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***Pulmona*[™] Product Information**

Medical Foods Classification

Pulmona is a Medical Food formulated to be used by practicing physicians for the management of pulmonary artery pressure in the presence of pulmonary hypertension and to reduce bronchospasm in the presence of asthma. ***Pulmona*** promotes nitric oxide in the bronchi and the pulmonary arteries. 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. 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 medical supervision.

Distinctive Nutritional Deficiencies

Patients with pulmonary hypertension and asthma may have nutritional deficiencies of arginine, choline, and certain antioxidants. Patients with pulmonary hypertension and asthma frequently exhibit reduced plasma levels of arginine. Patients with pulmonary hypertension and asthma respond to oral administration of arginine. Arginine reduced diets result in a fall of circulating arginine. Patients with pulmonary hypertension and asthma have activation of the arginase pathway that diverts arginine from 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. Clinical dietary management with antioxidants and arginine can restore the production of beneficial nitric oxide production

Indications for Use

1. Increased pulmonary artery pressure
2. Pulmonary hypertension
3. Bronchospasm
4. Asthma

Neurotransmitter Production in the Human Body

1. Arginine produces nitric oxide
2. Choline produces acetylcholine
3. Glutamine produces glutamate

Targeted Cellular Technology™

Targeted Cellular Technology™ is a unique five-component process that allows milligram quantities of neurotransmitter precursors to produce therapeutic effects of neurotransmitters. This process includes a neurotransmitter precursor, an uptake stimulator, a neuron activator, an adenosine brake inhibitor, and 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, ***Pulmona*** maintains its effectiveness and does not attenuate.

***Pulmona* Ingredients:**

L-Arginine, L-Glutamine, L-Histidine, L-Leucine, L-Cysteine, Choline Bitartrate, Whey Protein Hydrolysate, Cinnamon, Ginkgo Biloba, Grape Seed Extract, Caffeine, Cocoa Extract.

Targeted Cellular Technology and Pulmona

Pulmona is formulated to produce the neurotransmitters nitric oxide and acetylcholine. Nitric oxide is the neurotransmitter that initiates dilatation of the pulmonary arteries in the presence of pulmonary hypertension and dilates the bronchi in the presence of bronchoconstriction. Acetylcholine is the neurotransmitter that facilitates the action of nitric oxide on the pulmonary arteries and bronchi. ***Pulmona*** is formulated 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 lung.

Distinctive Nutritional Requirements

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.

“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 asthma responds to an arginine formulation by increasing FEV1, a deficiency of arginine is assumed to exist.

Patients with asthma are known to have nutritional deficiencies of arginine, choline, flavonoids, and certain antioxidants. Patients with asthma frequently exhibit reduced plasma levels of arginine and have been shown to respond to oral administration of an arginine formulation or nitric oxide inhalation. Research has shown that arginine reduced diets result in a fall of circulating arginine. Patients with asthma 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 asthma.

Choline is required to fully potentiate nitric oxide synthesis by the bronchi. A deficiency of choline leads to reduced nitric oxide production by the bronchi. Low fat diets are usually choline deficient. Flavonoids potentiate the production of nitric oxide by bronchi thereby increasing FEV1 in asthma. 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 bronchoconstriction.

***Pulmona* and Clinical Testing**

Physiologic testing of nitric oxide function has been performed on individuals taking ***Pulmona***. Patients with pulmonary hypertension have increased pulmonary artery pressures. Patients with asthma have decreased pulmonary flow rates as measured by FEV1. ***Pulmona*** has been shown to reduce pulmonary artery pressures as measured by right heart catheterization in patients with pulmonary hypertension. ***Pulmona*** increases FEV1 as measured by spirometry in patients with asthma.

Indications for Use

1. Asthma
2. COPD with obstructive component
3. Pulmonary Hypertension

Neurotransmitter Production in the Human Body

4. Arginine produces nitric oxide
5. Choline produces acetylcholine
6. Glutamine produces glutamate
7. Flavonoids increase nitric oxide use

***Pulmona* Dosage**

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

***Pulmona* and Prescription Drugs**

In patients taking pharmaceutical agents to treat pulmonary hypertension or asthma, it is suggested that the medication dosage should be maintained initially. ***Pulmona*** should be added and clinical state monitored by the physician and therapeutic doses modified according to clinical response. Patients with pulmonary hypertension and shortness of breath should be clinically monitored with assessment of pulmonary artery pressures. Patients with asthma should be clinically monitored and have intermittent FEV1 testing.

Side Effects

The side effect profile of ***Pulmona*** is comparable to the rate of food intolerance in the community. The ingredients of ***Pulmona*** 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 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

Pulmona 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 ***Pulmona*** contains 126 mg of L-arginine.

Drugs Interactions

No drug interactions have been reported by patients taking **Pulmona** 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:

Pulmona 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 **Pulmona** formula is designed to increase the function of the neurotransmitters nitric oxide and acetylcholine. The **Pulmona** 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 must be used to prevent attenuation of the response, to the precursor. **Pulmona** has been formulated with this five-component system. The **Pulmona** formula targets the neurotransmitters nitric oxide, and acetylcholine.

Pulmona is designed to produce two neurotransmitters including nitric oxide and acetylcholine. These two neurotransmitters are involved in pulmonary hypertension^{1-35 36-113} and asthma^{114-144, 144-206}. Normal pulmonary arteries do not significantly respond to nitric oxide while constricted pulmonary arteries in pulmonary hypertension dilate in response to nitric oxide. Exhaled nitric oxide production is increased by the inflammation associated with asthma²⁰⁷⁻²³⁸ largely through inducible NOS (iNOS)²³⁹⁻²⁴⁵ but inhaled nitric oxide reduces bronchodilation^{246, 247}. Importantly, however, certain sites of nitric oxide production (the constitutive NO produced by cNOS) are reduced in asthma inducing bronchoconstriction. Inhalation of nitric oxide or production of constitutive NOS (cNOS) induces bronchodilatation in diseased lungs²⁴⁸⁻²⁵⁵. Acetylcholine potentiates the activity of the inducible nitric oxide in the lung²⁵⁶⁻²⁷⁹.

Pulmona is designed to produce neurotransmitters that initiate vasodilatation in pulmonary hypertension and bronchodilatation in asthma. In the **Pulmona** formulation, arginine is used as the precursor to nitric acid and choline is used as a precursor to acetylcholine.

In the **Pulmona** formula, both Ginkgo Biloba and cinnamon are used as uptake stimulators²⁸⁰⁻²⁹⁶. Glutamine is used to produce glutamate to stimulate neurotransmitter

release²⁹⁷⁻³²⁸. Cocoa and caffeine are used to disinhibit the adenosine brake^{329-339 340-363}. Grape Seed Extract, containing polyphenols³⁶⁴⁻³⁶⁷, is used to prevent the attenuation usually associated with neurotransmitter precursor administration.

Nitric oxide is an important mediator of pulmonary artery pressure in the presence of pulmonary hypertension^{11, 368-436}. Nitric oxide has little effect on pulmonary arteries when pulmonary artery pressure is in the normal range. In the presence of increased pulmonary artery pressure, nitric oxide serves to provide pulmonary artery vasodilatation. Nitric oxide is a selective pulmonary artery dilator in the presence of pulmonary hypertension. Nitric oxide produced from arginine can potentiate other nitrate donors in pulmonary hypertension^{61, 430, 437-462}.

Nitric oxide is intimately involved in control of bronchial function in asthma^{137, 144, 463-498}. Nitric oxide is endogenously released in the airways after synthesis from arginine induced by the enzyme nitric oxide synthase (NOS). Functionally, three isoforms of this enzyme exist: neuronal, constitutive, and inducible⁴⁹⁹⁻⁵⁴⁸. The nitric oxide produced from neuronal and constitutive NOS (cNOS) appear to protect airways from excessive bronchoconstriction. The inducible form of NOS (iNOS) has a modulatory role in inflammatory disorders of the airways such as asthma, and is a marker for the inflammation process. Thus, the role of lung-produced nitric oxide is complex and reflects both the bronchodilatation of constricted bronchi by endogenous nitric oxide (cNOS) and the role of inducible nitric oxide as a marker for inflammation^{166, 171, 549-596}.

Nitric oxide has a major role in modulating airway tone in both normal subjects and patients with asthma. Nitric oxide (cNOS) opposes the bronchoconstriction induced by a variety of bronchial spasmogens. The bronchodilatory effect of nitric oxide is potentiated by endogenous histamine. In severe asthma there is a reduction in cNOS produced nitric oxide, indicating a reduced supply of the bronchomodulatory effects of nitric oxide but an increase in iNOS that facilitates inflammation. An early response to an allergen challenge induces nitric oxide production (iNOS) and inhibits cNOS. Blocking the early cNOS response results in an augmented bronchoconstrictive response to the allergen. Early release of nitric oxide in response to an allergen challenge protects the bronchi from severe bronchoconstriction. The ability of the bronchi to produce the favorable nitric oxide response is lost as the asthma worsens. The bronchoconstriction in severe asthma is related to a reduced availability of arginine and a shunt of the arginine from nitric oxide cNOS production to peroxynitrite production from arginase activity^{242, 597-612}.

Constitutive Nitric oxide (cNOS) reduces the inflammation associated with asthma, and directly reduces histamine release by mast cells. Brain histamine, however, promotes glucocorticoid production to inhibit prostaglandin mediated inflammation. The increased circulating levels of glucocorticoids play a role in suppressing excessive or inappropriate cytokine production. Constitutive nitric oxide also inhibits arginase activity leading to reduced peroxynitrite production. Thus constitutive nitric oxide has multiple beneficial effects in both early and late asthma. Arginine alone, without inhibition of the arginase activity may prolong the late allergic response. However, Pulmona is designed to decrease arginase activity.

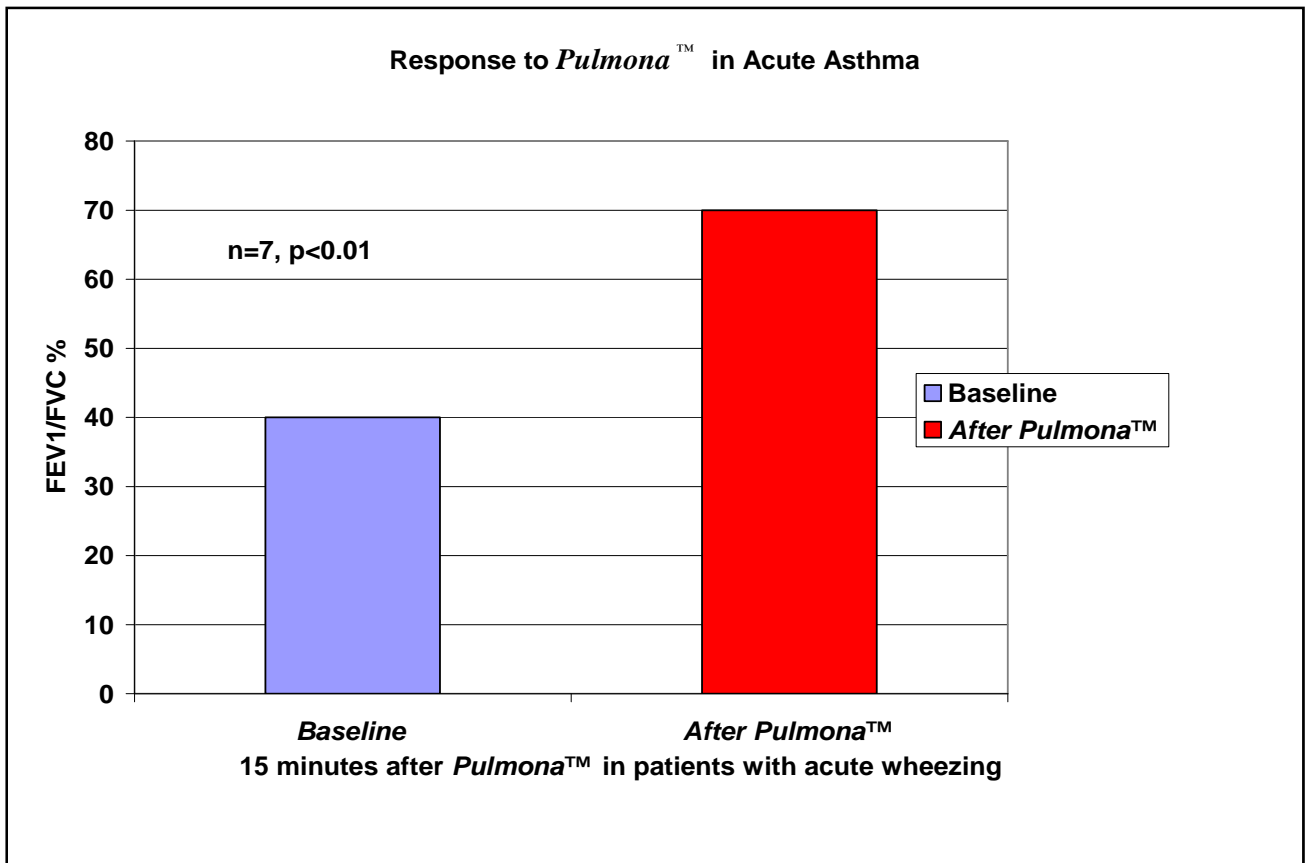
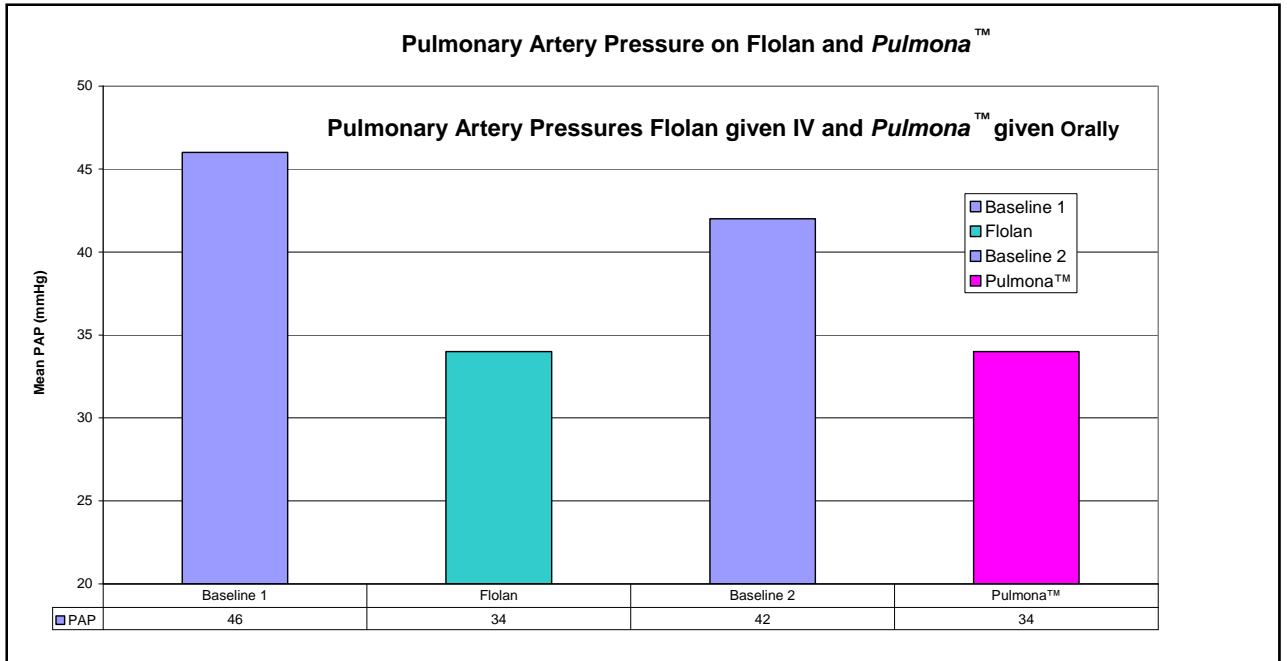
Accordingly, it is important to augment cNOS while inhibiting iNOS in treating asthma. When nitric oxide is increased by direct production of cNOS, asthma in both animal and human models is improved.

The ***Pulmona*** formula contains precise proprietary proportions of arginine, cocoa powder, caffeine, cinnamon, grape seed extract, glutamine, histidine, and choline. Several open label trials have been conducted using the ***Pulmona*** formula in patients with either pulmonary hypertension or asthma. In patients with documented pulmonary hypertension, these trials have shown a reduction of pulmonary artery pressures as measured by right heart catheterization. In patients with documented asthma, reduction of FEV1 as measured by spirometry was shown. ***Pulmona*** has been shown to increase nitric oxide production by the lung.

Nutritional Deficiency Associated with Pulmonary Hypertension and Asthma

Patients with pulmonary hypertension and asthma may have nutritional deficiencies of arginine, choline and certain antioxidants⁶¹³⁻⁶⁴⁵. Patients with pulmonary hypertension and asthma have reduced plasma levels of arginine, choline and histidine; moreover, plasma concentration of arginine and choline return toward normal as symptoms subside^{242, 646-661}. Patients with pulmonary hypertension and asthma respond to oral administration of arginine. Arginine reduced diets result in a fall of circulating arginine⁶⁶²⁻⁶⁹³. Patients with pulmonary hypertension and asthma 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 level⁶⁹⁴⁻⁷¹⁶. Supplementation with antioxidants and arginine can restore the production of beneficial nitric oxide production⁷¹⁷⁻⁷¹⁹.

The use of ***Pulmona*** may produce reduced pulmonary artery pressure and reduced FEV1 in patients with pulmonary hypertension and asthma. Thus, ***Pulmona*** may result in reduced shortness of breath and improved exercise tolerance in these patients.



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