Glytactin BetterMilk Lite™ 20 gram Protein Equivalent (modified glycomacropeptide)

MLT35101D1

PRODUCT INFORMATION

Glytactin BetterMilk Lite 20 gram Protein Equivalent (modified glycomacropeptide)
1.6 oz (46 g) packet Reimbursement Code: 24359-0351-01

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

DISPENSE BY PRESCRIPTION

Glytactin BetterMilk Lite (modified glycomacropeptide) is a medical food for the dietary management of phenylketonuria (PKU).

DESCRIPTION

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

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

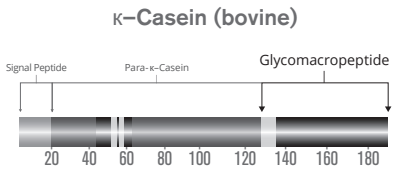
Congress defines "Medical Food" in the Orphan Drug Act and Amendments of 1988 as a formulation to be administered enterally (for oral or tube feeding) under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles are established by medical evaluation 21 U.S.C. 360ee(b)(3).

Glytactin Bettermilk Lite is supplied in single dose, 1.6 oz packets, thirty packets per case. Each packet contains 150 calories, 20 grams of protein equivalent and provides a complete micronutrient 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 BetterMilk Lite 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 by the body.



GMP in its pure form contains no phenylalanine. The process of extracting and refining glycomacropeptide results in the inclusion of trace quantities of phenylalanine (1.8mg of phenylalanine per protein equivalent gram).

Large Neutral Amino Acids

GMP is naturally high in the large neutral amino acids threonine, isoleucine, and valine. Glytactin BetterMilk Lite 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 BetterMilk Lite may inhibit the transport of ingested phenylalanine across the blood brain barrier.[2,3,4]

Micronutrients and Macronutrients

Individuals with phenylalanine hydroxylase deficiency should limit their intake of the essential amino acid phenylalanine. Phenylalanine is found naturally in all foods containing protein, including all meats, legumes, grains and to a lesser extent vegetables and fruits. Such a severely restricted diet brings meaningful risk and challenges in receiving recommended daily intake of many micronutrients. To compensate for this, Bettermilk Lite provides a low phenylalanine protein equivalent to help provide essential amino acids, adequate caloric intake with a balance of carbohydrates and fat and a complete micronutrient profile. Intake of some phenylalanine is essential and is typically consumed with a low protein diet.

Essential Fats

Bettermilk Lite contains 110 mg of algae-sourced docosahexaenoic acid (DHA) to help support brain and eye development.[5]

Digestive and Oral Health

Bettermilk Lite contains probiotics to help support digestive health and enhance mineral absorption.[6] Bettermilk Lite provides a more neutral pH compared to other amino acid based formulas. Amino acid formulas typically have a low or acidic pH. With frequent consumption, this may lead to oral health problems. A pH less than 5.5 may lead to dental erosion.[7] Bettermilk Lite has a pH of 6.6 making it gentler on digestion and tooth enamel.

Bone Health

Bettermilk Lite contains a bone health blend designed to optimize bone health. Bone health is a growing concern in individuals with inherited disorders of metabolism. Studies have found that those with phenylketonuria have a decreased bone mineral density[8,9,10] which may lead to osteoporosis and fractures if not detected and treated. Studies have shown 30-50% of individuals with phenylketonuria have reduced bone mineral density.[9,11,12] One 250 mL serving of Bettermilk Lite contains a unique blend of nutrients essential to bone health including 500 mg calcium (50% recommended dietary allowance or RDA), 668 IU vitamin D (111% RDA), 450 mg phosphorus (64% RDA), 5 mg zinc (45% RDA) and 176 mg

magnesium (44% RDA) per serving.[13] In addition, Bettermilk Lite contains 40 mcg of Vitamin K (33% RDA)[13] per serving in the forms of both K1 and K2. Vitamin K1 is activated to K2 in the body and plays an important role as a co-factor in the carboxylation of osteocalcin. Lower levels of carboxylated osteocalcin are associated with increased fracture risk.[14] Bettermilk Lite also contains 1.8 grams per serving of inulin, a soluble prebiotic fiber. Inulin consumed at 3 grams per day has been shown to aid in calcium absorption.[6]

Complete Ingredients

Whey protein isolate, vitamin and mineral blend (calcium lactate, monosodium phosphate, monopotassium phosphate, magnesium phosphate, magnesium citrate, choline bitartrate, sodium ascorbate, dl-alpha-tocopheryl acetate, ferrous fumarate, niacinamide, zinc sulfate, calcium d- pantothenate, manganese sulfate, thiamin HCl, vitamin B6 pyridoxine HCl, riboflavin, copper gluconate, folic acid, vitamin A palmitate, potassium iodide, sodium selenite, vitamin K1 phytonadione, vitamin K2 MK-7, sodium molybdate, chromium chloride, D3 cholecalciferol, biotin, vitamin B12 cyanocobalamin), trehalose, leucine, non-dairy creamer (sunflower oil, corn syrup solids, food starch-modified, mono and diglycerides, natural flavor, citric acid, carrageenan), natural flavors, maltodextrin, inulin, tyrosine, arginine, DHA algal oil, probiotic (skim milk powder, *Bacillus coagulans* GBI-30 6086), histidine, tryptophan, acesulfame potassium, methionine, sucralose. Contains milk and soy.

GENERALLY RECOGNIZED AS SAFE

The ingredients in Glytactin BetterMilk Lite 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 BetterMilk Lite is a medical food for the dietary management of individuals under a physician's care for phenylalanine hydroxylase deficiency (phenylketonuria) or hyperphenylalaninemia. Glytactin Bettermilk Lite contains 150 calories per 20 gram protein equivalent, providing greater protein equivalent per calorie than Glytactin Bettermilk.

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.[15]

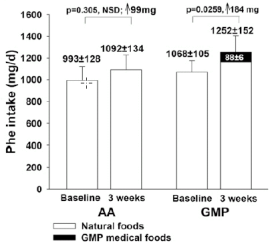


Figure 4B from page 8: This figure illustrates the total Phe intake and compares the Phe intake while on the amino acid based protein medical foods to the Phe intake while on the GMP medical foods. Phe intake did not increase significantly when on an amino acid medical foods but was higher when on the 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.[15]

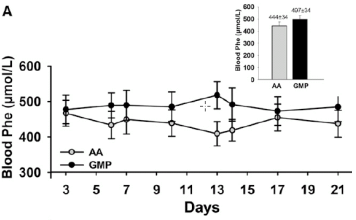
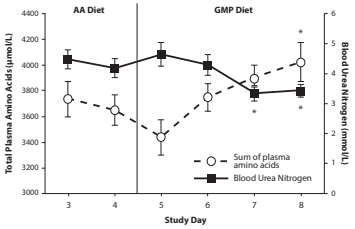
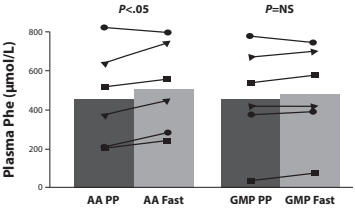


Figure 6 A from page 9: This figure shows fasting blood Phe levels done based on analysis of dried blood spots of subjects, analyzed with tandem mass spectrometry. No significant differences are seen in blood Phe levels due to treatment with an amino acid protein diet versus a GMP protein diet, even though the diet contained higher levels of natural phenylalanine.[15]

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 showedthat each phenylketonuria patient fed a glycomacropeptide medical food improved on three important biomarkers.[16]



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.[16]



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).[16]

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. This is because amino acid based formulas do not adequately suppress production of Ghrelin, a hunger hormone.[17] A glycomacropeptide based formula has been shown to provide satiety to patients by suppressing the production of Ghrelin similar to natural protein. It is also theorized that the branch chain amino acid content of GMP may stimulate the production of cholecystokinin, a peptide released after eating, which acts as an appetite suppressant.[17]

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 GMP improve satiety when compared to synthetic amino acid based formula.[18,19]

Skeletal fragility has been documented 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.[8,20,21] Studies have shown a range in 30-50% of patients with phenylketonuria have reduced bone mineral density (BMD).[9,11,12] 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. Reduction in femoral size and lower maximum load tolerance were observed in mice fed the low-phenylalanine synthetic amino acid diet compared with the glycomacropeptide diet. This suggests that providing dietary protein from glycomacropeptide rather than synthetic amino acids lessoned the phenylketonuric bone phenotype of skeletal fragility that is common in individuals with phenylketonuria.[22]

The traditional 100% synthetically derived amino acid diet for phenylketonuria has a high dietary acid load[23] and this is suspected to have a negative impact on bone health and add 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.[24]

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 build up as a neurotoxin leading to mental impairment for the patient with phenylketonuria.

As a primarily whole protein, Glytactin (modified glycomacropeptide) is digested more slowly than synthetic amino acids. This allows the passage of amino acids from the stomach, through the intestinal wall and into the bloodstream at a slower and more-steady rate.[25] This normal digestion process allows the body to efficiently break down and utilize digested proteins over a longer period of time.

Precautions and Contraindications

Glytactin Bettermilk Lite is intended for individuals with diagnosed phenylketonuria. Patients 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 Bettermilk Lite contains protein from whey. Therefore, it may not be suitable for those with an allergy to milk or milk products.

Glytactin Bettermilk Lite contains a small amount of phenylalanine (1.8 mg of phenylalanine per protein equivalent gram) due to the process of extracting and refining glycomacropeptide. This phenylalanine should be accounted for in the total daily phenylalanine prescription.

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.
- Glytactin BetterMilk Lite has not sought FDA approval for use in infants with phenylketonuria.
- Compliance to a low phenylalanine diet must accompany the use of Glytactin for all phenylketonuria patients. This is especially important for those considering having children or who are pregnant due to the potential birth defects with high phenylalanine levels.

DOSAGE AND ADMINISTRATION
Bettermilk Lite is a medical food to be re-hydrated with water and administered enterally by mouth or tube, under the supervision of a physician.

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

HOW SUPPLIED
Glytactin Bettermilk Lite 20g Protein Equivalent is supplied in 1.6 oz (46 g) packets. The packets are packaged 30 per case (reimbursement code: 24359-0351-01). Keep sealed in a cool, dry place.

REFERENCES

1 Etzel MR (2004) Manufacture and use of dairy protein fractions. J Nutr 134:996S-1002S.

2 Pietz J, Kreis R, Rupp A, et al. Large neutral amino acids block phenylalanine transport into brain tissue in patients with phenylketonuria. J Clin Invest 1999;103:1169–78.

3 Pardridge WM. Blood-brain barrier carrier-mediated transport and brain metabolism of amino acids. Neurochem Res. 1998;23:635–44. CrossRefMedline.

4 Hidalgo IJ, Borchardt RT. Transport of a large neutral amino acid (phenylalanine) in a human intestinal epithelial cell line: Caco-2. Biochim Biophys Acta. 1990;1028:25–30.

5 Singh M. Essential fatty acids, DHA and human brain. Indian J Pediatr. 2005 Mar;72(3):239-42.

6 Scholz-Ahrens KE, Schrezenmeir J. Inulin, oligofructose and mineral metabolism - experimental data and mechanism. Br J Nutr. 2002 May;87 Suppl 2:S179-86.

7 Touger-Decker, R., van Loveren, C. Sugars and dental caries. The American Journal of Clinical Nutrition. 78, 8815-8925

8 Allen JR, Humphries IRJ, Walters D., et al. Decreased Bone Mineral Density in Children with Phenylketonura. Am J Clin Nutrition 1994: Vol 59: 419-22.

9 Koura, H.M., Abdallah Ismail N., Kamel, A.F.,Ahmed, A.M., Saad Hussein, A., Effat, L.K. A long-term study of bone mineral density in patients with phenylketonuria under diet therapy, Arch. Med. Sci. 7 (2011) 493–500.

10 Miras, A. Boveda, M.D., et al. Risk factors for developing mineral bone disease in phenylketonuria patients. Mol. Gen.Met. 108 (2013) 149-154.

11 Pérez Dueñas, B., Cambra, F.J., Vilaseca, M.A., Lambruschini, N., Campistol, J., Camacho, J.A. New approach to osteopenia in phenylketonuric patients, Acta Paediatr. 91 (2002) 899–904

12 Modan-Moses, D., Vered, I., Schwartz, G., Anikster, Y., Abraham, S., Segev, R., Efrati,O., Peak bone mass in patients with phenylketonuria, J. Inherit.Metab. Dis. 30 (2007) 202–208

13 Dietary Reference Intakes (DRIs): Recommended Intakes for Individuals, Food and Nutrition Board, Institute of Medicine, National Academies, 2004.

14 Marieke, J. eta al. (2008). Vitamin K status is associated with childhood bone mineral content. British Journal of Nutrition, 100, 852-858.

15 Clayton M, Levy H, Murali, S, Ney D, Rice, G. Rohr,F, Stroup, B, Glycomacropeptide for nutritional management of phenylketonuria: a randomized, controlled, crossover trial. The American Journal of Clinical Nutritiion,10.3945, 116.135293, 2016

16 Van Calcar, S.C., MacLeod, E.L., Gleason, S.T., Etzel, M.R., Clayton, M.K., Wolff, J.A. and Ney, D.M. (2009) Improved nutritional management of phenylketonuria by using a diet containing glycomacropeptide compared with amino acids. The American Journal of Clinical Nutrition. 89:1068-1077, 2009.

17 Burton-Freeman BM. Physiol Behav. 2008 Jan 28;93(1-2):379-87. Epub 2007 Oct 26. Glycomacropeptide is not critical to whey-induced satiety, but may have a unique role in energy intake regulation through cholecystokinin (CCK).

18 MacLeod E, Clayton M, van Calcar S, Ney D. Breakfast with glycomacropeptide compared with Amino Acids Suppresses Plasma Ghrelin Levels in Individuals with Phenylketonuria. Molecular Genetics and Metabolism. 2010: Vol 100, Issue 4: 303-308.

19 Veldhorst MA, Nieuwenhuizen AG, Hochstenbach-Waelen A, et al. Effects of complete whey-protein breakfasts versus whey without glycomacropeptide-breakfasts on energy intake and satiety. Appetite. 2009;52:388–395. [PubMed]

20 Zeman J, Bayer M, Stephen J. Bone Mineral Density in Patients with Phenylketonuria. Acta Paediatric. 1999: Vol 88: 1348-51.

21 Al-Qadreh A, Schulpis KH, Athanasopoulou H, Mengreli C, Skarpalezou A, et al. (1998) Bone mineral status in children with phenylketonuria under treatment. Acta Paediatr 87: 1162–1166.

22 Solverson P, Murali SG, Litscher SJ, Blank RD, Ney DM (2012) Low Bone Strength Is a Manifestation of Phenylketonuria in Mice and Is Attenuated by a Glycomacropeptide Diet. PLoS ONE 7(9): e45165. doi:10.1371/journal.pone.0045165.

23 Manz F, Schmidt H, Scharer K, Bickel H. Acid-base status in dietary treatment of phenylketonuria. Pediatr Res 1977; 11(10 Pt 2):1084-1087.

24 Solverson P, Murali SG, Brinkman AS, Nelson DW, Clayton MK, et al. (2012) Glycomacropeptide, a low-phenylalanine protein isolated from cheese whey, supports growth and attenuates metabolic stress in the murine model of phenylketonuria. Am J Physiol Endocrinol Metab 302: E885–895.

25 Gropper SS, Acosta PB. Effect of simultaneous ingestion of L-amino acids and whole protein on plasma amino acid and urea nitrogen concentrations in humans. JPEN J Parenter Enteral Nutr 1991;20:48–53.