

Summary of Aller-7® Clinical Research Abstracts

Aller-7® Found to Reduce Major Symptoms of Airborne Allergies in Multicenter Clinical Trial

Aller-7®, a patented blend of seven standardized herbal extracts, has been shown to demonstrate potent anti-histaminic, anti-inflammatory, anti-spasmodic and antioxidant activity. Its safety and tolerability profile has also been determined in previous studies. The current 12-week investigation evaluated the effects of **Aller-7®** in established cases of chronic allergic rhinitis in 545 adult patients at 14 research centers. A double-blind, placebo-controlled trial with 171 patients was conducted at 3 clinical centers, while 374 patients were enrolled in an open-label trial at 11 sites. Patients in the placebo-controlled trial were randomly assigned to receive 4 capsules of **Aller-7®** daily (1,320 mg of **Aller-7®**), or placebo capsules identical in appearance. Clinical symptoms and objective parameters were assessed in the 151 and 352 subjects who completed the placebo-controlled and open-label trials, respectively. Over the 12-week period, 94% of patients in the open-label trials and 92% of patients in the placebo-controlled trials treated with **Aller-7®** reported an improvement in symptoms ranging from more than 40 to 100 percent. Complete relief from sneezing, runny nose and nasal congestion in open-label trials was seen in 28, 27 and 45 patients, respectively. Significant improvement was also seen in absolute eosinophil count (white blood cells active in allergic disease), mucociliary clearance (movement of mucous from the nasal passage), and peak nasal and expiratory flow rates—measures of nasal congestion. In the open-label study, over 90% of the participants using **Aller-7®** experienced an improvement of more than 40% in sneezing, runny nose and nasal congestion. No serious side-effects were observed, thus demonstrating that **Aller-7®** is both well-tolerated and efficacious in combating the symptoms of airborne allergies. These results are consistent with those of previous clinical studies and show that **Aller-7®** is useful in reducing the major symptoms of allergic rhinitis or “hay fever.”

Source: Saxena VS, Venkateshwarlu K, Nadig P, Barbhaiya HC, Bhatia N, Borkar DM, Gill RS, Jain RK, Katiyar, SK, Nagendra PKV, Nalinesha KM, Nasiruddin K, Rishi, JP, Roy Chowdhury J, Saharia PS, Thomas B, Bagchi D, Multicenter Clinical Trials On A Novel Polyherbal Formulation In Allergic Rhinitis, *International Journal of Clinical Pharmacology Research*, XXIV(2/3):79-94, 2004.

Aller-7® Shown to Reduce Inflammation in Animals

Allergic rhinitis occurs when the body's immune system over-reacts to a substance such as pollen or dust, resulting in inflammation of the mucous membranes that line the nasal passage. **Aller-7®**, a blend of seven standardized plant extracts, was developed to address the symptoms of this common immunologic disorder. **Aller-7®** has been shown in previous studies to promote respiratory health and to inhibit the release of histamine, a mediator of allergic symptoms. The present study investigated the anti-inflammatory activity of **Aller-7®** in several *in vivo* animal models. In one strain of mice, a dose of 250 mg/kg/bw **Aller-7®** inhibited chemically-induced paw edema or swelling by 62% compared to controls. **Aller-7®** was more effective than the anti-inflammatory medication prednisolone, which inhibited edema by 45% at an oral dose of 14 mg/kg/bw. In a second strain of mice, edema was reduced at doses ranging from 175 to 275 mg/kg/bw, with 225 mg/kg/bw exhibiting the most potent effect. In rats, **Aller-7®** (120 mg/kg p.o) inhibited chemically-induced acute inflammation by 31%, compared to 68% inhibition by ibuprofen

(50 mg/kg p.o.). In a model of artificially-induced arthritis, **Aller-7®** demonstrated a 63% inhibitory effect on swelling at a dose of 350 mg/kg po. Additionally, **Aller-7®** was observed to be a potent inhibitor of trypsin, a tissue-damaging enzyme released by immune cells (mast cells) during the inflammatory response. The consistency of these results, as well as those of previous studies, demonstrates the anti-inflammatory activity of **Aller-7®** and supports its use as a dietary supplement by those who suffer from allergic rhinitis.

Source: Pratibha N, Saxena VS, Amit A, D'Souza P, Bagchi M, Bagchi D, Anti-Inflammatory Activities of Aller-7, A Novel Polyherbal Formulation for Allergic Rhinitis, *International Journal of Tissue Reactions*, XXVI:43-51, 2004.

Aller-7® Demonstrates Safety and Free Radical Scavenging Activity

Recent studies have demonstrated the safety of **Aller-7®**, which has been clinically shown to reduce the symptoms of allergic rhinitis. To further assess safety, the potential toxicity of **Aller-7®** was evaluated in acute oral and dermal tests in animals. The oral LD50 was greater than 5,000 mg per kilogram of body weight (mg/kg bw), and no signs of toxicity were observed at this dose. When applied to skin, the LD50 was found to be more than 2,000 mg/kg bw. **Aller-7®** did not cause skin sensitization and had only minimal potential as an eye irritant. In addition, the *in vitro* ability of **Aller-7®** to inhibit key inflammatory mediators of lung tissue damage and airway constriction was compared to other known free radical scavengers. LC50 is the concentration of a compound that inhibits 50% of the free radical activity measured, with lower LC50 values indicating greater efficiency. For superoxide radical, the **Aller-7®** LC50 value was less than that of catechins (antioxidants commonly found in tea), and comparable to the value for gallic acid (a component of **Aller-7®** and a well-known antioxidant). **Aller-7®** was more efficient at quenching nitric oxide and hydroxyl radicals compared to catechins and curcuminoids (from turmeric). **Aller-7®** was also more effective than the potent antioxidant BHA in protecting red blood cells. These results extend the support for **Aller-7®** safety and its clinical antioxidant potential to scavenge free radicals encountered in allergic rhinitis.

Source: Bagchi M, Amit A, Saxena S, Pratibha N, Bagchi D, Toxicologic Evaluation and Antioxidant Potential of a Novel Botanical Extract for Use in Ameliorating Allergic Rhinitis, *Annual Meeting of the Society of Toxicology*, 78:Abs 1-S 1019, March, 2004.

ALLER-7® Demonstrates Potent Antioxidant Action *In vitro*

Aller-7®, a botanical formula consisting of seven medicinal plant extracts, was developed to promote immune health and normal breathing. Affecting about 60 million people worldwide, allergic rhinitis (commonly called hay fever) is an inflammation or irritation of the mucous membranes that line the nose caused by an over-active immune system in response to airborne allergens such as pollen or dust. Antioxidants are vital to a healthy immune system. To evaluate the antioxidant properties of **Aller-7®**, researchers compared the ability of **Aller-7®** and other known free radical scavengers to inhibit three important inflammatory mediators of bronchial constriction and lung tissue damage. In this study, IC₅₀ is the concentration of a compound (or compounds) that inhibit 50% of the radical activity measured. Lower IC₅₀ values indicate greater effectiveness. For superoxide radical, the **Aller-7®** IC₅₀ value was less than that of catechins (commonly found in tea), and similar to the value for gallic acid, an individual component of **Aller-7®**. The **Aller-7®** IC₅₀ value against nitric oxide was lower than that for curcuminoids,

components of the spice turmeric. **Aller-7®** was also more efficient than the catechins in scavenging hydroxyl radical, with IC₅₀ values of 741.7 and 2,193.4, respectively. These results show that the dietary supplement **Aller-7®** is a potent free radical scavenger *in vitro*, with the potential to serve as a novel antioxidant.

Source: D'Souza P, Amit A, Saxena VS, Bagchi D, Bagchi M, Antioxidant Properties of Aller-7, a Novel PolyHerbal Formulation for Allergic Rhinitis, *Drugs Under Experimental and Clinical Research*, XXX:99-109, 2004.

Aller-7® Clinically Shown to Promote Respiratory Health-A Review

According to the National Institutes of Health, the prevalence of allergic rhinitis or hay fever has increased substantially over the past 15 years. **Aller-7®**, a botanical formula consisting of seven medicinal plant extracts (*P. emblica*, *T. chebula*, *T. Bellerica*, *A. lebbek*, *P. nigrum*, *Z. officinale* and *P. longum*) was developed to help counter the common symptoms of hay fever such as sneezing, running nose, itchy and watery eyes. Research has demonstrated the ability of **Aller-7®** to intervene in key processes that underlie the allergic response. It exhibits potent anti-histaminic, anti-inflammatory, anti-spasmodic (bronchial artery relaxation) and antioxidant activity, as well as the capacity to stabilize histamine-releasing mast cells. Broad spectrum safety has been shown in standard *in vivo* and *in vitro* test models. Double-blind, placebo-controlled studies were subsequently conducted to assess its effectiveness. In the first study of 42 subjects, nasal symptom scores significantly improved over a 3-month period in those receiving 1,320 mgs of **Aller-7®** (660 mgs twice daily). Finally, a multi-center clinical trial involving 545 patients was conducted using the same daily dose of 1,320 mgs for a 12-week period. Compared to those in the placebo group, patients taking **Aller-7®** experienced significant improvement in nasal congestion, sneezing, runny nose, peak nasal flow rate and mucocilliary clearance. These clinical findings support the safety and effectiveness of **Aller-7®** at a daily dose of 1320 mgs per day.

Source: Bagchi D, Nadig P, Saxena VS, Bagchi M, Agarwal A, Human Clinical Studies on a Novel Botanical Formulation (Aller-7) Against Allergic Rhinitis, *FASEB Journal*, Volume II: A912, Abs. 600.8, 2004.

Aller-7™ Clinically Shown to Promote Respiratory Health and Normal Breathing

Over 40 million Americans suffer from allergic rhinitis or hay fever, characterized by inflamed and irritated nasal membranes. Recent studies have demonstrated the safety of **Aller-7™** and shown that it can intervene in processes that produce symptoms such as sneezing, running nose, itchy and watery eyes. A three-phase clinical trial was conducted to evaluate the effectiveness of **Aller-7™**, a blend of seven medicinal plant extracts. In Phase I, 20 patients received 1320 mg of **Aller-7™** (660 mgs twice daily) for 15 days. Phase II consisted of a double-blind, placebo-controlled evaluation of 1320 mg **Aller-7™** (660 mgs twice daily) in 48 subjects over a 3 month period. In Phase III, 545 patients were given 1,320 mg (660 mgs twice daily) of the botanical formulation for 3 months in a multi-center clinical trial. Compared to those taking placebo, all patients treated with **Aller-7™** experienced significant improvement in nasal congestion, runny nose, sneezing, peak nasal flow and mucocilliary clearance. These findings suggest that **Aller-7™**, at a daily dose of 1320 mg, can serve as a safe, natural dietary supplement to reduce the symptoms of allergic rhinitis.

Source: Bagchi M, Saxena VS, Pratibha N, Amit A, Bagchi D, Anti-Allergic Potential of a Novel Botanical Formulation (Aller-7) Against Allergic Rhinitis: Clinical Findings, *Journal of the American College of Nutrition* 22(5): Abs 46, 2003.

ALLER-7® Found to Promote Immune and Respiratory Health

The safety of a combination of seven plant extracts (**ALLER-7®**) has been demonstrated in previous research based on the results of standard tests, including acute and sub-acute toxicity, sub-chronic toxicity, mutagenicity (changes in genetic material), teratogenicity (presence of fetal abnormalities), and histopathologic (microscopic) changes to vital organs. The current studies evaluated the ability of **Aller-7®** to interfere with biochemical processes characteristic of allergic rhinitis, or hay fever. **Aller-7®** exhibited anti-histaminic activity, which was evaluated using the common drug, chlorpheniramine, as a control. Histamine mediates broncho-constriction and vessel dilation, important contributors to the symptoms of allergy. Anti-spasmodic effects were observed as **Aller-7®** was shown to antagonize common drugs with known spasmodic activity. **Aller-7®** produced a significant anti-inflammatory effect (31% inhibition) at an oral dose of 120 milligram per kilogram body weight. In addition, this botanical preparation was shown to stabilize mast cells and prevent their chemically-induced degranulation (breakdown). Mast cells release histamine when degranulated. Taken together, these results demonstrate the ability of **ALLER-7®** to intervene in key processes that contribute to the symptoms of hay fever. Thus, **ALLER-7®** may serve as a safe, natural therapy for promoting normal respiratory function.

Source: Saxena VS, Bagchi M, Amit A, Pratibha N, Safety and Efficacy of Aller-7, a Novel Botanical Extract Formulation for Allergic Rhinitis, *Journal of the World Allergy Organization*, Suppl 1 Abs P-3-22, 2003.

Aller-7® Shown to Promote Clear Airway Passages and Normal Breathing

Allergic rhinitis, or “hay fever,” is a public health concern. Affecting 40 million Americans, it causes significant loss in quality of life and productivity. Recent studies have demonstrated the safety of **Aller-7®**, and shown that it can influence biochemical actions that promote respiratory health. These findings led investigators to evaluate its clinical usefulness of **Aller-7®** (660 mg taken twice daily) in 48 patients with allergic rhinitis over a 3 month period. Nasal and eye symptoms, including sneezing, running nose, itchy and watery eyes, were significantly reduced in those receiving **Aller-7®** compared to placebo. Seventy percent of the supplemented patients reported improved quality of life. While relief of allergic symptoms was reported after 30 days of treatment, maximum improvement in both nasal and non-nasal scores was seen during the third month. The results of this double-blind, placebo-controlled clinical trial show that **Aller-7®** can help relieve symptoms and enhance the quality of life in those who suffer from seasonal or year-round allergic rhinitis.

Source: Vyjayanthi G, Subhashchandra S, Saxena VS, Nadig P, Venkateshwarlu K, Serene A, Sathyan S, Bagchi D, and Kulkarni C, Randomized, Double-Blind, Placebo-Controlled Trial of Aller-7 in Patients with Allergic Rhinitis, *Research Communications in Pharmacology and Toxicology*, 8:23-32, 2003.

Aller-7® Shown Effective in Promoting Respiratory Health

Allergic rhinitis (commonly known as "hay fever") is an inflammation or irritation of the mucous membrane that lines the nose. Common symptoms include sneezing, coughing, stuffy or running nose, and itchy and watery eyes. **Aller-7®**, a combination of seven plant extracts from *Phyllanthus emblica*, *Terminalia chebula*, *Terminalia bellerica*, *Albizia lebbek*, *Piper nigrum*, *Zingiber officinale* and *Piper longum*, was evaluated against various biochemical and physiological parameters involved in respiratory health and normal breathing, and compared with common allergy drugs. Histamine is an important mediator of allergic reactions. The antihistaminic activity of **Aller-7®** was compared with the common drug chlorpheniramine. The anti-spasmodic effect (relieving spasm in the bronchial arteries) was compared with the drugs Papaverine and Cetirizine. Inflammation is an important aspect of immediate- and late-phase (3-24 hr) allergic reactions. Anti-inflammatory activity of **Aller-7®** was compared with ibuprofen. Since antioxidant activity works against inflammation, the antioxidant activity of **Aller-7®** was evaluated and compared with gallic acid. These studies demonstrate the efficacy of **Aller-7®** as a potent anti-histaminic, anti-inflammatory, anti-spasmodic and antioxidant agent, which may serve as a safe, natural dietary supplement for promoting respiratory health and normal breathing during allergy season.

Source: Bagchi D, Bagchi M, Saxena VS, Pratibha N, Amit A, Anti-Allergic Potential of a Novel Botanical Extract Formula, *FASEB*, 17:A1061, Abs. 660.1, 2003.

Aller-7® Shown to Enhance Respiratory Immune Function

Inflamed, irritated nasal mucous membranes are the hallmark of allergic rhinitis, a condition caused by repeated exposure to an allergen. When an allergen is encountered, the rapid release of histamine and other mediators causes immediate symptoms. A secondary response, 3-24 hrs later, is triggered by a cascade of events, including the formation of intercellular and vascular adhesion molecules (ICAM-1 and VCAM-1). These molecules recruit and adhere ("stick") leukocytes (white blood cells) to endothelial cells of blood vessel walls, resulting in increased local inflammation and symptoms such as sneezing, running nose, itchy and watery eyes. In experimental studies, a combination of seven plant extracts (**Aller-7®**) was shown to down-regulate TNF-alpha-induced expression of both ICAM-1 and VCAM-1, and to impede the interaction between leukocytes and endothelial cells. Blocking or modifying leukocyte adhesion is an important strategy for controlling inflammation. In separate studies, **Aller-7®** was shown to exhibit anti-histaminic, anti-spasmodic (relaxing bronchial arteries), and anti-inflammatory activity. The effect of **Aller-7®** was compared with that of a common allergy drug in each experiment. **Aller-7®** also displayed free-radical scavenging activity. Excess free radicals play a role in inflammation. These findings demonstrate the ability of **Aller-7®** to intervene in key processes that underlie both the early and later stages of allergic response. **Aller-7®** may serve as a safe, novel and all-natural therapy for promoting normal respiratory function.

Source: Bagchi D, "Novel Anti-Allergic, Anti-Inflammatory and Anti-Spasmodic Activities of Aller-7, A Safe, Novel Botanical Formulation," International Symposium on Inflammatory and Oxidative Cell Death and Tissue Damage, Seoul, South Korea, May, 2003.

Aller-7® Shown to Stabilize Mast Cells and Promote Respiratory Health

Allergens such as pollen, mold and dust can cause allergic rhinitis or hay fever, a condition which affects about 40 million Americans. A blend of seven botanical extracts, **Aller-7®**, has been

clinically shown to reduce the symptoms of allergic rhinitis, while its safety has been demonstrated in toxicity studies. The present experiments examine the mechanisms underlying its anti-allergic effects. When activated by allergen exposure, mast cells degranulate and release their stores of inflammatory mediators, including tissue-damaging enzymes and histamine. Histamine is mainly responsible for the clinical symptoms of allergy such as sneezing, itching and runny nose. **ALLER-7®** was found to stabilize incubated mast cells exposed to degranulating agents. **Aller-7®** also inhibited lipoxygenase and hyaluronidase, key enzymes that activate inflammation within mast cells. Both **Aller-7®** and the common anti-allergy medication cetirizine significantly inhibited the effects of histamine in isolated tissue. Lastly, **Aller-7®** was comparable to anti-allergy drugs (cetirizine, papavarine) in protecting isolated airway tissue from chemicals that cause bronchial muscle constriction and spasms. The potent anti-allergy activity observed in these test models is consistent with clinical findings that **ALLER-7®** helps relieve symptoms in those suffering from hay fever.

Source: Amit A, Saxena VS, Pratibha N, D'Souza P, Bagchi M, Bagchi D, Stohs, SJ, Mast Cell Stabilization, Lipoxygenase inhibition, Hyaluronidase Inhibition, Antihistaminic and Antispasmodic Activities of Aller-7, A Novel Botanical Formulation for Allergic Rhinitis, *Drugs Under Experimental and Clinical Research*, XXIX:107-15, 2003.

Aller-7® Demonstrates Broad Spectrum of Safety

Previous research has shown that **ALLER-7®** can interfere with biochemical processes involved in producing the symptoms of allergic rhinitis or "hay fever." A variety of standard animal tests were conducted to assess its safety. Testing examined the potential for acute and sub-acute toxicity, as well as mutagenicity (changing genetic material) and teratogenicity (causing fetal abnormalities). No histopathological (microscopic) changes were observed in vital organs after animals were fed increasing doses during a two-week period. No signs of toxicity were found at doses up to 2 grams (g) per kilogram (kg) of body weight (bw). Lower doses, gradually increased over 28 days, also revealed no toxic signs. In one sub-chronic toxicity study, a no observed adverse effect level (NOAEL) was noted at a dose of 1g/kg/bw. **ALLER-7®** showed no evidence of mutagenic or teratogenic activity in assays, nor were any maternal changes observed when it was fed during pregnancy and lactation. The amount employed in the teratologic test (1.8 g/kg/bw) was approximately 20 times higher than the level typically recommended for daily human consumption. Together, these findings strongly support the safe use of this novel blend of plant extracts as a dietary supplement.

Source: Amit A, Saxena VS, Pratibha N, Bagchi M, Bagchi D, Stohs SJ, Safety of a Novel Botanical Extract Formula for Ameliorating Allergic Rhinitis, *Toxicology Mechanisms and Methods*, 13:253-61, 2003.