12 - 16.9 FL OZ (500 ML)
NET 1.6 GAL (6 L)

PREPARATION Ready to drink. Shake well.
STORAGE Store in cool, dry place. **BEST BY** See carton or individual bottle.
PRECAUTIONS Give only to those under medical supervision for proven tyrosinemia.
NOT FOR PARENTERAL USE • USE AS DIRECTED BY PHYSICIAN

MACRONUTRIENTS

	16.9 fl oz (500mL)	per 100mL		16.9 fl oz (500mL)	per 100mL		16.9 fl oz (500mL)	per 100mL
Calories	170	34	Carbohydrate, g	31	6	Saturated Fat, g	0	0
Calories from Fat	1	0	Sugar, g	30	6	Trans Fat g	0	0
Protein Equivalent, g	10	2	Dietary Fiber, g	0	0	Cholesterol, mg	0	0
Tyrosine mg	2	0	Fat, g	0	0			

MICRONUTRIENTS

Thiamin (B1), mg	0.6	0.6	Vitamin B12, mcg	1.5	0.4	Phosphorus, mg	40.0	8.0
Riboflavin (B2), mg	0.4	0.1	Pantothenic acid (B5), mg	2.5	0.5	Potassium, mg	200.0	40.0
Niacin (B3), mg	5.0	1.0	Biotin, mcg	75.0	15.0	Sodium, mg	350.0	75.0
Vitamin B6, mg	0.5	0.1	Calcium, mg	10.0	2.0	Chloride, mg	8.0	1.6
Folic acid, mcg	100.0	20.0	Magnesium, mg	6.4	1.3	Glutamic acid, g	1.6	0.3

INGREDIENTS Water, sucrose, whey protein isolate (glycomacropeptide), leucine, citric acid, arginine, sodium citrate, natural flavors (ethyl alcohol, natural flavors, propylene glycol, glycerine, polysorbate 60, citric acid), histidine, cysteine, tryptophan, potassium sorbate (preservative), sodium benzoate (preservative), vitamin/mineral blend (sugar, niacin [vitamin B3], pantothenate [vitamin B5], pyridoxine [vitamin B6], riboflavin [vitamin B2], folic acid, biotin, cyanocobalamin [vitamin B12]), FD&C yellow #5, FD&C Red #40.
Contains milk.

MANUFACTURED BY
CAMBROOKE THERAPEUTICS, INC.
AYER, MA 01432

866 456 9776
info@cambrooke.com
www.cambrooke.com

s 04795 35076 6

Figure 5

CAMBROOKE THERAPEUTICS™

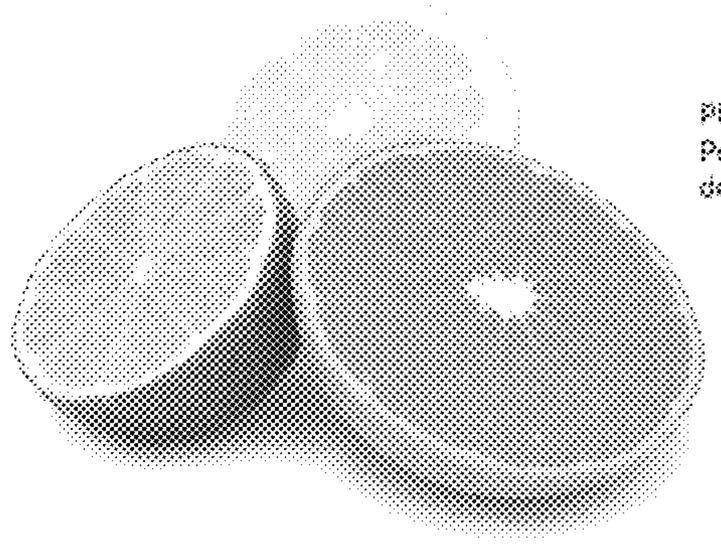
TYR

10 FL OZ

TYLACTIN RESTORE™

MODIFIED GLYCOMACROPEPTIDE

AGRUME



PRODUIT ALIMENTAIRE MÉDICAL
Pour la prise en charge diététique de la tyrosinémie (TYR)

12 - 500 ML
NET 6 L

PRÉPARATION Prêt à servir. Bien agiter.
ENTREPOSER Garder dans un endroit sec et frais.
DATE LIMITE DE CONSOMMATION Voir carton ou une bouteille individuelle.
PRÉCAUTIONS Donner seulement à ceux sous surveillance médicale avec un diagnostic éprouvé de tyrosinémie.
PAS POUR USAGE PARENTÉRAL • SUIVEZ LES INDICATIONS DU MÉDECIN

MACRO-ÉLÉMENTS

	500mL par 100mL			500mL par 100mL			300mL par 100mL	
Calories	170	34	Glucides, g	31	6	Saturés, g	0	0
Calories des lipides	1	0	Sucres, g	30	6	Trans, g	0	0
Protéine équivalente, g	10	2	Fibres, g	0	0	Cholestérol, mg	0	0
Tyrosine, mg	2	0	Lipides, g	0	0			

MICRO-ÉLÉMENTS

Thiamine (B1), mg	0.9	0.6	Vitamine B12, mcg	1.8	0.4	Phosphore, mg	400	80
Riboflavine (B2), mg	0.4	0.1	Acide pantothénique (B5), mg	2.5	0.5	Potassium, mg	2000	400
Niacine (B3), mg	5.0	1.0	Biotine, mcg	75.0	15.0	Sodium, mg	380	760
Vitamine B6, mg	0.5	0.1	Calcium, mg	100	20	Chlorure, mg	80	16
Acide folique, mcg	100.0	20.0	Magnésium, mg	84	1.3	Acide glutamique, g	1.6	0.3

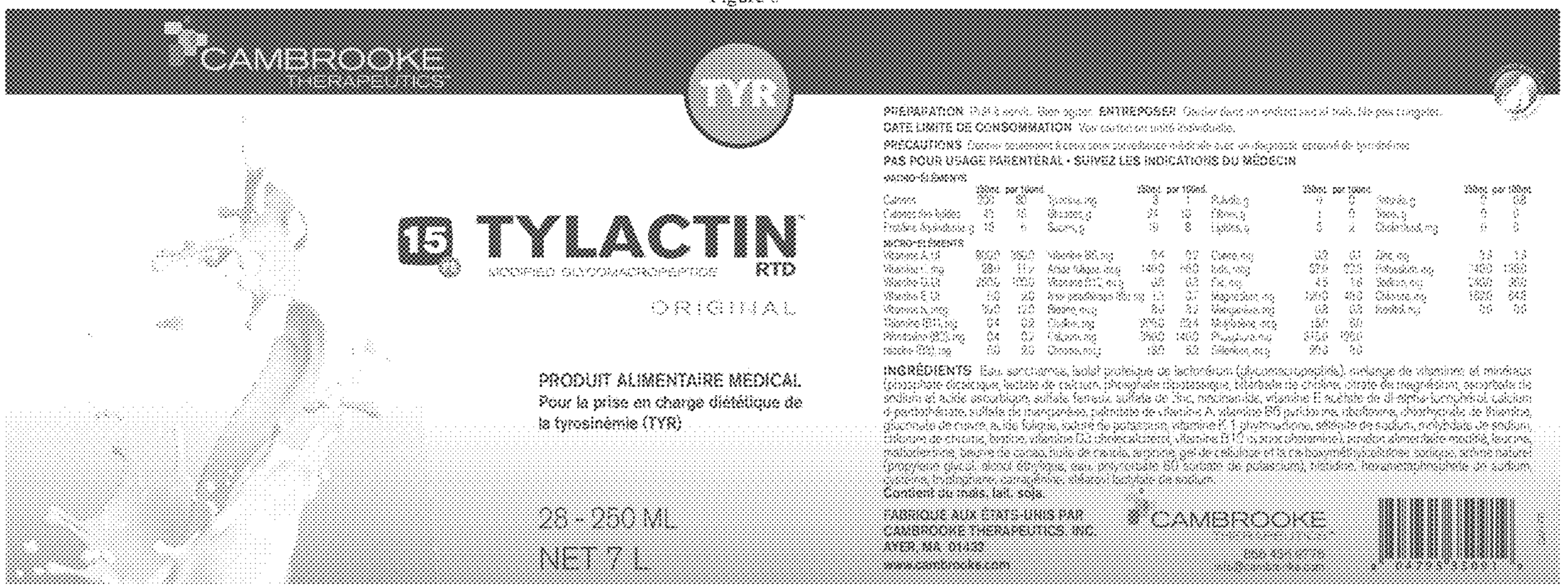
INGRÉDIENTS Eau, saccharose, isolat protéique de lactosérum (glycomacropeptide), leucine, acide citrique, arginine, citrate de sodium, arômes naturels (alcool éthylique, arômes naturels, propylène glycol, glycérine, polysorbate 80, acide citrique), histidine, cystéine, tryptophane, sorbate de potassium (préservatif), benzoate de sodium (préservatif), mélange de vitamines et minéraux (sucre, niacine [vitamine B3], pantothénate [vitamine B5], pyridoxine [vitamine B6], riboflavine [vitamine B2], acide folique, biotine, cyanocobalamine [vitamine B12]), FD & C jaune # 5, FD & C rouge # 40. **Contient du lait.**

FABRIQUÉ AUX ÉTATS-UNIS PAR
CAMBROOKE THERAPEUTICS, INC.
AYER, MA 01432

866 456 9776
info@cambrooke.com www.cambrooke.com

s 04795 35076 6

Figure 6


CAMBROOKE
THERAPEUTICS
TYR
15
TYLACTIN
RTD
MODIFIED GLYCOMACROPEPTIDE
ORIGINAL
PRODUIT ALIMENTAIRE MEDICAL
Pour la prise en charge diététique de la tyrosinémie (TYR)
28 - 250 ML
NET 7 L
PRÉPARATION
ENTREPOSER
DATE LIMITE DE CONSOMMATION
PRÉCAUTIONS
PAS POUR USAGE PARENTERAL - SUIVEZ LES INDICATIONS DU MÉDECIN
MACRO-ÉLÉMENTS
MICRO-ÉLÉMENTS
INGRÉDIENTS
Contient du maïs, lait, soja.
FABRIQUE AUX ÉTATS-UNIS PAR
CAMBROOKE THERAPEUTICS, INC.
BYFIELD, MA 01922
www.cambrooke.com
CAMBROOKE

LIQUID NUTRITIONAL FORMULA FOR TYROSINEMIA PATIENTS

BACKGROUND

Tyrosinemia is a genetic disorder characterized by elevated blood levels of the amino acid tyrosine. Tyrosinemia is caused by deficiency of tyrosine metabolism, which leads to increased levels of tyrosine and tyrosine products in the body. There are three types of tyrosinemia, classed by the particular enzyme deficiency of the patient. Type 1 tyrosinemia, also known as hepatorenal tyrosinemia, is the most severe form of the disease and is caused by a deficiency of the enzyme fumarylacetoacetate hydrolase, which catalyzes the final step in tyrosine metabolism. Type 1 tyrosinemia can lead to liver and kidney failure, problems affecting the nervous system and increased risk of liver cancer. Type 2 tyrosinemia is caused by a deficiency of the enzyme aminotransferase and affects the eyes, skin and mental development. Type 3 tyrosinemia is the rarest form and is caused by a deficiency of the enzyme 4-hydroxyphenylpyruvate dioxygenase. Type 3 tyrosinemia is characterized by intellectual disability, seizures and intermittent ataxia.

Treatment of tyrosinemia typically involves a diet that is low in phenylalanine and low in tyrosine (low Phe/Tyr). However in children, the low Phe/Tyr diet must also be designed to provide enough of the two amino acids to support growth while avoiding excesses of both. This low Phe/Tyr diet must be consumed for life and compliance is an issue for many. Treatment may also include the administration of nitisinone, a medication that blocks the formation of fumarylacetoacetate.

SUMMARY

Nutritional Formulation

Described herein are metabolic formulas for the dietary management of tyrosinemia. In one embodiment, the metabolic formulation is a nutritional formula (also referred to as a nutritional formulation) that has a balanced amino acid profile suitable for therapy for individuals who have tyrosinemia; they include complete, peptide-based, ready-to-drink (RTD) nutritional formulas, such as shelf-stable, ready-to-drink (liquid), nutritional formulas that have a balanced amino acid profile and are suitable therapy for patients suffering from tyrosinemia. The RTD nutritional formulas can be packaged using known methods. For example, the container can be a bottle, a carton or a can. In some embodiments, packaging is carried out under aseptic conditions. The RTD formula can be canned (e.g. placed in containers that are then hermetically sealed and sterilzed, such as by heat) or bottled. In some embodiments, the formula is bottled by a hot fill bottling process.

In a second embodiment, the metabolic formula is a hydration beverage (also referred to as a sports drink).

The nutritional formulas have a balanced amino acid profile suitable for therapy for individuals who have tyrosinemia, are low in phenylalanine and tyrosine, have a lower osmolality than a purely synthetic amino acid formula and have an acceptable taste. For example, the osmolality of a nutritional formula described herein is generally about 330 milliosmoles per liter. In contrast, the osmolality of purely synthetic amino acid formulas is generally about 1000 milliosmoles per liter.

The nutritional formula comprises in one embodiment: (a) a protein source that comprises (i) whey protein, such as caseino-glyco-macropeptide (cGMP) and (ii) complementary essential amino acids which are a mixture of arginine, tryptophan, leucine, histidine and cysteine and provides a balanced amino acid profile; (b) a carbohydrate source, which typically includes non-reducing sugars to minimize/reduce browning potential; (c) a fat (lipid/oil) source; and (d) vitamins and minerals in sufficient quantities to meet the daily requirements for each. In alternative embodiments, in (ii) the complimentary essential amino acids are a mixture of arginine, tryptophan, leucine, histidine and methionine or the complimentary essential amino acids are a mixture of arginine, tryptophan, leucine, histidine, cysteine and methionine. The nutritional formula comprises no added tyrosine or phenylalanine; tyrosine and phenylalanine in the nutritional formula are contributed by cGMP.

In addition, the nutritional formula typically, but optionally, includes flavors, which can be natural or artificial or a combination of both; coloring agents, which can be natural or artificial or a combination of both; sweetener, which can be natural or artificial or a combination of both; gelling agents, thickening agents, stabilizing agents, sequestrants, emulsifiers or a combination of two or more of gelling agents, thickening agents, stabilizing agents, sequestrants, emulsifiers, each of which can be natural or artificial or a combination of both.

In one embodiment, the nutritional formula comprises: water, sucrose, whey protein isolate, vitamin and mineral blend (dicalcium phosphate, calcium lactate, dipotassium phosphate, choline bitartrate, magnesium citrate, sodium ascorbate and ascorbic acid, ferrous sulfate, zinc sulfate, niacinamide, vitamin E dl-alphatocopheryl acetate, calcium d-pantothenate, manganese sulfate, vitamin A palmitate, vitamin B6 pyridoxine, riboflavin, thiamin hydrochloride, copper gluconate, folic acid, potassium iodide, vitamin K 1 phytonadione, sodium selenite, sodium molybdate, chromium chloride, biotin, vitamin D3 cholecalciferol, vitamin B12 cyanocobalamin), food starch modified, leucine, maltodextrin, cocoa butter, canola oil, arginine, cellulose gel and carboxymethylcellulose sodium, natural flavor (propylene glycol, ethyl alcohol, water, polysorbate 80 potassium sorbate), histidine, one or more food grade polyphosphate chelator, such as sodium hexametaphosphate, cysteine, tryptophan, carrageenan, sodium stearoyl lactylate.

Also described are methods for producing the nutritional formula described herein. One embodiment of the method is represented schematically in FIG. **1**. In one embodiment, the method comprises: (a) kitting together dry ingredients; (b) kitting together a mineral mixture; (c) producing an oil incorporation mixture; (d) combining, in order, the mixtures produced in steps (a) to (c) in a high shear blender under conditions under which a stable emulsion formula is formed; (e) adding vitamin C to the formula (emulsion); (f) sterilizing the formula by ultra-high temperature aseptic treatment of the emulsion under conditions sufficient to sterilize the formula, for example at 140° C. for 5-6 seconds; (g) optionally, storing the sterilized formula in an aseptic storage tank; and (h) aseptically packaging the formula.

Hydration Beverage

In some embodiments, the metabolic formula is a hydration beverage or sports drink for dietary management of individuals who have tyrosinemia. The hydration beverage or sports drink comprises: (a) a protein source that comprises (i) caseino-glyco-macropeptide (cGMP) and (ii) complementary essential amino acids which are a mixture of arginine, tryptophan, leucine, histidine and cysteine, and provides a balanced amino acid profile; (b) a carbohydrate source, which typically includes non-reducing sugars to minimize/reduce browning potential; and (c) vitamins and

minerals. In addition, the hydration beverage or sports drink typically, but optionally, includes preservatives; flavors, which can be natural or artificial or a combination of both; coloring agents, which can be natural or artificial or a combination of both; sweetener, which can be natural or artificial or a combination of both; gelling agents, thickening agents, stabilizing agents, sequestrants, emulsifiers or a combination of two or more of gelling agents, thickening agents, stabilizing agents, sequestrants, emulsifiers, each of which can be natural or artificial or a combination of both. In one specific embodiment, the hydration beverage or sports drink comprises the components listed in Table 3. In one specific embodiment, the hydration beverage or sports drink comprises the components listed in Table 4. In a specific embodiment, the hydration beverage consists essentially of the components listed in Table 3 or consists essentially of the components listed in Table 4.

In a specific embodiment, the hydration beverage or sports drink comprises: water, sugar (e.g., sucrose), a protein source, such as whey protein isolate (glycomacropeptide), citric acid, amino acids (e.g., leucine, arginine, histidine, cysteine, tryptophan), sodium citrate, natural flavors, (ethyl alcohol, natural flavors, propylene glycol, glycerine, polysorbate 60, citric acid), potassium sorbate (preservative), sodium benzoate (preservative), vitamin/mineral blend (sugar, niacin [vitamin b3], pantothenate [vitamin b5], pyridoxine [vitamin b6], riboflavin [vitamin b2], folic acid, biotin, cyanocobalamin [vitamin b12]), FD&C yellow #5, FD&C red #40. The hydration beverage or sports drink may optionally include flavors, which can be natural or artificial or a combination of both; coloring agents, which can be natural or artificial or a combination of both; sweetener, which can be natural or artificial or a combination of both; gelling agents, thickening agents, stabilizing agents, sequestrants, emulsifiers or a combination of two or more of gelling agents, thickening agents, stabilizing agents, sequestrants, emulsifiers, each of which can be natural or artificial or a combination of both.

The hydration beverage or sports drink described herein is produced, using methods also described herein and other methods known to those of skill in the art. In one embodiment, the method comprises: (a) kitting together the dry ingredients; (b) blending together with the kitted dry ingredients in the following order (i) preservatives, (ii) a carbohydrate source (such as sucrose), (iii) a protein source (such as cGMP), (iv) amino acids (e.g., leucine, arginine, histidine, cysteine, tryptophan) with buffers and citric acid, (v) flavorings, (vi) coloring, and (vii) sweeteners to form a hydration beverage; (c) titrating the pH of the hydration beverage; (d) optionally, ultra-heat treating the hydration beverage; (e) bottling the hydration beverage by a hot fill bottling process; and, (f) cooling the bottled hydration beverage in a cool water bath. In some embodiments, the bending is performed at ambient temperature (e.g., room temperature). In some embodiments, the blending, pH titrating and ultra-heat treating are performed while the hydration beverage is being continuously mixed. In some embodiments the preservatives are sorbate and benzoate. In some embodiments, the amount of sorbate ranges from about 0.05 g to about 1.0 g per 1030.4158 g of hydration beverage. In some embodiments, the amount of benzoate ranges from about 0.05 g to about 1.0 g per 1030.4158 g of hydration beverage. In some embodiments, the hydration beverage pH is titrated to between about pH 4.0 and about pH 5.0. In some embodiments, the hydration beverage pH is titrated to between about pH 4.3 and about pH 4.4.

BRIEF DESCRIPTION OF THE FIGURES

FIG. **1** is a schematic representation of a method by which nutritional formulas are produced.

FIG. **2** is a label for TYLACTIN RTD 15 ORIGINAL

FIG. **3** is a label for TYLACTIN RESTORE 10 CITRUS

FIG. **4** is a label for TYLACTIN RESTORE CITRUS

FIG. **5** is a label for TYLACTIN RESTORE (FRENCH)

FIG. **6** is a label for TYLACTIN RTD ORIGINAL

DETAILED DESCRIPTION

Dietary compliance is the primary issue for tyrosinemia patients whose diets are based on amino acid formulas. Compliance is an issue and there have been many attempts to improve acceptance of foods and beverages for those with tyrosinemia but those efforts have not been successful.

Ready-to-drink, shelf-stable formulae, such as beverages, pose particular challenges, at least in part because the components essential for complete sustenance components must be combined to produce the nutritional formula in such a way that they remain dissolved, suspended or otherwise retained in the formula (beverage). This is a challenge because each ingredient in the nutritional formula has unique requirements for making it stable. Particularly difficult to incorporate is the caseino-glycomacro-peptide, which contains sialic acid attached to an amino acid residue on the chain. This sialic acid reduces the isoelectric point of the peptide as a function of the fraction of sites occupied by sialic acid. Thus, the isoelectric point can change as the peptide is being processed. Peptides are not soluble at or near their isoelectric pH and tend to precipitate or gel. Described herein is a method by which nutritional formulas described are made, with the result that the formula is ready-to-drink and shelf-stable.

Nutritional Formula Preparation

Nutritional formula preparation is carried out using the method represented schematically in the Figure. Kitting of ingredients is carried out as indicated: Kitting of dry ingredients, to produce a dry ingredient mixture, is carried out by combining dry ingredients without food grade polyphosphate chelator, such as sodium hexametaphosphate (SHMP), or mineral blend; kitting together of food grade polyphosphate chelator, such as SHMP, $CuSO_4$, $FeSO_4$ and, if needed, other minerals; and kitting of ingredients for oil incorporation. The SHMP and minerals are mixed in water separately. Ingredients for oil incorporation are heated and incorporated together. These include octenyl succinate starch (OSS), sodium stearoyl lactylate (SSL), cocoa butter, vegetable oil and other oil-soluble ingredients. They are subjected to high shear and homogenization. The resulting three combinations (see the Figure) are combined with water and other components as shown in FIG. **1** and subjected to the conditions shown, beginning with the step "Sequentially add to high shear blender". The resulting formula is packaged, such as aseptically or by canning. In some embodiments, the dry ingredients include caseino glycomacropeptides (GMP), amino acids, and vitamins.

SHMP is combined with minerals, such as a metal fortification mixture, which comprises at least one type of metallic ions to produce a SHMP-minerals in water SHMP-metal mixture. In some embodiments, the metal fortification mixture comprises two or more types of metallic ions. In some embodiments, the metallic ions are copper (e.g., Cu^{2+})

and/or iron (e.g., Fe^{2+}) and/or Zinc (Zn^{+2}). In some embodiments, the metallic ions are from sources such as $CuSO_4$ and/or $FeSO_4$ and/or $ZnSO_4$. In some embodiments, a sequestrant or chelator other than a food grade polyphosphate chelator such as SHMP, is combined with minerals. Sequestrants include but are not limited to Calcium disodium ethylene diamine tetra-acetate (E385), Glucono delta-lactone (E575), Potassium gluconate (E577), Sodium gluconate (E576), Sodium triphosphate and EDTA.

An emulsion is prepared by combining and heating oil ingredients, which includes modified starch, sodium stearoyl lactylate (SSL), oils such as cocoa butter and vegetable oil, and other oil soluble ingredients. The modified starch used herein is an amphiphilic starch, which is hydrophilic and hydrophobic in nature. The modified starch is used to bind to fat to prevent the fat from interacting with the proteins by steric hindrance. For example, a normally hydrophilic starch is modified to incorporate hydrophobic moieties such as octenyl groups which binds to fats. The resulting modified starch has an amphiphilic nature and thus surface active properties which are useful in stabilizing oil/water emulsions. In some embodiments, the modified starch is octenyl succinate starch (OSS) or another amphiphilic starch. The hydrophobic octenyl moiety binds the fats in the emulsion assuring that the starch remains attached to the fat globule, preventing the fats from interacting with the proteins by steric hindrance.

The heated and combined oil ingredients are then added to a mixer, such as a high shear mixer, with water and are homogenized to form an emulsion. In some embodiments, the oil ingredients are homogenized with water at about 60-80° C. and about 400 psi to about 3000 psi. In some embodiments, the oil ingredients are homogenized in two steps. In some embodiments, the first emulsion step is performed at between about 60° C. and about 80° C. and at a pressure between about 1200 psi and 3000 psi. In some embodiments, the second emulsion step is performed at between about 60° C. and about 80° C. and at a pressure between about 300 psi and about 700 psi. In one embodiment, the oil ingredients is homogenized at about 70° C. and about 500 psi to about 2000 psi.

As shown, the mixtures are sequentially added to a blender such as a high shear blender in the following order: the dry ingredient mixture is mixed into metered volume of water, the fortified SHMP mixture is added, the emulsion is incorporated, and vitamin C is added last. In some embodiments, the vitamin C is sodium ascorbate and/or ascorbic acid. In some embodiments, the amount of vitamin C added is between about 120 mg and about 450 mg. In some embodiments, the final amount of vitamin C present in the formula is equal to 50% of the recommended daily allowance (RDA) of vitamin C. The combined mixture is subjected to ultra-high temperature processing (UHT). The resulting formula is subsequently placed/stored in aseptic tank and then aseptically packaged. In some embodiments, the aseptic packaging is a Prisma package. In some embodiments, the aseptic packaging is a can.

Hydration Beverage Preparation

Hydration beverage or sports drink preparation is carried out using the method described herein. In one embodiment, the method comprises: (a) kitting together the dry ingredients; (b) blending together with the kitted dry ingredients in the following order (i) preservatives, (ii) a carbohydrate source (e.g., sucrose), (iii) a protein equivalent source (e.g., cGMP), (iv) amino acids (e.g., leucine, arginine, histidine, cysteine, tryptophan) with buffers and citric acid, (v) flavorings, (vi) coloring, and (vii) sweeteners to form a hydration beverage; (c) titrating the pH of the hydration beverage; (d) ultra-heat treating the hydration beverage; (e) bottling the hydration beverage by a hot fill bottling process; and, (f) cooling the bottled hydration beverage in a cool water bath. In some embodiments, the bending is performed at ambient temperature (e.g., room temperature). In some embodiments, the blending, pH titrating and ultra-heat treating are performed while the hydration beverage is being continuously mixed. In some embodiments, the hydration beverage pH is titrated to between about pH 4.0 and about pH 5.0. In some embodiments, the hydration beverage pH is titrated to between about pH 4.3 and about pH 4.4.

Example 1: Preparation of Complete Nutritional Formulation

Dry ingredient mixture was prepared by kitting together the dry ingredients without sodium hexametaphosphate (SHMP), vitamins, or mineral. Table 1 lists dry ingredients used, such as whey protein isolate (such as caseino glycomacropeptides (GMP)), amino acids, vitamins, sugar, dextrin, natural flavoring products, natural food coloring, sodium chloride, cellulose gum, carrageenan, and sweeteners. In another step, SHMP is combined with a copper and iron fortification mixture. In another step, vitamins and minerals are mixed together in water to provide a vitamin and mineral fortification mixture. Subsequently, the SHMP with the copper and iron fortification mixture is mixed with the vitamin and mineral fortification mixture, thereby forming a metal/mineral fortified SHMP mixture.

In a separate step, an emulsion is prepared by combining and heating oil ingredients.

The foregoing mixtures are then sequentially added to a blender such as a high shear blender in the following order: the dry ingredient mixture is mixed into metered volume of water, the fortified SHMP mixture is added, the emulsion is incorporated, and Vitamin C (sodium ascorbate and ascorbic acid) is added last. The table below provides the amounts of each ingredient used to prepare the formula. The combined mixture is subjected to ultra-high temperature processing (UHT) at about 140° C. for about 5 to about 6 seconds The resulting formula is subsequently stored in aseptic tank and then aseptically packaged using Prisma Packages.

TABLE 1

Tylactin RTD Original
Tylactin RTD Original
Number of 250 ml Servings: 4
Weight: 1064 g

	Range	Units	% Weight Range
Water	635-955	Gram	
Caseino glycomacropeptides (GMP)	40-60	Gram	3.76-5.64
Vitamin and mineral fortification	16-25	Gram	1.5-2.35
Amino Acids	16-25	Gram	1.5-2.35
Sugar	56-84	Gram	5.26-7.89
dextrin sweetener	8-12	Gram	0.75-1.13
Emulsion	72-108	Gram	6.77-10.15
Natural flavors	2.4-3.6	Gram	0.23-0.34
Natural color	0.4-0.6	Gram	0.04-0.06
sodium hexametaphosphate	1-2	Gram	0.09-0.19
cellulose gum	3.8-6	Gram	0.36-0.56
carrageenan	0.2-0.5	Gram	0.02-0.05
	.05-1.0	Gram	0.004-0.09
	.05-1.0	Gram	0.004-0.09

TABLE 2

Tylactin RTD 15 Original

TYLACTIN RTD 15 ORIGINAL	per serving 8.5 fl oz (250 mL)	Range	% Weight Range	per 100 mL
Nutrients				
Calories	200	160-240		80
Calories From Fat	45	36-54		18
Protein Equivalent, g	15	12-18	4.51-6.77	6
Free Amino Acids, g		0		
Tyrosine, mg	3	2.4-3.6	<.01%	1
Carbohydrates, g	24	19.2-28.8	7.22-10.83	10
Sugar, g	19	15.2-22.8	5.71-8.57	8
Sugar Alcohols, g	0	0		0
Dietary Fiber, g	1	0.8-1.2	0.30-0.45	0
Fat, g	5	4-6	1.50-2.26	2
Saturated Fat, g	2	1.6-2.4	0.60-0.90	0.8
Trans Fat, g	0	0		0
Cholesterol, mg	0	0		0
Vitamin A, IU (mcg)	900 (495 mcg)	720-1080 (396-594 mcg)	<0.01%	360
Vitamin C, mg	28	22.4-33.6	8.42-12.63	11.2
Vitamin D, IU (mcg)	250 (6.25 mcg)	200-300 (5-7 mcg)	<0.01%	100
Vitamin E, IU	5 (5 mg)	4-6 (4-6 mg)	<0.01%	2
Vitamin K, mcg	30	24-36	<0.01%	12
Thiamin (B1), mg	0.4	0.32-0.48	<0.01%	0.2
Riboflavin (B2), mg	0.4	0.32-0.48	<0.01%	0.2
Niacin (B3), mg	5	4-6	<0.01%	2
Vitamin B6, mg	0.4	0.32-0.48	<0.01%	0.2
Folic acid, mcg	140	112-168	<0.01%	56
Vitamin B12, mcg	0.8	0.64-0.96	<0.01%	0.3
Pantothenic Acid (B5), mg	1.8	1.44-2.16	<0.01%	0.7
Biotin, mcg	8	6.4-9.6	<0.01%	3.2
Choline, mg	206	164.8-247.2	0.06-0.09	82.4
Calcium, mg	350	280-420	0.11-0.16	140
Chromium, mcg	13	10.4-15.6	<0.01%	5.2
Copper, mg	0.2	0.16-0.24	<0.01%	0.1
Iodine, mcg	57	45.6-68.4	<0.01%	22.8
Iron, mg	4.5	3.6-5.4	<0.01%	1.8
Magnesium, mg	120	96-144	0.04-0.05	48
Manganese, mg	0.8	0.64-0.96	<0.01%	0.3
Molybdenum, mcg	15	12-18	<0.01%	6
Phosphorus, mg	315	252-378	0.09-0.14	126
Selenium, mcg	20	16-24	<0.01%	8
Zinc, mg	3.3	2.64-3.96	<0.01%	1.3
Potassium, mg	340	272-408	0.10-0.15	136
Sodium, mg	300	240-360	0.09-0.14	120
Chloride, mg	162	129.6-194.4	0.05-0.07	64.8
Inositol, mg	0	0	0.00-0.00	0
L-alanine mg	700	560-840	0.21-0.32	280
L-arginine mg	1593	1274.4-1911.6	0.48-0.72	637.2
L-aspartate mg	1000	800-1200	0.30-0.45	400
L-cysteine, mg	162	129-194	0.05-0.07	64.8
L-glutamate, mg	2250	1800-2700	0.68-1.01	900
L-glycine, mg	148	118.4-177.6	0.04-0.07	59.2
L-histidine, mg	361	288.8-433.2	0.11-0.16	144.4
L-isoleucine, mg	1300	1040-1560	0.39-0.59	520
L-leucine, mg	3000	2400-3600	0.90-1.35	1200
L-lysine, mg	818	654.4-981.6	0.25-0.37	327.2
L-methionine, mg	180	144-216	0.05-0.08	72
L-phenylalanine, mg	25	20-30	0.01-0.01	10
L-proline, mg	1400	1120-1680	0.42-0.63	560
L-serine, mg	800	640-960	0.24-0.36	320
L-threonine, mg	2200	1760-2640	0.66-0.99	880
L-tryptophan, mg	218	174.4-261.6	0.07-0.10	87.4
L-tyrosine, mg	3	2.4-3.6		1.2
L-valine, mg	900	720-1080	0.27-0.41	360

TABLE 3

Tylactin Restore 10 Citrus
Tylactin Restore 10 Citrus
Number of Servings: 2 (515 g per serving)
Weight: 1030 g

	Range	Measure	% Weight Range
Water	752-1129	Gram	
(Vitamins and minerals)	0.06-0.08	Gram	0.01-0.01
Complementary Amino Acids	5.6-8.4	Gram	0.54-0.82
Caseinglycomacropeptides	12.8-19.2	Gram	1.24-1.86

TABLE 4

Tylactin Restore 10 Citrus
Tylactin Restore 10 Citrus

Nutrients	per serving 16.9 fl oz (500 mL)	Range	% Weight Range	per 100 mL
Calories	170	136-204		34
Calories From Fat	1	0.8-1.2		0
Protein Equivalent, g	10	8-10	0.78-1.16	2
Free Amino Acids, g				
Tyrosine, mg	2	1.6-2.4	<0.01%	0
Carbohydrates, g	31	24-38	2.41-3.61	6
Sugar, g	30	24-36	2.33-3.49	6
Sugar Alcohols, g				
Dietary Fiber, g	0			0
Fat, g	0			0
Saturated Fat, g	0			0
Trans Fat, g	0			0
Cholesterol, mg	0			0
Vitamin A, IU	0			0
Vitamin C, mg	0			0
Vitamin D, IU				
Vitamin E, IU				
Vitamin K, mcg				
Thiamin (B1), mg	0			0
Riboflavin (B2), mg	0.4	0.32-0.48	<0.01%	0.1
Niacin (B3), mg	5	42100	<0.01%	1
Vitamin B6, mg	0.5	0.4-0.6	<0.01%	0.1
Folic acid, mcg	100	80-120	<0.01%	20
Vitamin B12, mcg	1.8	1.44-2.16	<0.01%	0.4
Pantothenic Acid (B5), mg	2.5	42038	<0.01%	0.5
Biotin, mcg	75	60-90	<0.01%	15
Choline, mg				
Calcium, mg	10	42228	<0.01%	2
Chromium, mcg				
Copper, mg				
Iodine, mcg				
Iron, mg				
Magnesium, mg	6.4	5.12-7.68	<0.01%	1.3
Manganese, mg				
Molybdenum, mcg				
Phosphorus, mg	40	32-48	<0.01%	8
Selenium, mcg				
Zinc, mg				
Potassium, mg	200	160-240	0.02-0.02	40
Sodium, mg	380	304-456	0.03-0.04	76
Chloride, mg	8	6.4-9.6	<0.01%	1.6
Inositol, mg				
L-alanine, mg	520	416-624	0.04-0.06	104
L-arginine, mg	1100	880-1320	0.09-0.13	220
L-aspartate, mg	730	584-876	0.06-0.09	146
L-cysteine, mg	107.7	86-129	<0.01%	21.5
L-glutamate, mg	1600	1280-1920	0.12-0.19	320
L-glycine, mg	95	76-114	0.01-0.01	19
L-histidine, mg	250	200-300	0.02-0.03	50
L-isoleucine, mg	900	720-1080	0.07-0.10	180

TABLE 4-continued

Nutrients	Tylactin Restore 10 Citrus Tylactin Restore 10 Citrus per serving 16.9 fl oz (500 mL)	Range	% Weight Range	per 100 mL
L-leucine, mg	2110	1688-2532	0.16-0.25	422
L-lysine, mg	520	416-624	0.04-0.06	104
L-methionine, mg	170	136-204	0.01-0.02	34
L-phenylalanine, mg	16	12.8-19.2	<0.01%	3.2
L-proline, mg	1000	800-1200	0.08-0.12	200
L-serine, mg	640	512-768	0.05-0.07	128
L-threonine, mg	1400	1120-1680	0.11-0.16	280
L-tryptophan, mg	150	120-180	0.01-0.02	30
L-tyrosine, mg	2	1.6-2.4	<0.01%	0.4
L-valine, mg	700	560-840	0.05-0.08	140

We claim:

1. A shelf-stable, liquid nutritional formula for dietary management of tyrosinemia comprising:

(a) a protein source that includes:

(i) caseino-glyco-macropeptide (cGMP); and

(ii) complementary amino acids which are a mixture of arginine, tryptophan, leucine, histidine and cysteine, wherein the cGMP is between about 3% and about 6% of the total weight of the formula, and wherein the protein source provides 20-35% of the energy of the nutritional formula;

(b) a fat source which provides 20% to 30% of the energy of the nutritional formula, wherein the fat source is about 1.5% to about 2.2% of the total weight of the nutritional formula;

(c) a carbohydrate source which provides 40% to 60% of the energy of the nutritional formula,

(d) octenyl succinate starch (OSS); and,

(e) a sodium hexametaphosphate-metal (SHMP-metal) mixture comprising SHMP bound to copper and iron,

wherein the nutritional formula contains less than 0.01% by weight of tyrosine.

2. The shelf-stable, liquid nutritional formula of claim **1**, wherein together the complementary amino acids are about 1.5% to about 2.35% of the total weight of the formula.

3. The shelf-stable, liquid nutritional formula of claim **1**, wherein the formula comprises no added tyrosine or phenylalanine.

4. The shelf-stable, liquid nutritional formula of claim **1**, further comprising at least one vitamin and at least one mineral, wherein together the at least one vitamin and the at least one mineral are between about 1.5% and about 2.35% of the total weight of the formula.

5. The shelf-stable, liquid nutritional formula of claim **4**, wherein the at least one mineral is dicalcium phosphate, calcium lactate, dipotassium phosphate, magnesium citrate, sodium ascorbate, zinc sulfate, calcium d-pantothenate, manganese sulfate, potassium iodide, sodium selenite, sodium molybdate, or chromium chloride, and wherein the at least one vitamin is choline bitartrate, ascorbic acid, niacinamide, vitamin E dl-alphatocopheryl acetate, vitamin A palmitate, vitamin B6 pyridoxine, riboflavin, thiamin hydrochloride, folic acid, vitamin K 1 phytonadione, biotin, vitamin D3 cholecalciferol, or vitamin B12 cyanocobalamin.

6. A shelf-stable, liquid nutritional formula for dietary management of tyrosinemia comprising:

(a) a protein source that includes:

(i) caseino-glyco-macropeptide (cGMP); and

(ii) complementary amino acids which are a mixture of arginine, tryptophan, leucine, and histidine;

(b) a fat source, wherein the fat source provides between about 18% to about 27% of the total calories in the formula,

(c) octenyl succinate starch (OSS); and,

(d) a sodium hexametaphosphate-metal (SHMP-metal) mixture comprising SHMP bound to copper and iron,

wherein the protein source provides between about 28% and about 43% of the total calories in the formula, and the formula contains less than 0.01% by weight of tyrosine.

7. The shelf-stable, liquid nutritional formula of claim **6**, wherein the formula comprises no added tyrosine or phenylalanine.

8. The shelf-stable, liquid nutritional formula of claim **6**, further comprising vitamins and additional minerals, wherein the vitamins and additional minerals are present in an amount sufficient to make the formula nutritionally complete.

9. The shelf-stable, liquid nutritional formula of claim **8**, wherein the additional minerals are dicalcium phosphate, calcium lactate, dipotassium phosphate, magnesium citrate, sodium ascorbate, zinc sulfate, calcium d-pantothenate, manganese sulfate, potassium iodide, sodium selenite, sodium molybdate, and chromium chloride, and wherein the vitamins are choline bitartrate, ascorbic acid, niacinamide, vitamin E dl-alphatocopheryl acetate, vitamin A palmitate, vitamin B6 pyridoxine, riboflavin, thiamin hydrochloride, folic acid, vitamin K 1 phytonadione, biotin, vitamin D3 cholecalciferol, and vitamin B12 cyanocobalamin.

10. The shelf-stable, liquid nutritional formula of claim **3**, wherein the formula comprises between about 2.4 mg and about 3.6 mg tyrosine.

11. The shelf stable, liquid nutritional formula of claim **7**, wherein the formula comprises between about 2.4 mg and about 3.6 mg tyrosine.

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