

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use APTRIM safely and effectively. See full prescribing information for APTRIM.

APTRIM[®] capsules for oral administration

US Patent 7,582,315; 7,585,523; 7,595,067; 7,601,369.

-----INDICATIONS AND USAGE-----

APTRIM is a specially formulated, amino acid based Medical Food, consisting of a proprietary blend of amino acids, biogenic amines, nutrients and polyphenol ingredients in specific proportions, for the dietary management of the metabolic processes associated with obesity, morbid obesity, and metabolic syndrome.

Must be administered under physician supervision.

-----DOSAGE AND ADMINISTRATION-----

Dose Range: 1-3 capsules taken 2-3 times daily or as directed by physician.

Recommended start dose: Take 2 capsules twice daily or as directed by physician. An evening dose of (2) capsules can be added if necessary.

As with most amino acid formulations *APTRIM* should be taken without food to increase the absorption of key ingredients.

-----DOSAGE FORMS AND STRENGTHS-----

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

The total combined amount of amino acids in each APTRIM capsule does not exceed 400mg.

-----PRECAUTIONS AND CONTRAINDICATIONS-----

APTRIM is contraindicated in an extremely small number of patients with hypersensitivity to any of the nutritional components of *APTRIM*. Patients with a history of melanoma should avoid *APTRIM*. Products containing L-tyrosine are contraindicated in those with the inborn errors of metabolism alkaptonuria and tyrosinemia type I and type II. Products containing tyrosine are also contraindicated in patients taking non-selective monoamine oxidase (MAO) inhibitors.

-----ADVERSE REACTIONS-----

Ingestion of L-tryptophan and/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. Some patients may experience these symptoms at lower doses. The total combined amount of amino acids in each *APTRIM* capsule does not exceed 400 mg.

-----DRUG INTERACTIONS-----

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

-----USE IN SPECIFIC POPULATIONS-----

APTRIM has not been studied in children under the age of 12 years and in women who are pregnant or breastfeeding.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

APPTRIM is indicated as a source of neurotransmitter precursors and dietary factors formulated to control appetite and meet the distinctive nutritional requirements that may exist for adults due to altered physiologic requirements of obese individuals.

1.1 OBESITY DISORDERS (OB) OB as a Metabolic Deficiency Disease

A critical component of the definition of a Medical Food is the requirement that it meet the dietary needs of patient suffering a disease or abnormal condition. FDA scientists have proposed a physiologic definition of a distinctive nutritional requirement 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 an obese patient responds to a tryptophan formulation by decreasing appetite and carbohydrate cravings, a deficiency of tryptophan is assumed to exist.

Many patients with obesity, morbid obesity, and metabolic syndrome are known to have increased requirements for tryptophan, choline, tyrosine, histidine, flavonoids, and certain antioxidants. Many patients with obesity, morbid obesity, and metabolic syndrome frequently exhibit reduced plasma levels of tryptophan and have been shown to respond to oral administration of tryptophan or a 5-hydroxytryptophan formulation to aid in reducing appetite and carbohydrate cravings. Research has shown that tryptophan reduced diets result in a fall in circulating tryptophan. Patients with obesity, morbid obesity, and metabolic syndrome frequently experience activation of the tryptophan degradation pathway that increases the turnover rate of tryptophan leading to a reduced level of production of serotonin for a given tryptophan blood level. Research has also shown that a genetic predisposition to accelerated tryptophan utilization can lead to increased tryptophan requirements in certain obese and morbidly obese patients and patients with metabolic syndrome.

Choline is required to fully potentiate acetylcholine synthesis by brain neurons. Acetylcholine is required by presynaptic ganglia to produce adequate quantities of epinephrine and norepinephrine. In addition, tyrosine deficiencies have been reported in the medical literature in obese and morbidly obese patients. Thus, obesity is frequently associated with a distinct nutritional deficiency of tyrosine, tryptophan, histidine, and choline. Obese patients frequently consume increased calories because they lack adequate quantities of the key amino acids that produce the neurotransmitter precursors needed to curb appetite and control satiety. Provision of tryptophan, choline, tyrosine, histidine, and flavonoids with antioxidants, in specific proportions can enhance appetite control, carbohydrate craving control, early satiety, thermogenesis, and preferential fat utilization.

2 DOSAGE AND ADMINISTRATION

The recommended dose of *APPTRIM* is 2 capsules taken 2 times daily at mid-morning and mid-afternoon. Some patients appear to respond well to a dose of 1 capsule, while others have found that 3 capsules taken in the morning and 1 capsule in the afternoon is effective. As with all Medical Food products, the best dosing protocol is established by the healthcare provider based on the individual requirements of each patient.

Take *APPTRIM*[®] exactly as your doctor tells you.
Swallow *APPTRIM* tablet with a full glass (6-8 oz) of water.

Take 2 **APPTRIM** capsules twice daily or as directed by physician.

3 DOSAGE FORMS AND STRENGTHS

APPTRIM is supplied in clear, size 0 capsules in bottles of 120 capsules. The total combined amount of amino acids in each **APPTRIM** capsule does not exceed 400 mg.

4 PRECAUTIONS AND CONTRAINDICATIONS

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

5 ADVERSE REACTIONS

Ingestion of L-tryptophan and/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. Some patients may experience these symptoms at lower doses.

6 DRUG INTERACTIONS

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

7 USE IN SPECIFIC POPULATIONS

APPTRIM has not been studied in children under 12 years of age and in women who are pregnant or breastfeeding.

8 OVERDOSAGE

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

9 DESCRIPTION

9.1 Primary Ingredients

APPTRIM consists of a proprietary formulation of L-Glutamic Acid, Choline Bitartrate, L-Tyrosine, L-Serine, Whey Protein Hydrolysate (Milk Sourced Isolate), Griffonia Seed Extract, Cocoa, Caffeine, and Grape Seed Extract. 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

9.2 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 **APPTRIM** are equivalent to those found in the usual human diet. Obese patients 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 appetite and carbohydrate cravings. Obese and morbidly obese patients frequently have altered serotonin

metabolism. Some obese and morbidly obese patients have a resistance to the use of tryptophan that is similar to the mechanism found in insulin resistance. Some obese and morbidly obese patients cannot acquire sufficient tryptophan from the diet without ingesting a prohibitively large amount of calories, particularly calories from protein.

9.3 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 **APPTRIM** cannot be obtained from conventional foods in the necessary proportions to elicit a therapeutic response.

9.4 Other Ingredients

APPTRIM contains the following “inactive” or other ingredients, as fillers and excipients: Gelatin, vegetable magnesium stearate, silicon dioxide,.

9.5 Physical Description

APPTRIM is a yellow to light brown powder. L-Glutamic Acid, Choline Bitartrate, L-Tyrosine, L-Serine, Whey Protein Hydrolysate (Milk Sourced Isolate), Griffonia Seed Extract (20% 5-HTP), Cocoa Extract (6% Theobromine)(Fruit), Caffeine, and Grape Seed Extract (85% Polyphenols).

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

APPTRIM acts by restoring and maintaining the balance of the neurotransmitters, serotonin, acetylcholine, and norepinephrine that are required to maintain appetite control and carbohydrate cravings. A deficiency of these neurotransmitters is associated with obesity, morbid obesity, and metabolic syndrome.

10.2 Pharmacodynamics

APPTRIM has been formulated using Targeted Cellular Technology (TCT), an integrated molecular system that facilitates the uptake and utilization of neurotransmitter precursors by targeting cells within the nervous system. This 5-component patented system consists of: (1) specific neurotransmitter precursors; (2) a stimulus for the neuronal uptake of these precursors by specific neurons; (3) an adenosine antagonist that blocks the inhibitory effect of adenosine on neuronal activity (adenosine brake); (4) a stimulus to trigger the release of the required neurotransmitters from targeted neurons; and (5) a mechanism to prevent attenuation of the precursor response, a well-known phenomenon associated with precursor administration.

10.3 Pharmacokinetics

Absorption & Metabolism: The amino acids in **APPTRIM** are primarily absorbed by the stomach and small intestines. All cells metabolize the amino acids in **APPTRIM**. Circulating tryptophan, tyrosine and choline blood levels determine the production of serotonin, norepinephrine, and acetylcholine.

Excretion: **APPTRIM** 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.

11 CLINICAL STUDIES

The clinical effectiveness of *APPTRIM* has been demonstrated in 2 randomized, double-blind, placebo-controlled studies in overweight and obese adults.

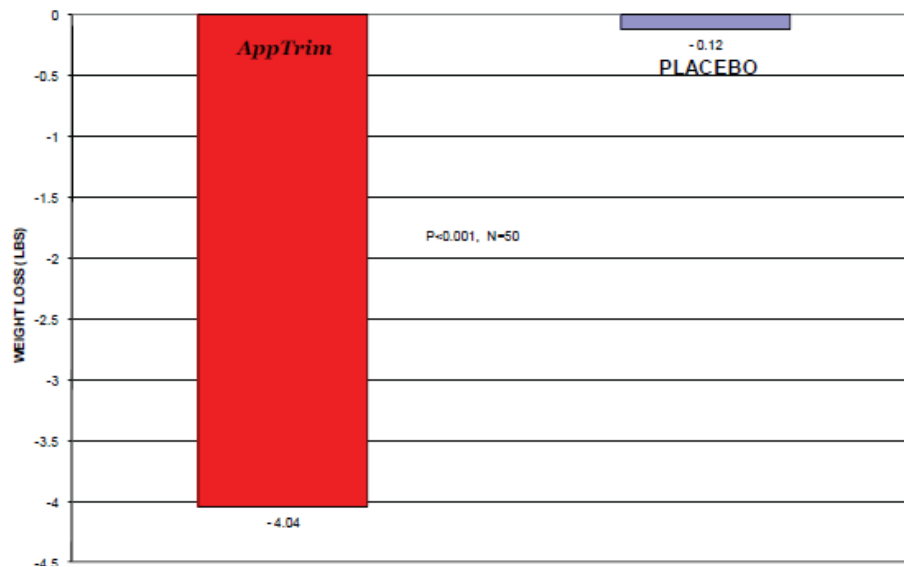
Effect on appetite suppression and dietary adherence associated with weight loss and percent reduction in body fat. In the second trial, 50 subjects were enrolled in a randomized double-blind, placebo-controlled study to examine weight loss and appetite suppression following a 14-hour fast after taking *APPTRIM* twice daily for a 6-week period.

All subjects were given a calorie-reduced diet providing 1200 kcal/day for women and 1500 kcal/day for men.

Twenty-five subjects were randomized to receive either *APPTRIM* or placebo.

The mean weight loss in the *APPTRIM* group after 6 weeks was 4.04 lbs compared with a gain of 0.08 lbs in the placebo group ($p < 0.01$) (Figure 1).

Figure 1. Change in Weight at 6 Weeks: *APPTRIM* vs. Placebo



12 HOW SUPPLIED/STORAGE AND HANDLING

12.1 Supply

Bottles of 120

12.2 Storage

Keep tightly closed in a cool dry place 8-32° C (45-90° F), relative humidity below 50%. *APPTRIM* is supplied in a recyclable plastic bottle.

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