# Glytactin RTD™ 10 gram Protein Equivalent (modified glycomacropeptide)

MLT35064-35074D1

**PRODUCT INFORMATION**

**Original Glytactin RTD 10 gram Protein Equivalent (modified glycomacropeptide)**
**250 mL carton (8.5 fl. oz) Reimbursement Code: 24359-0574-03**

**Chocolate Glytactin RTD 10 gram Protein Equivalent (modified glycomacropeptide)**
**250 mL carton (8.5 fl. oz) Reimbursement Code: 24359-0564-03**

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

**DISPENSE BY PRESCRIPTION**

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

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## DESCRIPTION

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

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

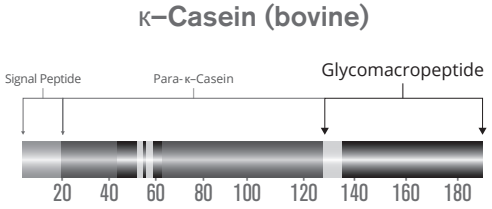
Congress defines "Medical Food" in the Orphan Drug Act and Amendments of 1988 as a formulation to be administered enterally (or orally) *under the supervision of a physician* and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements,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

Glytactin RTD is a ready-to-drink version of Glytactin. Glytactin RTD is supplied in single dose, opaque 250 ml, shelf-stable cartons, thirty cartons per case. Available in two formulations with 10 or 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 (1.8mg 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 RTD 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 may inhibit the transport of ingested phenylalanine across 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. To compensate for this, Glytactin RTD includes a full profile of micronutrients and macronutrients.

**Complete Ingredients**

Water, trehalose, whey protein isolate, sucrose, vitamin and mineral blend (dicalcium phosphate, calcium lactate, dipotassium phosphate, choline bitartrate, magnesium citrate, sodium ascorbate and ascorbic acid, ferrous sulfate, niacinamide, zinc sulfate, 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, vitamin D3 cholecalciferol, biotin, vitamin B12cyanocobalamin), maltodextrin, leucine, food starch modified, cocoa butter, canola oil, cellulose gel and carboxymethylcellulose sodium, arginine, tyrosine, natural flavors (Original: propylene glycol, ethyl alcohol, water, polysorbate 80, potassium sorbate; Chocolate flavor: maltodextrin, natural flavors, acacia gum and propylene glycol), sodium hexametaphosphate, histidine, tryptophan, carrageenan, (Chocolate flavor: natural color [fruit juice, water, maltodextrin]), (Chocolate flavor: acesulfame potassium), sodium stearoyl lactylate, (Chocolate flavor: salt, sucralose). Contains corn, milk and soy.

## GENERALLY RECOGNIZED AS SAFE

The ingredients in Glytactin RTD 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.

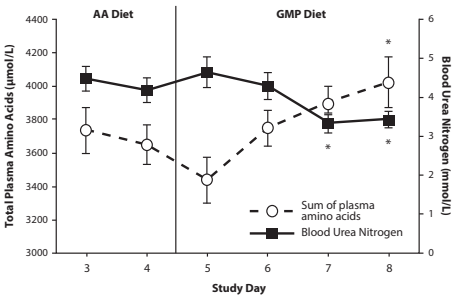
## MEDICAL FOOD STATUS

## INDICATIONS FOR USE

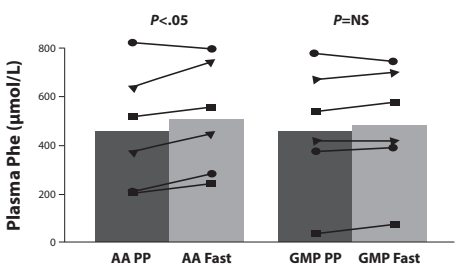
Glytactin RTD is a medical food for the dietary management of individuals under a physician's care for phenylalanine hydroxylase deficiency (phenylketonuria) or hyperphenylalaninemia.

## CLINICAL EXPERIENCE

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 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.[5]




*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.*




*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).*

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 do 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.[6] 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.[7,8]

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.[9,10,11] Studies have shown a range in 30-50% of patients with phenylketonuria have reduced bone mineral density (BMD).[12,13,14] 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. 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. 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.[15]

The traditional 100% synthetically derived amino acid diet for phenylketonuria has a high dietary acid load[16] that may not just affect the skeletal system. 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.[17]

**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.[18] This normal digestion process allows the body to efficiently break down and synthesize the protein.

**Precautions and Contraindications**

Glytactin RTD is intended for the complete protein and micronutrient needs for patients with diagnosed 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 contains protein from whey. Therefore, it may not be suitable for those with an allergy to milk or milk products.

Glytactin RTD contains a small amount of phenylalanine (1.8mg of phenylalanine per protein equivalent gram) due to the process of extracting and refining glycomacropeptide; the phe content needs to be accounted for in the total daily phe 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 RTD has not sought FDA approval for use 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.

## DOSAGE AND ADMINISTRATION

Must be administered under physician supervision.

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 10g Protein Equivalent is supplied in 250 mL (8.5 fl. oz.) cartons. The cartons are packaged 30 per case (reimbursement code: Original 24359-0574-03; Chocolate 24359-0564-03). Keep sealed in a cool, dry place. Refrigerate after opening. Do not freeze.

## 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 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.

6 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).

7 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.

8 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]

9 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.

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

11 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.

12 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.

13 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.

14 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.

15 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.

16 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.

17 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.

18 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;15:48–53.