AppTrim® PRODUCT INFORMATION

AppTrim capsules by oral administration. A specially formulated Medical Food product, consisting of a proprietary formula of amino acids and polyphenol ingredients in specific proportions, for the nutritional management of the metabolic processes associated with obesity, morbid obesity, and metabolic syndrome.
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. ***AppTrim*** has been developed, manufactured, and labeled in accordance with both the statutory definition of a Medical Food and FDA's regulatory labeling guidelines. ***AppTrim*** must be used while the patient is under the ongoing care of a physician.

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.

PRODUCT DESCRIPTION

Primary Ingredients

AppTrim is a proprietary formulation of amino acids and other dietary factors to support induction, maintenance, and enhancement of the specific neurotransmitter activity involved in the physiology of obesity. The formulation consists of L-Glutamic Acid, Choline Bitartrate, L-Histidine HCL, L-Tyrosine, L-Serine, Whey Protein Isolate (Milk), Griffonia Seed Extract, Cocoa Extract, 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

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.

Other Ingredients

AppTrim contains the following "inactive" or other ingredients, as fillers, excipients, and colorings: Gelatin, vegetable magnesium stearate, silicon dioxide.

Physical Description

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

CLINICAL PHARMACOLOGY

Mechanism of Action

AppTrim acts by providing the nutritional requirements that support the synthesis and physiological activities of neurotransmitters involved in metabolic syndrome and obesity. These nutrients include choline, glutamine, histidine, tryptophan, tyrosine and serine which support the balance of the neurotransmitters dopamine, histamine, serotonin, and acetylcholine that are associated with obesity and metabolic syndrome. Correcting nutritional deficiencies is critical to the physiological functions that must be balanced in the highly integrated and complex multiple feedback interactions that determine input to the brain. A balance is required between the activities of the excitatory and inhibitory

neurotransmitters in the complex relationship between the various activities of the neurotransmitters. An imbalance in the intake of a nutrient or dietary factor which supports the synthesis or activity of any one neurotransmitter can influence the activities of the others, and negatively impact neurotransmitter-mediation. Metabolic efficiency requires an adequate supply of the precursors, delivery to targeted cells. Specific ratios, appropriate timing and uptake stimulation are required to reduce fractional absorption that would otherwise cause the liver to rapidly deaminates the absorbed nutrients.

Targeted Cellular Technology™ a patented integrated molecular system facilitates the uptake and utilization of neurotransmitter precursors by target cells in the nervous system. This 5-component system consists of (1) specific neurotransmitter precursors; (2) a stimulus for the neuronal update of the precursors by specific neurons; (3) an adenosine antagonist that blocks the inhibitory effect of adenosine on neuronal activity; (4) a stimulus to trigger the release of the required neurotransmitters from the targeted neurons, and (5) a mechanism to prevent attenuation of the precursor response.

Metabolism
Under usual physiological conditions, glutamine, serine, tyrosine, and choline are considered nonessential because endogenous synthesis is sufficeint to satisfy metabolic demand. When needs are altered due to increase demands as with metabolic syndrome, the usual rate of synthesis is no longer sufficient and these nutrients become conditionally essential, requiring that supplemental amounts be consumed. 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.

INDICATIONS FOR USE
AppTrim is intended for the clinical nutritional management of the metabolic processes in patients with obesity, morbid obesity, and metabolic syndrome.

CLINICAL EXPERIENCE
AppTrim has demonstrated significant functional improvements when used for the nutritional management of the metabolic processes associated with obesity, morbid obesity, and metabolic syndrome. The use of ***AppTrim*** in patients with obesity disorders results in the induction and maintenance of appetite suppression and suppression of carbohydrate cravings. ***AppTrim*** does not increase blood pressure.

PRECAUTIONS AND CONTRAINDICATIONS
AppTrim is contraindicated in an extremely small number of patients with hypersensitivity to any of the nutritional components of ***AppTrim.*** 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 ***AppTrim*** capsule does not exceed 400 mg.

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.

OVERDOSE
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.

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 ***AppTrim*** flavonoid ingredients, including cocoa, caffeine, and grape seed extract. 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 obesity and metabolic disorders. Take (2) capsules twice daily; once in mid morning and once in mid afternoon or as directed by a physician. An additional evening dose of (2) capsules may be added to the daily dose if needed. As with most amino acid formulations, ***AppTrim*** should be taken without food to increase the absorption of key ingredients.

How Supplied
AppTrim is supplied in clear, size 0 capsules in bottles of 120 capsules.

Physician Supervision
AppTrim is a Medical Food product available by prescription and may be used per FDA law, and product labeling only while the patient is under ongoing physician supervision.

Storage
Keep tightly closed in a cool dry place 8-32º C (45-90º F), relative humidity below 50%.
AppTrim is supplied to physicians in a recyclable plastic bottle.
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