Hypertensa™ Product Information
For Elevated Blood Pressure

Medical Foods Classification

Hypertensa is a Medical Food formulated to be used by practicing physicians for the nutritional management of hypertension. ***Hypertensa*** helps to promote nitric oxide in the arterioles.

Under the regulations of the Food and Drug Administration, Medical Foods may only be used when a patient is under the ongoing care of a physician or other healthcare provider. Medical Foods are used for the dietary management of disease states with known nutritional deficiencies. Medical Foods must contain ingredients from the human diet. Medical Foods cannot be sold directly to patients without physician supervision.

Distinctive Nutritional Deficiencies

A critical component of the definition of Medical Foods is the requirement that products are formulated to address a distinctive nutritional deficiency. Medical Foods are foods that are specially formulated and processed (as opposed to a naturally occurring foodstuff used in a natural state) for the patient who is seriously ill or who requires the product as a major treatment modality.

FDA scientists have proposed a physiologic definition of a distinctive nutritional deficiency as follows[1]:

“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 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 reflect 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 for the nutrient is assumed to exist. For example, if a patient with hypertension responds to an arginine formulation by decreasing the blood pressure, a deficiency of arginine is assumed to exist.

Patients with hypertension are known to have nutritional deficiencies of arginine, choline, flavonoids, and certain antioxidants. Patients with hypertension frequently exhibit reduced plasma levels of arginine and have been shown to respond to oral administration of an arginine formulation. Research has shown that arginine reduced diets result in a fall of circulating arginine. Patients with hypertension have activation of the arginase pathway that diverts arginine from the production of nitric oxide to production of deleterious nitrogen molecules such as peroxynitrite leading to a reduced level of production of nitric oxide for a given arginine blood level. Research has also shown that a genetic predisposition can lead to increased arginine requirements in hypertension.

Choline is required to fully potentiate nitric oxide synthesis by arterioles. A deficiency of choline leads to reduced nitric oxide production by arterioles. Low fat diets, frequently used in patients with hypertension, are usually choline deficient. Flavonoids potentiate the production of nitric oxide by arterioles thereby reducing blood pressure in hypertension. Low fat diets and diets deficient in flavonoid rich foods result in inadequate flavonoid concentrations, impeding nitric oxide production.

Provision of arginine, choline, and flavonoids with antioxidants, in the correct proportions can restore the production of beneficial nitric oxide, thereby reducing blood pressure.

Indications for Use

1. Increased blood pressure
2. Hypertension
3. Metabolic Syndrome

Neurotransmitter Production in the Human Body

1. Arginine produces nitric oxide
2. Choline produces acetylcholine
3. Glutamine produces glutamate
4. Flavonoids increase nitric oxide use

Targeted Cellular Technology™

This unique five-component process allows milligram quantities of neurotransmitter precursors to produce the therapeutic effects of neurotransmitters. This process includes a neurotransmitter precursor, an uptake stimulator, a neuron activator, an adenosine brake inhibitor, and an attenuation releaser. Previous attempts to use neurotransmitter precursors have required much larger quantities of the precursors to elicit a therapeutic effect, making it functionally impossible for a patient to ingest large, gram quantities of a precursor agent on a daily basis. The use of the *Targeted Cellular Technology* process also prevents the development of tolerance. Unlike pharmaceutical agents that lose their effectiveness in a relatively short period of time, ***Hypertensa*** maintains its effectiveness and does not attenuate.

Hypertensa Ingredients:
L-Arginine, L-Glutamine, Histidine (as Histidine HCL), Choline Bitartrate, Dextrose, Cinnamon, Ginkgo Biloba, Grape Seed Extract, Caffeine, Cocoa, Ginseng

Targeted Cellular Technology and ***Hypertensa***

Hypertensa is designed to produce the neurotransmitters nitric oxide and acetylcholine. Nitric oxide is the neurotransmitter that initiates dilatation of the arterioles and arteries in the presence of hypertension. Acetylcholine is the neurotransmitter that facilitates the action of nitric oxide on the hypertensive arteries. ***Hypertensa*** is designed to provide the nitric oxide precursor arginine, and the acetylcholine precursor choline, to enhance the production of the nitric oxide and acetylcholine neurotransmitters in the arterioles and arteries.

Hypertensa and Clinical Testing

Physiologic testing of nitric oxide function has been performed on individuals taking ***Hypertensa*** Patients with increased blood pressure and hypertension have been shown to reduce both systolic and diastolic pressures with the use of ***Hypertensa.***

Hypertensa Dosage

Hypertensa should be taken as a dose of two (2) capsules three times per day. An additional dose of ***Hypertensa*** may be used if needed. As with all Medical Food products, the best dosing protocol is established by the healthcare provider in coordination with the requirements of each individual patient.

Hypertensa and Prescription Drugs

In patients taking pharmaceutical agents to treat hypertension, it is suggested that the medication dosage should be maintained initially. ***Hypertensa*** should be added to the treatment regime and clinical responses monitored by the healthcare provider. The response to ***Hypertensa*** can occur within 15 minutes of the first dose. The maximal effect of ***Hypertensa*** will accumulate within two weeks from the beginning of therapy. The patient can be monitored in the office after first dose to observe changes in blood pressure. ***Hypertensa*** exerts its effects only in constricted blood vessels and dilatation of vessels beyond the normal range does not occur, thereby eliminating the possibilities of overdose. The addition of ***Hypertensa*** to the treatment regime allows the dosage of prescription drugs to be reduced with the concomitant reduction in drug side effects.

Side Effects

The side effect profile of ***Hypertensa*** is comparable to the rate of food intolerance in the community. The ingredients of ***Hypertensa*** are derived from nutrient based compounds found in the normal food chain. Food intolerance is an adverse reaction to food that does not involve the body's immune system.

When first starting any amino acid therapy, some patients complain of mild headaches, stomach upset, and nausea or mouth dryness. These symptoms are mild and temporary and can be managed by drinking plenty of fluids and carefully titrating the dose. These side effects are relieved by lowering the initial dose and titrating upward as tolerated.

L-Arginine Contraindications, Precautions, Adverse Reactions

Hypertensa is contraindicated in patients who may be hypersensitive to any component of an arginine-containing preparation.

Precautions

Because of absence of long-term safety studies, and because of the possibility of growth hormone stimulation, pregnant women and nursing mothers should avoid L-arginine supplementation. Individuals with renal or hepatic failure should exercise caution in the use of supplemental L-arginine.

Adverse Reactions

Oral supplementation with L-arginine at high doses 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.

A two capsule dose of ***Hypertensa*** contains 126 mg of L-arginine.

Drugs Interactions

No drug interactions have been reported by patients taking ***Hypertensa*** at the recommended doses

Sildenafil citrate: Theoretically, L-arginine supplements taken concomitantly with sildenafil citrate may potentiate the effects of the drug.

Herbs

Yohimbe: L-Arginine, if used concomitantly, may enhance the effect of Yohimbe

Background:

Hypertensa contains a formula blend of selected GRAS (generally regarded as safe) ingredients that are found in the normal human food chain. The primary ingredients are key amino acids, the building blocks of proteins. The ***Hypertensa*** formula is designed to increase the function of the neurotransmitters nitric oxide and acetylcholine. The ***Hypertensa*** formula is based on a five-component, patent pending process. This five -component system initiates the conversion of a precursor into a neurotransmitter, allows for its release and prevents attenuation. The five component system includes: (1) an amino acid precursor for each neurotransmitter (2) stimulation of the uptake of the precursor to initiate the conversion into a neurotransmitter, (3) an adenosine antagonist such as cocoa powder is added to disinhibit the neuron, (4) stimulation of neurons to release a specific neurotransmitter, and (5) a system is used to prevent attenuation of the response, to the precursor. ***Hypertensa*** has been formulated with this five-component system and targets the neurotransmitters nitric oxide, and acetylcholine.

Hypertensa is designed to produce two neurotransmitters, nitric oxide[2-70] and acetylcholine[30, 47, 71-88]. These two neurotransmitters are involved in hypertension[89-123 124-151]and asthma[152-195]. Normal arteries do not significantly respond to nitric oxide, while constricted hypertensive arteries dilate in response to nitric oxide[86, 196-233]. Acetylcholine potentiates the activity of nitric oxide on the constricted arteries and arterioles. Thus, nitric oxide in conjunction with acetylcholine acts to regulate artery and arteriole constriction in hypertensive states.

Hypertensa is designed to produce neurotransmitters that initiate vasodilatation in hypertension. In the ***Hypertensa*** formulation, L-arginine is used as the precursor to nitric oxide and choline is used as a precursor to acetylcholine.

In the ***Hypertensa*** formula, both Ginkgo Biloba and cinnamon are used as uptake stimulators[234-239]. Glutamine is used to produce glutamate to stimulate neurotransmitter release [240-271]. Cocoa and caffeine are used to disinhibit the adenosine brake[272-282 283-292]. Hawthorn Berry, containing polyphenols[293-297], is used to prevent the attenuation usually associated with neurotransmitter precursor administration.

L-arginine is a conditional essential amino acid in humans and is the substrate for the endothelial nitric oxide (NO) synthase (cNOS), that metabolizes this amino acid to L-citrulline and NO, a powerful vasodilator with antiplatelet properties[52, 298-322]. While the impaired availability of NO in endothelium and platelets has been associated with cardiovascular risk factors, and with aging, experimental and clinical studies have shown that the attenuation of vascular and platelet NO activity can be managed by providing the proper nutrients that are deficient and deficiency contributes to the disease state[42, 43, 323-331].

In humans, maintenance of plasma L-arginine is mainly dependent on the dietary intake of L-arginine[42, 51, 52, 54, 149, 149, 202, 325, 332-335, 335-384]. Studies indicate that L-arginine therapy is associated with an increase in surrogate markers of NO production, such as plasma nitrates and exhaled NO[31, 48, 52, 342, 364, 373, 385-400]. Since circadian patterns[80, 379, 401-404] have been described for several phenomena occurring in the cardiovascular system, including regulation of vascular tone and platelet aggregation[306, 313, 381, 405-411] physiological variations of plasma L-arginine concentrations influence endothelial NO production and thus modify vascular tone and platelet function. Therefore, timing and amount of arginine ingestion is important in regulation of plasma arginine and NO production that cannot be achieved by diet alone.

Nitric oxide is an important mediator of blood pressure in the presence of hypertension[99, 412-456]. Nitric oxide has little effect on arterioles and arteries when blood pressure is in the normal range. In the presence of increased blood pressure, nitric oxide serves to provide vasodilatation.

It is recognized that the endothelium modulates vascular tone through the synthesis and elaboration of vasodilator mediators including NO[21, 24, 41, 43, 54, 55, 63, 73, 74, 197, 202, 207, 208, 334, 335, 358, 457-485]. Endothelium-derived nitric oxide (EDNO) regulates arterial tone through a dilator action on vascular smooth muscle cells that depends on soluble guanylyl cyclase activation and consequent increases in intracellular cyclic 3'5'-guanosine monophosphate (cGMP). Studies demonstrating increased blood pressure in animals lacking endothelial nitric oxide synthase (cNOS) provide evidence for a role of NO in the regulation of arterial pressure. Pharmacological evidence supporting this contention is provided by the observation that infusion of NOS inhibitors such as N^G-monomethyl-L-arginine (L-NMMA) produces acute blood pressure elevation in animals, and long-term NOS inhibition leads to chronic arterial hypertension. Human studies of clinical hypertension that examined vasomotor responses also provide evidence for loss of NO bioaction in this disease state. Coronary vascular dilation to EDNO-agonists is impaired in patients with essential hypertension, and similar findings are reported in clinical studies of forearm circulation in hypertensive patients. L-NMMA reduces resting blood flow less in patients with hypertension, suggesting a derangement in basal as well as stimulated release of EDNO in hypertension. Reduced NO synthesis or increased inactivation may play an important role in alterations of vascular tone contributing to increased arterial resistance.

Nitric oxide is endogenously released in the arterioles after synthesis from L-arginine induced by the enzyme nitric oxide synthase (NOS). Functionally, three isoforms of this enzyme exist: neuronal, constitutive, and inducible. The nitric oxide produced from neuronal and constitutive NOS appear to protect arterioles from excessive vasoconstriction. The inducible form of NOS does not appear to have a significant role in blood pressure control

Nitric oxide has little role in modulating basal blood pressure in normal subjects or patients without hypertension. Nitric oxide synthesis in arterioles is closely linked to the simultaneous production of acetylcholine. The vasodilatory effects of nitric oxide are potentiated by endogenous acetylcholine. In hypertension there is a reduction in cNOS produced nitric oxide, indicating a reduced supply of the vasodilatory effects of nitric oxide. The vasoconstriction in hypertension is related to a reduced bioavailability of L-arginine and a shunt of the L-arginine from nitric oxide production to peroxynitrite production from arginase activity as well as a reduction of acetylcholine dependent NO production that is genetically induced.

Accordingly, it is important to augment cNOS in treating hypertension. When nitric oxide is increased by direct production of cNOS, blood pressure control in both animal and human models is improved.

In addition, flavonoids contained in a variety of plant sources including cocoa and grape seed influence L-arginine utilization and impact on blood pressure[72, 289, 323, 486-492]. Flavonoids are a group of polyphenolic compounds that occur widely in fruit, vegetables, tea, grape, red wine, and chocolate[490, 493, 493-496, 496-499]. Cocoa and chocolate products have the highest concentration of flavonoids among commonly consumed food items[500, 501, 501]. Over 10% of the weight of cocoa powder consists of flavonoids, catechin, and epicatechin. As with most plants, genetic and agronomic factors can markedly influence the contents of phytochemicals available at the time of harvest. Post harvest handling also plays a critical role, because most cocoas undergo fermentation steps that subject flavonoids in the cocoa to heat and acidic conditions. Subsequent processing steps, such as roasting and alkali treatment, can also reduce the flavonoid content. Lastly, the actual recipe for the finished food or beverage product determines the amount of a given cocoa (and flavonoid) added. In addition, many sources of cocoa polyphenols are foods high in fat and calories. Interestingly, cocoa powder and cocoa extracts have been shown to exhibit greater antioxidant capacity than many other flavanol-rich foods and food extracts, such as green and black tea, red wine, blueberry, garlic and strawberry in vitro.

Atherosclerosis, heart failure, hypertension, and hypercholesterolemia can activate several pro-inflammatory enzyme systems, such as xanthine oxidase, NADH/NADPH oxidase, and myeloperoxidase. Once activated, these enzymes produce reactive oxygen species and other radicals that can modify nitric oxide (NO) availability and LDL and contribute to endothelial dysfunction. Flavanol-rich cocoa has been shown to stimulate NO production and to significantly reduce the activities of xanthine oxidase and myeloperoxidase after ethanol-induced oxidative stress. In addition, cocoa flavanols and procyanidins may modulate other mediators of inflammation. Platelets have a prominent role in the development and manifestation of acute myocardial infarction, stroke, and venous thromboembolism. Polyphenols, by increasing NO production seem to benefit cardiovascular health through regulation of platelet reactivity. Cocoa inhibits platelet adhesion and even a modest decrease in platelet reactivity can be of value because it reduces the probability of clotting[500].

The ***Hypertensa*** formula contains precise, proprietary proportions of L-arginine, cocoa powder, caffeine, cinnamon, grape seed extract, glutamine, histidine, and choline. Several open label trials have been conducted using the ***Hypertensa*** formula in patients with hypertension. In patients with documented hypertension, these trials have shown a reduction in blood pressure.

Nutritional Deficiencies Associated with Hypertension

Patients with hypertension may have nutritional deficiencies of L-arginine, choline[30, 72, 73, 76, 84, 86, 323, 484, 502-527] and certain antioxidants [471, 504, 528-558]. Patients with hypertension have reduced plasma levels of L-arginine and have been shown to respond to oral administration of [22, 42, 43, 326, 559-568] L-arginine. Arginine reduced diets result in a fall of circulating L-arginine. Patients with hypertension have activation of the arginase pathway that diverts arginine from production of nitric oxide to production of deleterious nitrogen molecules such as peroxynitrite thus leading to a reduced production of nitric oxide for a given arginine blood level[569-591]. Supplementation with antioxidants and arginine can restore the production of beneficial nitric oxide production[34, 229, 325, 331, 333, 343, 371, 470, 592-621].

The removal of L-arginine from the diet for one day in healthy individuals causes a significant decrease in plasma L-arginine concentrations during the awake period followed by a spontaneous return to normal morning basal concentrations overnight[149, 379, 622, 623]. In the same subjects, a normal amount of L--arginine in the diet (3.8 g/d) was associated with a rise in plasma L-arginine concentration after each meal. Plasma L-arginine changes reflect the balance between complex inter-organ processes leading to movement of the amino acid into and out of the circulation. Endogenous synthesis of L-arginine occurs primarily in the kidney and to a lesser extent in the liver via conversion of citrulline to L-arginine. However, the liver does not contribute significantly to the maintenance of the plasma concentrations of L-arginine, since the amino acid synthesized in this organ is routed towards its local utilization

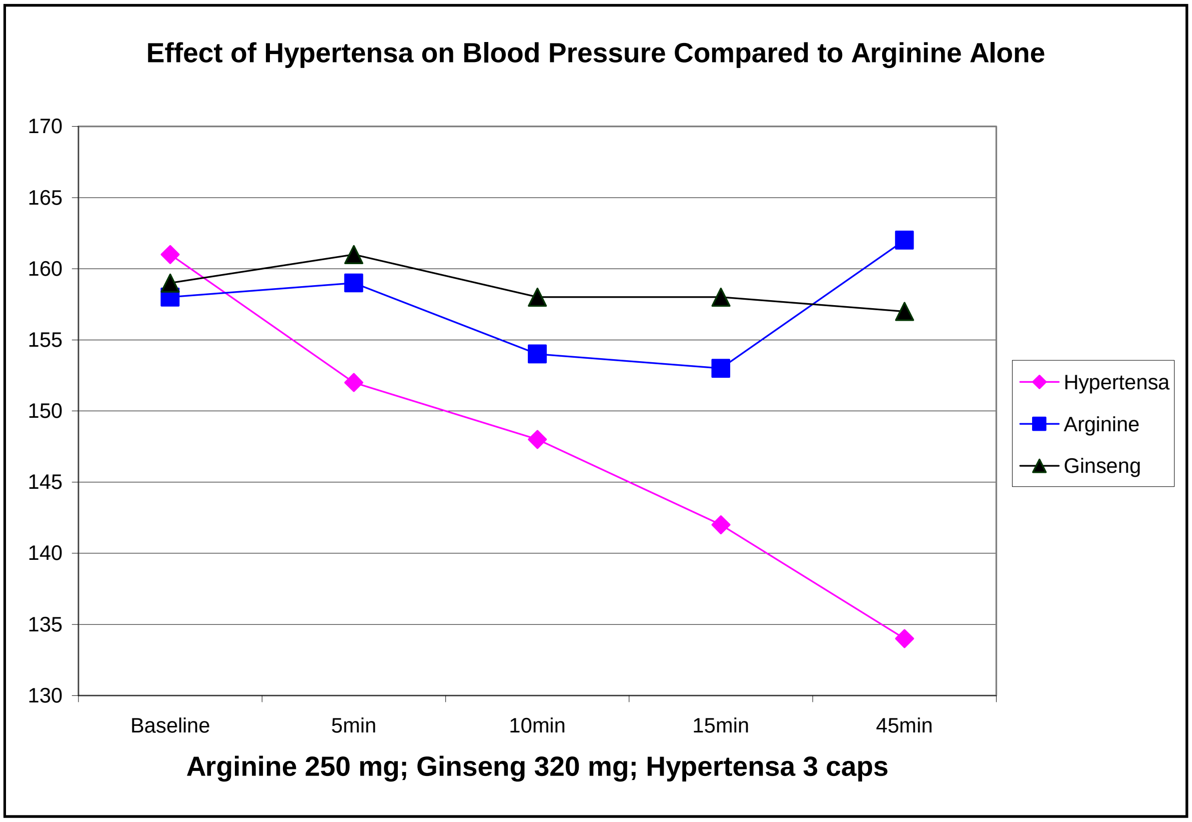
The mean dietary intake of L-arginine in industrialized countries is 3–6 g/day[149, 335, 344, 381, 383, 622, 624-627]; 60% of this exogenous source appears in the general circulation. Isotopic studies have shown that the net rate of de novo arginine synthesis in healthy humans is not affected by a 6–7 day arginine-free diet. [25, 26]. Consequently, it has been proposed that whole-body arginine homeostasis in healthy adults may be achieved principally via a modulation in the level of dietary arginine intake and/or with regulation in the rate of its catabolism to ornithine and glutamate. An L-arginine-free diet is associated with a gradual decrease in plasma concentration– reaching 47% of the baseline value after 7 hours. Comparison with the normal diet also demonstrated a significant decrease in the 3-h AUC intervals.0. L-arginine is the substrate for endothelial NO synthesis, a reaction that is catalyzed by the constitutive endothelial enzyme eNOS. NO plays a key role in the regulation of vascular tone and platelet aggregation and adhesion. Changes due to hypercholesterolemia, hypertension, and aging, conditions associated with impairment of the L-arginine/NO pathway result in increased need for L-arginine compared to normal subjects.

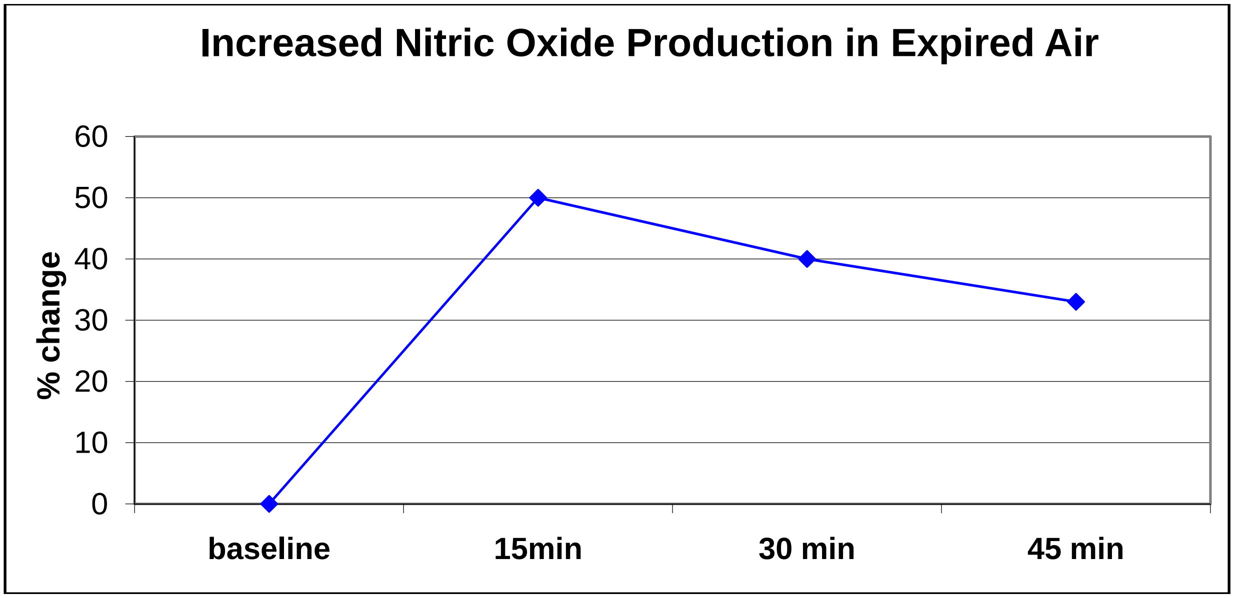
Physiological variations of plasma L-arginine concentrations are either induced by an increase in arginine utilization or reduced arginine in the diet. Altered plasma L-arginine concentrations influence endothelial NO production impairing blood pressure regulation. Patients with hypertension, hypercholesterolemia, and aging require additional L-arginine in the diet compared to normal individuals.

As indicated in the summary above, a critical component of the definition of a Medical Food is the requirement for a distinctive nutritional deficiency. The FDA has proposed a physiologic definition of a distinctive nutritional deficiency[628]:

“However, 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 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 reflect 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 has also been proposed if a patient with the disease responds to the nutrient, a physiologic deficiency for the nutrient exists. For example, if a patient with hypertension responds to arginine by decreasing the blood pressure, a deficiency of arginine exists.

The use of ***Hypertensa*** produced reduced blood pressure in patients with documented hypertension.





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