Glytactin RTD LITE™ 15 gram Protein Equivalent (modified glycomacropeptide)

MLT35144-35184D1

PRODUCT INFORMATION

Glytactin RTD LITE 15 Coffee Mocha, 15 gram Protein Equivalent (modified glycomacropeptide)
250 mL carton (8.5 fl. oz) Reimbursement Code: 24359-0514-03 (USA only)

Glytactin RTD LITE 15 Vanilla, 15 gram Protein Equivalent (modified glycomacropeptide)
250 mL carton (8.5 fl. oz) Reimbursement Code: 24359-0518-03 (USA only)

Manufactured by Cambrooke Therapeutics, Inc. Ayer, MA 01432 www.cambrooke.com

DISPENSE BY PRESCRIPTION

Glytactin RTD LITE 15 (modified glycomacropeptide) is a medical food for the dietary management of phenylketonuria (PKU).

DESCRIPTION

Glytactin RTD LITE 15 (modified glycomacropeptide) is a specially formulated prescription medical food for the clinical dietary management of phenylalanine hydroxylase deficiency (phenylketonuria) and hyperphenylalanemia.

Glytactin RTD LITE 15 is to be used only under medical supervision. Glytactin RTD LITE 15 has been developed, labeled and should be administered in accordance with the FDA statutory and regulatory definition of Medical Foods.

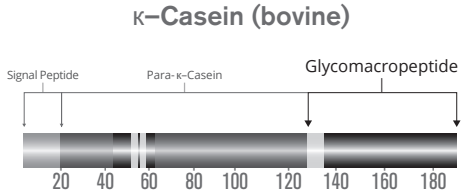
Congress defines "Medical Food" in the Orphan Drug Act and Amendments of 1988 as a formulation to be administered enterally (or orally) *under the supervision of a physician* and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles are established by medical evaluation.

Glytactin RTD LITE 15 is a ready-to-drink version of Glytactin. Glytactin RTD LITE 15 is supplied in single dose, opaque 250 ml, shelf-stable cartons, thirty cartons per case. Available in two two flavors, coffee mocha or vanilla, with 15 grams of protein equivalent per serving, each with a complete micronutrient and macronutrient profile.

PRIMARY INGREDIENTS

Glycomacropeptide

Glycomacropeptide (GMP) is a 64-amino acid whole protein derived from whey. GMP has a unique amino acid profile, which includes an absence of the aromatic amino acids, phenylalanine, tryptophan and tyrosine and higher concentrations of isoleucine and threonine, compared to other dietary proteins.[1] The naturally low levels of phenylalanine contained in commercial GMP make this protein an alternative to synthetic free amino acid based protein for the management of PKU. The GMP in Glytactin RTD is modified by enhancing levels of tryptophan, arginine, leucine, histidine, and tyrosine which are naturally deficient in pure GMP. The addition of these amino acids is necessary to meet daily-required intake of these essential and indispensable amino acids, which cannot be synthesized de novo by the body.



While GMP in its pure form contains no phenylalanine, the process of extracting and refining glycomacropeptide results in the inclusion of trace quantities of phenylalanine (1 mg of phenylalanine per gram of protein equivalent).

Large Neutral Amino Acids

GMP is naturally high in the large neutral amino acids threonine, isoleucine, and valine. Glytactin RTD LITE 15 is further supplemented with additional large neutral amino acids including: histidine, leucine, tryptophan and tyrosine. Phenylalanine is the offending amino acid in phenylalanine hydroxylase deficiency and intake must be severely restricted to prevent neurodevelopmental and physiological consequences. The LNAA profile of Glytactin RTD LITE 15 may inhibit the transport of ingested phenylalanine across intestinal lumen and the blood brain barrier.[2,3,4]

Micronutrients and Macronutrients

Patients with phenylalanine hydroxylase deficiency have a severely restricted diet to minimize intake of phenylalanine found naturally in all foods containing protein, including all meats, legumes, and many vegetables, fruits and grains. As such, there is meaningful risk and challenges in receiving recommended daily intake of many micronutrients. A recent study documented that patients following the low protein diet for PKU without adequate supplementation will be deficient in 11 key vitamins and minerals.[5] To compensate for this, Glytactin RTD LITE 15 includes a full profile of micronutrients and macronutrients. However, additional supplementation may be needed for some individuals and should be discussed with your physician or dietitian.

Complete Ingredients

Water, glycomacropeptide, high oleic canola oil, (Chocolate flavor: natural flavors), vitamin and mineral blend (magnesium phosphate, calcium carbonate, potassium chloride, calcium phosphate, sodium phosphate, potassium phosphate, dl-alpha tocopheryl acetate, potassium iodide, vitamin A palmitate, niacinamide, phytonadione, cholecalciferol, choline bitartrate, manganese sulfate, d-calcium pantothenate, sodium selenite, sodium molybdate, sodium ascorbate, chromium chloride, copper gluconate, ferrous sulfate, zinc sulfate, folic acid, biotin, thiamin mononitrate, pyridoxine hydrochloride, riboflavin, cyanocobalamin), (Vanilla flavor: natural flavors), L-leucine, L-arginine, cellulose gel, cellulose gum, L-tyrosine, inulin, L-lysine acetate, citric acid ester of mono and di-glycerides, L-histidine, sodium hexametaphosphate, L-tryptophan, carrageenan, DHA algal oil, acesulfame-K, salt, sucralose. Contains milk.

GENERALLY RECOGNIZED AS SAFE

The ingredients in Glytactin RTD LITE 15 are Generally Recognized As Safe (GRAS). This is the statutory safety standard of the U.S. Food and Drug Administration (FDA). The standard for an ingredient to achieve GRAS status requires technical demonstration of non-toxicity and safety, general recognition of safety through widespread usage and agreement by experts in the field.

MEDICAL FOOD STATUS

INDICATIONS FOR USE

Glytactin RTD LITE 15 is a medical food for the dietary management of individuals under a physician's care for phenylalanine hydroxylase deficiency (phenylketonuria) or hyperphenylalaninemia.

CLINICAL EXPERIENCE

Published in the American Journal of Clinical Nutrition in July 2016, an outpatient randomized crossover trial was led by the University of Wisconsin's Department of Nutritional Science to test the safety and efficacy of a diet using traditional amino acid medical foods versus glycomacropeptide (GMP) based medical foods as part of the dietary management of PKU. Thirty early-treated PKU subjects completed the study at The Waisman Center, Madison, WI and Boston Children's Hospital, Boston, MA. Cambrooke Therapeutics Glytactin medical food products were solely used in the GMP medical food arm of the study.

Following a three-week wash out period where amino acid-based medical foods were used, each subject completed three weeks of a low phenylalanine (Phe) diet treatment using amino acid medical foods as their primary source of protein equivalent and three weeks using GMP medical foods as their primary source of protein equivalent. The same daily-prescribed protein equivalents were used throughout the study. Subjects were counseled and monitored for their nutrient intake from supplemental standard food products.

Serum chemistry profiles were analyzed routinely to monitor phenylalanine and tyrosine levels and the change in plasma Phe concentrations in subjects following the use of amino acid–based metabolic formula and compared to plasma Phe concentrations of the same patients following the consumption of GMP medical foods. Neuropsychological, behavioral, and intelligence testing was done on each subject to assess executive function.

Following the study, researchers concluded that there was no significant increase in plasma Phe in spite of the fact that the GMP medical foods contains low levels of Phe. They also noted that the patients had fewer side effects of gastrointestinal distress. Behavior ratings and executive function results were not significantly different following consumption of either forms of protein. Patients felt less hunger during the day on a GMP-based protein diet and found the medical foods products, in general, more acceptable. In conclusion, the GMP medical foods products were found to be a safe and acceptable option for the nutritional management of PKU.[7]

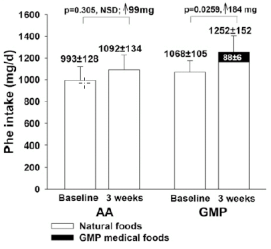
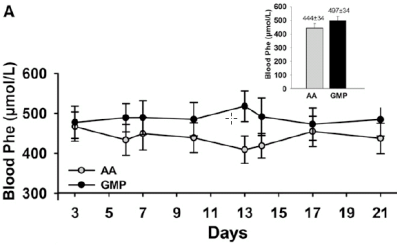
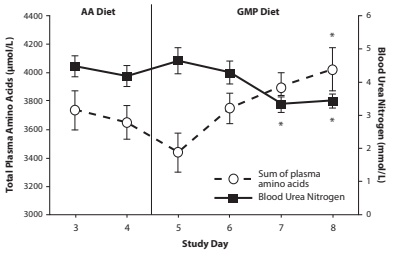


Figure 4B from page 8: This figure illustrates the total Phe intake and compares the Phe intake while on the amino acid based protein medical foods to the Phe intake while on the GMP medical foods. Phe intake did not increase significantly when on an amino acid medical foods but was higher when on the GMP medical foods (P=0.0259) because of the natural Phe contained in the GMP. The intake of Phe from natural diet sources was not significantly different for either protein treatment.[7]

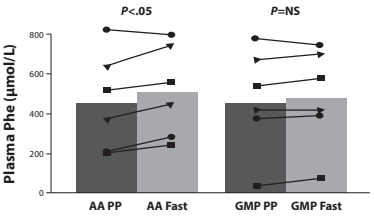
Figure 6 A from page 9: This figure shows fasting blood Phe levels done based on analysis of dried blood spots of subjects, analyzed with tandem mass spectrometry. No significant differences are seen in blood Phe levels due to treatment with an amino acid protein diet versus a GMP protein diet, even though the diet contained higher levels of natural phenylalanine.[7]



Inpatient clinical studies completed at the University of Wisconsin with eleven phenylketonuria patients were conducted to investigate the safety and acceptability of substituting protein from glycomacropeptide for synthetic amino acid formula. Subjects consumed their usual amino acid based formula for four days followed by a glycomacropeptide formula sparingly supplemented with essential amino acids for four days. Two of the tests measured blood urea nitrogen (BUN) and plasma insulin levels. These tests suggested that protein from the glycomacropeptide formula was retained better by the body than the synthetic amino acid formula. The results showed that each phenylketonuria patient fed a glycomacropeptide medical food improved on three important biomarkers.[6]



This figure shows that the concentration of total amino acids in plasma was significantly greater, and the concentration of BUN was significantly lower, with Glycomacropeptide compared with the synthetic amino acid diet when measured 2.5 hours after consumption. This result is consistent with slower absorption of amino acids from an intact natural source of protein. It also suggests that fewer amino acids are degraded for urea production and instead are retained for protein synthesis when glycomacropeptide is substituted for synthetic amino acids as a protein source.[6]



This figure shows the concentration of phenylalanine in postprandial (PP) plasma compared with fasting (Fast) plasma in subjects with phenylketonuria fed glycomacropeptide (GMP) compared with 100% synthetic amino acids (AA) as the sole protein source for four days. There was no significant change in plasma phenylalanine concentration comparing fasting postprandial concentrations when consuming a glycomacropeptide diet (P= 0.349), however, the synthetic amino acid diet showed a significant increase in plasma phenylalanine (P= 0.048).[6]

Patients who use 100% synthetically derived amino acid as their primary protein source in metabolic formulas are commonly known to experience a feeling of hunger shortly after consumption when amino acid formula does not adequately suppress production of Ghrelin (hunger hormone). A glycomacropeptide based formula has been shown to provide satiety to patients by suppressing the production of Ghrelin similar to natural protein and it is theorized that the branch chain amino acids stimulate the production of Cholecystokinin, a peptide released after eating, that may act as an appetite suppressant by providing a sense of satiety.[8]

A study measuring postprandial concentrations of insulin and total plasma amino acid levels, demonstrated both to be higher after consuming formula based on natural glycomacropeptide than what is seen after consuming 100% synthetically derived amino acid based formulas. Concentrations of Ghrelin (the hunger hormone) were 30% lower following consumption of the glycomacropeptide based formula than the synthetic amino acid based formula. Patients felt fuller longer, suggesting that products made with glycomacropeptide improve satiety when compared to synthetic amino acid based formula.[9,10]

Skeletal fragility has been observed in individuals with phenylketonuria. Researchers have observed a decrease in bone mineral density and higher incidence of fractures in patients with phenylketonuria compared to control subjects without the disorder.[11,12,13] Studies have shown a range in 30-50% of patients with phenylketonuria have reduced bone mineral density (BMD).[14,15,16] A 2018 cross sectional study reported up to 50% of males with PKU may have lower bone mineral density due to their increased protein needs and higher intake of amino acid medical foods.[17] Mouse studies compared mice with phenylketonuria fed low-phenylalanine synthetic amino acid diets with phenylketonuria mice that were fed low-phenylalanine diets based on glycomacropeptide sparingly supplemented with limited essential amino acids.[18] Reductions in both femoral size and tolerance before maximum load tolerated before fracture were observed in mice fed the low-phenylalanine synthetic amino acid diet compared with the glycomacropeptide diet.[19] In humans, Glytactin medical foods reduced urinary loss of calcium by 40% and magnesium by 30% allowing them to be available for bone synthesis.[19] This suggests that providing dietary protein from glycomacropeptide rather than synthetic amino acids lessoned the phenylketonuric bone phenotype of skeletal fragility that is common to phenylketonuria patients.

The traditional 100% synthetically derived amino acid diet for phenylketonuria has a high dietary acid load that may not just affect the skeletal system.[20] It is suspected to carry an additional metabolic burden to the body. Adverse effects of synthetically derived amino acid diets in mouse studies include metabolic stress as reflected in increased energy expenditure and intake of food and water, increased renal and spleen mass, and elevated plasma cytokine concentrations consistent with systemic inflammation. The glycomacropeptide diet significantly reduced these adverse effects in mice. Total fat mass, % body fat, and the respiratory exchange ratio (CO2 produced/O2 consumed) were significantly lower in PKU mice fed glycomacropeptide compared with synthetic amino acid diets.[21]

PHARMACOKINETICS

Glytactin (modified glycomacropeptide) contains glycomacropeptide as a primary ingredient. The low level of aromatic amino acids (phenylalanine, tryptophan and tyrosine) and concentration of large neutral amino acids (LNAAs) threonine, valine and isoleucine make glycomacropeptide an ideal protein replacement therapy for phenylketonuria patients. The naturally high concentration of LNAAs in glycomacropeptide are enhanced with supplemental LNAAs to compete with the offending amino acid phenylalanine for specific carrier proteins that transport LNAAs across the intestinal mucosa and blood-brain barrier.[2,3,4] This increased competition likely restricts the ability of phenylalanine to enter the brain where it can become a neurotoxin leading to mental impairment for the patient with phenylketonuria.

As primarily whole protein, Glytactin (modified glycomacropeptide) is digested more slowly than synthetic amino acids, allowing the passage from the stomach, through the intestinal wall and into the bloodstream.[22] This normal digestion process allows the body to efficiently break down and synthesize the protein.

Precautions and Contraindications

Glytactin RTD LITE 15 is intended for the dietary management of individuals with a diagnosis of phenylketonuria. Individuals with other inborn errors of protein metabolism or those without a phenylketonuria diagnosis can experience complications if using this product due to its extremely low level of phenylalanine which contributes to mood regulation, alertness, dopamine transmission, learning and memory.

Glytactin RTD LITE 15 contains protein from whey. Therefore, it may not be suitable for those with an allergy to milk or milk products.

Glytactin RTD LITE 15 contains a small amount of phenylalanine (1 mg of phenylalanine per gram of protein equivalent) due to the process of extracting and refining glycomacropeptide. Recent studies indicate the daily Phe prescription from natural food does not need to be modified to accommodate the natural Phe inherent to Glytactin.

Adverse Reactions

Post – marketing surveillance has shown no adverse reactions.

Drug Interactions

None known.

Toxicity
None known.

SPECIAL POPULATIONS

- Approved for phenylketonuria patients over 12 months of age. Always check with physician for proper dosage recommendations.
- Cambrooke Therapeutics has not sought FDA approval for use of Glytactin RTD LITE 15 in infants with phenylketonuria, but glycomacropeptide is widely found in infant formula containing whey protein.
- Compliance to a low phenylalanine diet must accompany the use of Glytactin for all phenylketonuria patients, including those considering having children or who are pregnant.
- Glytactin RTD LITE 15 is ideal for individuals with PKU, that have also been diagnosed with Diabetes Mellitus Type II or those that are obese/overweight, due to the low calories and carbohydrates. Always check with your physician for proper dosage recommendations.

DOSAGE AND ADMINISTRATION

Glytactin RTD LITE 15 is a medical food that can be administered enterally by mouth or feeding tube, under the supervision of a physician.

Recommended daily requirements vary with age, weight and activity levels. Follow recommendation of medical practitioner to determine the best amount of Glytactin RTD to be used each day.

HOW SUPPLIED

Glytactin RTD LITE 15, contains 15 g of Protein Equivalent per each 250 mL (8.5 fl. oz.) carton. The cartons are packaged 30 per case (reimbursement code: Coffee Mocha 24359-0514-03, USA only; Vanilla 24359-0518-03, USA only). Keep sealed in a cool, dry place. Refrigerate after opening. Do not freeze.

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