Tylactin RTD™ 15 gram Protein Equivalent
(modified glycomacropeptide for tyrosinemia)

MLT59203D1

PRODUCT INFORMATION

Original Tylactin RTD 15 gram Protein Equivalent
(modified glycomacropeptide for tyrosinemia)

250 mL carton (8.5 fl. oz) Reimbursement Code: 24359-0592-03

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

DISPENSE BY PRESCRIPTION

Tylactin RTD (modified glycomacropeptide for tyrosinemia) is a medical food for the dietary management of tyrosinemia (TYR).

DESCRIPTION

Tylactin RTD (modified glycomacropeptide for tyrosinemia) is a specially formulated prescription medical food for the clinical dietary management of of Hereditary Furmarylacetoacetase Deficiency (Tyrosinemia Type I), Oculocutaneous Tyrosinemia (Tyrosinemia Type II), and Type III.

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

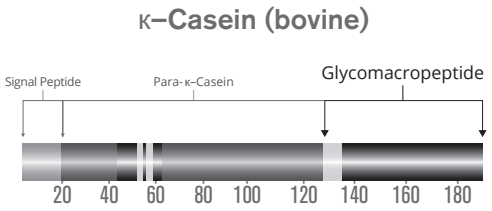
Congress defines "Medical Food" in the Orphan Drug Act and Amendments of 1988 as a formulation to be administered enterally (or orally) *under the supervision of a physician* and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements,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

Tylactin RTD is a ready-to-drink medical food, supplied in single dose, opaque 250 mL, shelf-stable cartons, thirty cartons per case. Tylactin RTD comes with a complete micronutrient and macronutrient profile. Tylactin RTD contains a small amount of tyrosine and phenylalanine: 3 mg tyrosine, 25 mg phenylalanine per 8.5 fl oz (250 mL).

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 tyrosine and phenylalanine contained in commercial GMP make this protein an alternative to synthetic free amino acid based protein for the management of TYR. The GMP in Tylactin RTD is modified by enhancing levels of tryptophan, arginine, leucine, histidine, and cysteine 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 tyrosine or phenylalanine, the process of extracting and refining glycomacropeptide results in the inclusion of trace quantities of tyrosine and phenylalanine (about 0.02 mg of tyrosine and 1.8 mg of phenylalanine per protein equivalent gram). Tyrosine and phenylalanine are the offending amino acids in Tyrosinemia Type I, II, and III and intake must be severely restricted to prevent neurodevelopmental and physiological consequences.

Micronutrients and Macronutrients

Patients with Tyrosinemia have a severely restricted diet to minimize intake of amino acids phenylalanine and tyrosine that are found naturally in all foods containing protein, including all meats, dairy, legumes, and many vegetables, fruits and grains. Tyrosine is low in natural protein but phenylalanine is a precursor of tyrosine, so limiting phenylalanine intake limits the phenylalanine-tyrosine conversion. As such, there is meaningful risk and challenges in receiving recommended daily intake of many micronutrients. To compensate for this, Tylactin RTD includes a full profile of micronutrients and macronutrients.

Complete 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.

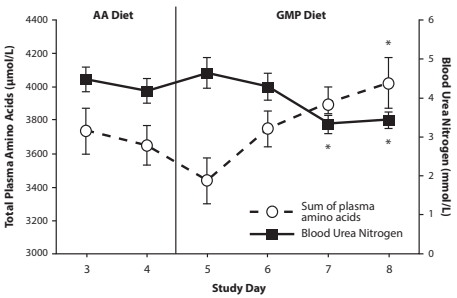
GENERALLY RECOGNIZED AS SAFE
The ingredients in Tylactin RTD are Generally Recognized As Safe (GRAS). This is the statutory safety standard of the U.S. Food and Drug Administration (FDA). The standard for an ingredient to achieve GRAS status requires technical demonstration of non-toxicity and safety,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

MEDICAL FOOD STATUS

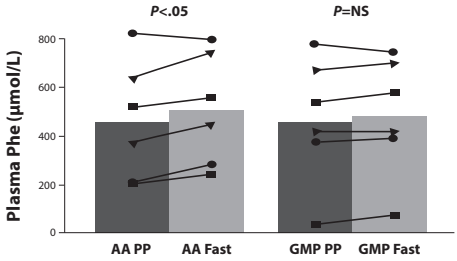
INDICATIONS FOR USE
Tylactin RTD is a medical food for the dietary management of individuals under a physician's care for Hereditary Furmarylacetoacetase Deficiency (Tyrosinemia Type I), Oculocutaneous Tyrosinemia (Tyrosinemia Type II), and Type III.

TYROSINEMIA, PHENYLALANINE AND PHENYLKETONURIA (PKU)
Tyrosinemia patients have a defective enzyme fumarylacetoacetate which affects the conversion of tyrosine to neurotransmitters and metabolites. Tyrosine is present in very low levels in natural dietary protein but is biosynthesized within the body based on the level of consumption of phenylalanine. Blood levels and dietary monitoring must be done for both phenylalanine and tyrosine. Tyrosinemia is similar to phenylketonuria (PKU) which involves an enzyme defect in the same phenylalanine-tyrosine pathway. (PKU patients have a defect in the enzyme phenylalanine hydroxylase which affects the conversion of phenylalanine to tyrosine.) Both disorders require that strict attention be paid to the levels of phenylalanine that are consumed.

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.[2]



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 tyrosinemia 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.[3] 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.[4,5]

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.[6,7,8] Studies have shown a range in 30-50% of patients with phenylketonuria have reduced bone mineral density (BMD).[9,10,11] 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.[12]

The traditional 100% synthetically derived amino acid diet for phenylketonuria has a high dietary acid load[13] 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.[14]

PHARMACOKINETICS

Tylactin (modified glycomacropeptide for tyrosinemia) 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 tyrosinemia patients. The naturally high concentration of LNAAs in glycomacropeptide are enhanced with supplemental LNAAs to compete with the offending amino acids tyrosine and phenylalanine for specific carrier proteins that transport LNAAs across the intestinal mucosa and blood-brain barrier .[15,16,17] This increased competition likely restricts the ability of tyrosine and phenylalanine to enter the brain where it can become a neurotoxin leading to mental impairment for the patient with tyrosinemia.

As primarily whole protein, Tylactin (modified glycomacropeptide for tyrosinemia) 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

Tylactin RTD is intended for the complete protein and micronutrient needs for patients with diagnosed tyrosinemia. Individuals with other inborn errors of protein metabolism or those without a tyrosinemia diagnosis can experience complications if using this product due to its extremely low level of tyrosine and phenylalanine which contribute to mood regulation, alertness, dopamine transmission, learning and memory.

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

Tylactin RTD contains a small amount of tyrosine and phenylalanine (0.2 mg of tyrosine and 1.8 mg of phenylalanine per protein equivalent gram) due to the process of extracting and refining glycomacropeptide; the tyrosine and phenylalanine content needs to be accounted for in the total daily tyrosine and phenylalanine prescription.

Adverse Reactions

Post – marketing surveillance has shown no adverse reactions.

Drug Interactions
None known.

Toxicity
None known.

SPECIAL POPULATIONS

- Approved for tyrosinemia patients over 12 months of age. Always check with physician for proper dosage recommendations.
- Tylactin RTD has not sought FDA approval for use in infants with tyrosinemia, but glycomacropeptide is widely found in infant formula containing whey protein.
- Compliance to a low tyrosine/phenylalanine diet must accompany the use of Tylactin for all tyrosinemia 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 Tylactin RTD to be used each day.

HOW SUPPLIED

Tylactin RTD 15g Protein Equivalent is supplied in 250 mL (8.5 fl. oz.) cartons. The cartons are packaged 30 per case (reimbursement code: 24359-0592-03). Keep sealed in a cool, dry place. Refrigerate after opening. Do not freeze.

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