

Theramine® PRODUCT INFORMATION

Theramine capsules by oral administration. A specially formulated Medical Food product, consisting of a proprietary blend of amino acids and polyphenol ingredients in specific proportions, for the dietary management of the metabolic processes associated with pain disorders and inflammatory conditions. (PD) (IC). **Must be administered under physician supervision.**

Medical Foods

Medical Food products are often used in hospitals (e.g., for burn victims or kidney dialysis patients) and outside of a hospital setting under a physician's care for the dietary management of diseases in patients with particular, unique or distinctive medical or metabolic needs due to their disease or condition. Congress defined "Medical Food" in the Orphan Drug Act and Amendments of 1988 as "a food which is formulated to be consumed or 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." Medical Foods are complex formulated products, requiring sophisticated and exacting technology, and that are used only for a patient receiving active and ongoing medical supervision wherein the patient requires medical care on a recurring basis for, among other things, instructions on the use of the Medical Food. **Theramine** has been developed, manufactured, and labeled in accordance with both the statutory definition of a Medical Food and FDA's regulatory labeling guidelines. **Theramine** must be used while the patient is under the ongoing care of a physician.

PAIN DISORDERS (PD) INFLAMMATORY CONDITIONS (IC)

PD and IC as a Metabolic Deficiency Disease

A critical component of the definition of a Medical Food is that the product must address the distinct nutritional requirements of a particular disease or condition. FDA scientists have proposed a physiologic definition of distinctive nutritional requirements as follows: "the dietary management of patients with specific diseases requires, in some instances, the ability to meet nutritional requirements that differ substantially from the needs of healthy persons. For example, in establishing the recommended dietary allowances for the general, healthy population, the Food and Nutrition Board of the Institute of Medicine National Academy of Sciences recognized that different or distinctive physiologic requirements may exist for certain persons with "special nutritional needs arising from metabolic disorders, chronic diseases, injuries, premature birth, other medical conditions and drug therapies. **Thus, the distinctive nutritional needs associated with a disease reflects the total amount needed by a healthy person to support life or maintain homeostasis, adjusted for the distinctive changes in the nutritional needs of the patient as a result of the effects of the disease process on absorption, metabolism and excretion.**" It was also proposed that in patients with certain disease states who respond to nutritional therapies, a physiologic deficiency of the nutrient is assumed to exist. For example, if a patient with a pain disorder responds to a tryptophan formulation by decreasing perceived pain, then a deficiency of tryptophan is assumed to exist.

Patients with pain disorders and inflammatory conditions are known to have increased nutritional requirements for tryptophan, choline, arginine, GABA, flavonoids, and certain antioxidants. These nutritional requirements are such that they cannot be achieved by the modification of the normal diet alone, or by supplementing the diet. Patients with pain disorders and inflammatory conditions frequently exhibit reduced plasma levels of tryptophan and GABA, and have been shown to respond to oral administration of GABA, arginine, tryptophan, or a 5-hydroxytryptophan formulation. Research has shown that tryptophan, arginine or GABA reduced diets result in a fall of circulating tryptophan, arginine, and/or GABA. Patients with pain disorders frequently exhibit activation of the degradation pathways that increases the turnover rate of GABA, arginine and tryptophan leading to a reduced level of production of serotonin, GABA or nitric oxide for a given precursor blood level. Research has also shown that a genetic predisposition to accelerated degradation can lead to increased precursor requirements in certain patients with pain disorders and inflammatory conditions.

Choline is required to fully potentiate acetylcholine synthesis by brain neurons. A deficiency of choline leads to reduced acetylcholine production by the neurons. Provision of tryptophan, arginine, GABA, choline and flavonoids with antioxidants, in specific proportions can restore the production of beneficial serotonin, nitric oxide, and acetylcholine, thereby reducing the perception of pain and reducing inflammation. L-Histidine is known to produce brain histamine that stimulates production of ACTH, producing cortisol to reduce inflammation.

PRODUCT DESCRIPTION

Primary Ingredients

Theramine consists of a proprietary formulation of Gamma Aminobutyric Acid (GABA), Choline Bitartrate, Hydrolyzed Whey Protein Isolate (Milk), L-Arginine HCL, Cocoa Fruit Extract, L-Histidine HCL, L-Glutamine, Griffonia Seed Extract, Grape Seed Extract, Cinnamon Bark and L-Serine, in specific proportions. These ingredients fall into the classification of Generally Recognized as Safe (GRAS) as defined by the Food and Drug Administration (FDA) (Sections 201(s) and 409 of the Federal Food, Drug, and Cosmetic Act). A GRAS substance is distinguished from a food additive on the basis of the common knowledge about the safety of the substance for its intended use. The standard for an ingredient to achieve GRAS status requires not only technical demonstration of non-toxicity and safety, but also general recognition of safety through widespread usage and agreement of that safety by experts in the field. Many ingredients have been determined by the FDA to be GRAS, and are listed as such by regulation, in Volume 21 Code of Federal Regulations (CFR) Sections 182, 184, and 186.

Amino Acids

Amino Acids are the building blocks of protein and are GRAS listed as they have been safely ingested by humans for thousands of years. The formulations of the amino acids in **Theramine** are equivalent to those found in the usual human diet. Patients with pain disorders may require an increased amount of certain amino acids that cannot be obtained from normal diet alone. Tryptophan, for example, is an obligatory amino acid. The body cannot make tryptophan and must obtain tryptophan from the diet. Tryptophan is needed to produce serotonin. Serotonin is required to reduce pain. Patients with pain disorders and inflammatory conditions have altered serotonin metabolism.

Flavonoids

Flavonoids are a group of phytochemical compounds found in all vascular plants including fruits and vegetables. They are a part of a larger class of compounds known as polyphenols. Many of the therapeutic or health benefits of colored fruits and vegetables, cocoa, red wine, and green tea are directly related to their flavonoid content. The specially formulated flavonoids found in **Theramine** cannot be obtained from conventional foods in the necessary proportions to elicit a therapeutic response.

Other Ingredients

Theramine contains the following "inactive" or other ingredients, as fillers, and excipients: Gelatin, Silicon Dioxide, Tricalcium Phosphate, Microcrystalline Cellulose, Vegetable Magnesium Stearate.

Physical Description

Theramine is a yellow to light brown powder encapsulated in a clear, dye-free capsule.

CLINICAL PHARMACOLOGY

Mechanism of Action

Theramine acts by restoring and maintaining the balance of the neurotransmitters GABA, nitric oxide, serotonin, and acetylcholine that are associated with pain disorders and inflammatory conditions.

Metabolism

The amino acids in *Theramine* are primarily absorbed by the stomach and small intestines. All cells metabolize the amino acids in *Theramine*. Circulating tryptophan, arginine and choline blood levels determine the production of serotonin, nitric oxide, and acetylcholine.

Excretion

Theramine is not an inhibitor of cytochrome P450 1A2, 2C9, 2C19, 2D6, or 3A4. These isoenzymes are principally responsible for 95% of all detoxification of drugs, with CYP3A4 being responsible for detoxification of roughly 50% of drugs. Amino acids do not appear to have an effect on drug metabolizing enzymes.

INDICATIONS FOR USE

Theramine is intended for the clinical dietary management of the altered metabolic processes of pain disorders and inflammatory conditions.

CLINICAL EXPERIENCE

Administration of *Theramine* has demonstrated significant reduction in symptoms of pain and inflammation in patients with acute and chronic pain when used for the dietary management of the metabolic processes associated with pain disorders and inflammatory conditions. Administration of *Theramine* results in the induction and maintenance of pain relief in patients with pain disorders and inflammatory conditions.

PRECAUTIONS AND CONTRAINDICATIONS

Theramine is contraindicated in an extremely small number of patients with hypersensitivity to any of the nutritional components of *Theramine*.

ADVERSE REACTIONS

Ingestion of L-Tryptophan, L-Arginine, or Choline at high doses of up to 15 grams daily is generally well tolerated. The most common adverse reactions of higher doses — from 15 to 30 grams daily — are nausea, abdominal cramps, and diarrhea. *Theramine* contains less than 1 gram per dose of amino acids however, some patients may experience these symptoms at lower doses. The total combined amount of amino acids in each *Theramine* capsule does not exceed 400 mg.

DRUG INTERACTIONS

Theramine does not directly influence the pharmacokinetics of prescription drugs. Clinical experience has shown that administration of *Theramine* may allow for lowering the dose of co-administered drugs under physician supervision.

OVERDOSE

There is a negligible risk of overdose with *Theramine* as the total amount of amino acids in a one month supply (120 capsules) is less than 50 grams. Overdose symptoms may include diarrhea, weakness, and nausea.

POST-MARKETING SURVEILLANCE

Post-marketing surveillance has shown no serious adverse reactions. Reported cases of mild rash and itching may have been associated with allergies to *Theramine* flavonoid ingredients, including Cinnamon, Cocoa, and Grape Seed. One in five thousand patients may have a rash from the histamine. This rash is temporary and will subside within 24-hours.

DOSAGE AND ADMINISTRATION

Recommended Administration

For the dietary management of the metabolic processes associated with pain disorders and inflammatory conditions. Take two (2) capsules twice daily or as directed by physician. As with most amino acid formulations *Theramine* should be taken without food to increase the absorption of key ingredients.

How Supplied

Theramine is supplied in a clear, size 0 capsules in bottles of 120 capsules.

Physician Supervision

Theramine is a Medical Food product intended to be administered under the supervision of a physician.

Storage

Keep tightly closed and away from direct sunlight in a cool dry place 8-32° C (45-90° F), relative humidity below 50%. *Theramine* is supplied in a recyclable plastic bottle with a cap.

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Manufactured for:

Physician Therapeutics, a wholly owned subsidiary of Targeted Medical Pharma Inc.
2980 Beverly Glen Blvd, Suite 100
Los Angeles, CA 90077 USA
(844) 474-3111

For more information, visit www.tmedpharma.com

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