

Clinical Evaluation of  
Allergenic Extracts Used in Allerdent

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**1. Introduction**

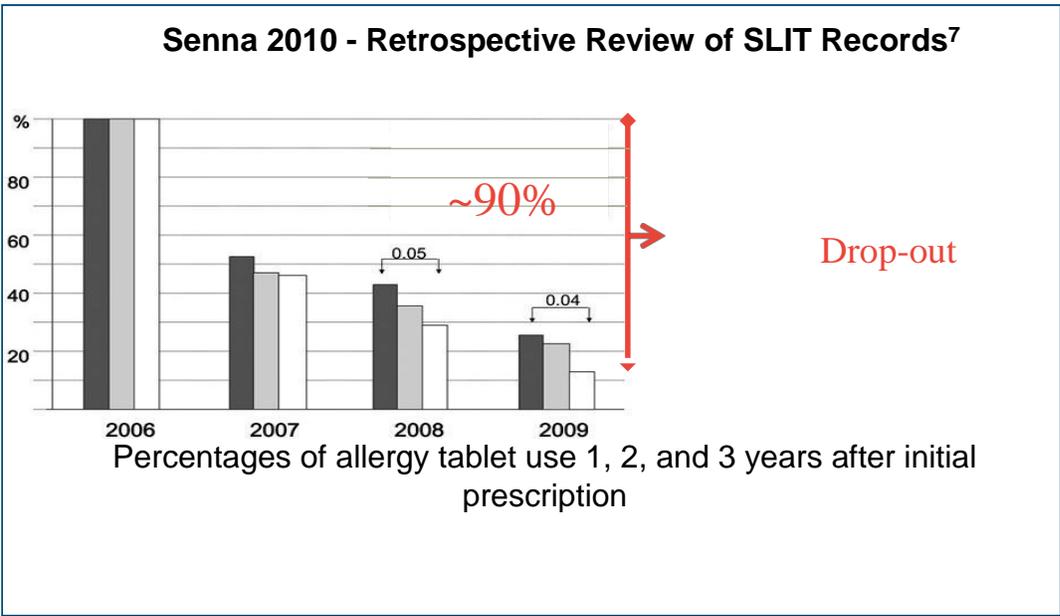
Allergies and asthma, with their associated significant secondary health effects and costs remain significant health care issues in the world. Current demographic studies show:

Demographics of Allergy			
	Population	Allergy Prevalence	People with allergy
USA	319M	20-25% <sup>1</sup>	60-80M
EU	743M	22% <sup>2</sup>	160M
Japan	127M	30-39% <sup>3</sup>	38-50M (Japanese cedar)
China	1.4B	18% <sup>4</sup>	240M
RoW	4.6B	22% <sup>5</sup>	>1B

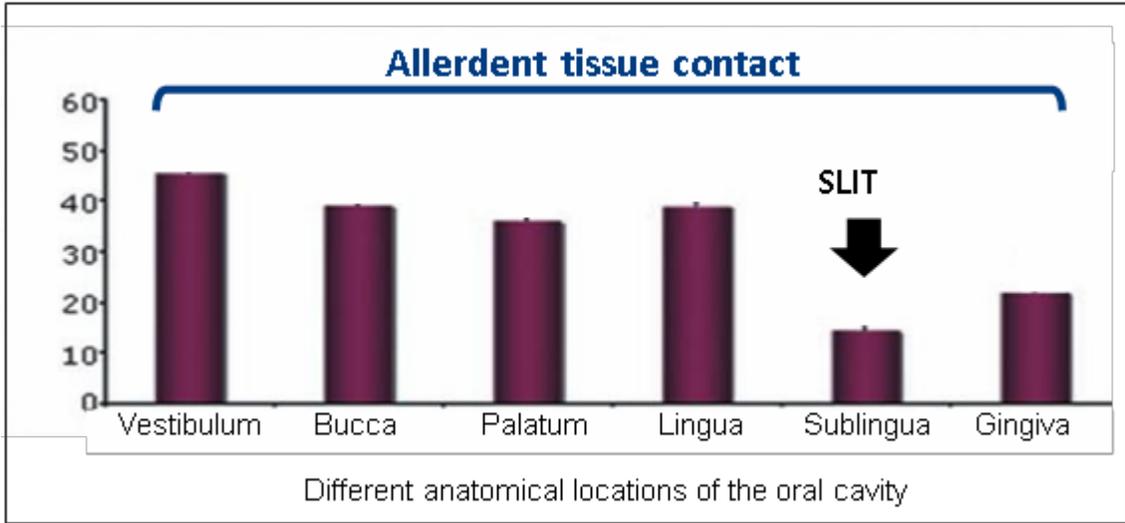
In addition, costs of over the counter (OTC) health care associated with allergy treatment still remain very high, with over 15 billion dollars spent in the United States (6). However, OTC care of allergies remain palliative, in comparison to allergic immunotherapy (AIT), which is disease modifying in nature. Due to difficulty of administration directly related to adherence, AIT remains the last resort used in less than 5% of all eligible patients.

**2. Allergic Immunotherapy Associated with Allerdent**

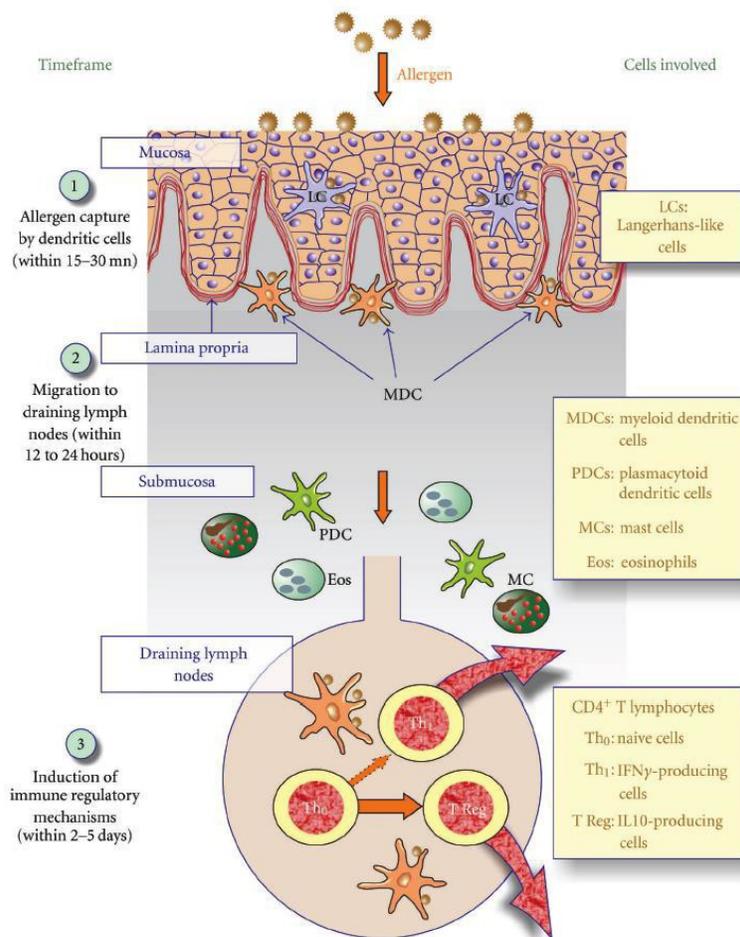
For allergen specific immunotherapy, adherence to treatment remains one of the most important factors associated with efficacy (7). Even with sublingual immunotherapy with tablets have significant decreases in patient adherence and compliance over the necessary minimum 3 years needed for full immune therapy to be effective:



Standard of care SLIT immunotherapy for respiratory allergies has shown up to 90% drop-off in adherence to therapy before full clinical effects are achieved (8).



**Due to Allerdent’s mechanism of action using Oral Mucosal Immunotherapy (OMIT) in combination with FDA approved serum antigens, direct activation of oral Langerhan’s cell receptors sites occur at higher binding and receptor affinity due to more activation of receptors located in the vestibulum, buccal, palatum, lingual and gingival sites of the mouth, in comparison to only sublingual receptor sites bound by SLIT. Allerdent’s very high patient adherence rates of over 80% are crucial to the successful treatment of non-food based allergies (9), successfully modifying the body’s tolerance to the specific IgE associated allergen diagnosed on the PAS/OAS fingerstick macroarray assay at time of clinical diagnosis, as follows:**



1. Using Allerdent's OMIT administration, allergen **proteins bind to epithelial cells within minutes**, then cross the oral mucosa 15-30 minutes later. Allergen is subsequently captured by Langerhans cells within the mucosa itself and myeloid dendritic cells along the lamina propria. These cells process the allergens into small peptides that are presented in association with MHC class I and class II molecules at the cell surface.
2. Those cells loaded with allergen-derived peptides reach cervical lymph nodes within 12 to 24 hours, where they interact with naive CD4<sup>+</sup> T cells to support the differentiation of Th1 and TReg cells within two to five days.
3. These CD4<sup>+</sup> T cells subsequently migrate back to mucosal tissues, resulting in allergen tolerance with down-regulation of preexisting Th2 responses.
4. TReg and Th0 cells inhibit Th2 cells, which in turn inhibits Th2 production of cytokines such as IL-3, IL-4, IL-5, and IL-9. These cytokines drive the differentiation, survival and activity of mast cells, basophils, eosinophils – the cells whose disproportionately high populations and errant activation cause the acute clinical symptoms of food allergies, including anaphylaxis.

### **3. Allerdent's Use of FDA Cleared Serum Allergen Solutions**

The clinical use of serum allergenic solutions for subcutaneous immunotherapy have been done for over 50 years and have been documented in multiple peer reviewed literature sources (10). The mode of action of immunotherapy with allergenic extracts is still under investigation. Subcutaneous injections of increasing doses of allergenic extract into patients with allergic disease have been shown to result in both humoral and cellular changes including the production of allergen-specific IgG antibodies, the suppression of histamine release from target cells, decrease in circulating levels of antigen specific IgE antibody over long periods of time and suppression of peripheral blood T- lymphocyte cell responses to antigen (11,12,13).

After appropriate clinical studies showing safety and efficacy, the FDA has cleared over 500 serum extracts used for diagnostic testing and for the treatment (immunotherapy) of patients whose histories indicate that upon natural exposure to the allergen, they experience allergic symptoms. These serum concentrates of known allergenic extracts are listed extensively on the FDA website, [www.drugs.com](http://www.drugs.com) (14). Allerdent uses this extensive clinical knowledge of prior FDA approved serum antigenic extracts, commercially available since the 1970's, as all serum antigenic extracts used in Allerdent are already FDA approved for clinical use in the treatment of allergies in the United States (15). These same serum antigenic extracts used in Allerdent are already in current clinical use in the world for several decades in the treatment of allergies and asthma in patients receiving sublingual immunotherapy (SLIT) and subcutaneous immunotherapy (SCIT).

The following list of commonly compounded FDA approved serum allergenic extracts are used in Allerdent, based on findings of the clinical examination, family history and appropriate fingerstick microarray assay by PAS/OAS. All are commercially available for use in a compounding pharmacy for Allerdent by known FDA approved pharmacologic manufacturers and have undergone extensive safety testing prior to their FDA approval:

Acremonium kiliense 1.1mL 1:10 w/v  
Alder, Red 1.1mL 1:20 w/v  
Alternaria alternata 1.1mL 1:20 w/v  
Ash, White 1.1mL 1:20 w/v  
Aspergillus fumigatus 1.1mL 1:10 w/v  
Aureobasidium pullulans 1.1mL 1:10 w/v  
Bahia grass 1.1mL 1:20 w/v  
Bermuda grass 1.1mL 10,000 BAU/mL  
Birch mix (PRW) 1.1mL 1:20 w/v  
Boxelder/Maple mix (BHR) 1.1mL 1:20 w/v  
Candida albicans 1.1mL 1:10 w/v  
Cat Epithelium 1.1mL 10,000 BAU/mL  
Cedar, Mountain (Juniper) 1.1mL 1:20 w/v  
Cladosporium herbarum 1.1mL 1:10 w/v  
Cocklebur 1.1mL 1:20 w/v  
Cockroach mix 1.1mL 1:10 w/v

Common pigweed 1.1mL 1:20 w/v  
 Common Ragweed (GS) 1.1mL 1:20 w/v  
 Cottonwood, Common (Populus) 1.1mL 1:20 w/v  
 Curvularia lunata 1.1mL 1:10 w/v  
 Dog Epithelium 1.1mL 1:10 w/v  
 Elm, American 1.1mL 1:20 w/v  
 Epicoccum purpurascens 1.1mL 1:10 w/v  
 Firebush (Kochia) 1.1mL 1:20 w/v  
 Fusarium proliferatum 1.1mL 1:10 w/v  
 Goosefoot, Lamb's quarters 1.1mL 1:20 w/v  
 Hickory/Shagbark (Carya) 1.1mL 1:20 w/v  
 Johnson grass 1.1mL 1:20 w/v  
 Mesquite 1.1mL 1:20 w/v  
 Mite farinae 1.1mL 10,000 AU/mL  
 Mite pteronyssinus 1.1mL 10,000 AU/mL  
 Mucor racemosus 1.1mL 1:10 w/v  
 Mulberry mix (RW) 1.1mL 1:20 w/v  
 Oak mix (RVW) 1.1mL 1:20 w/v  
 Oil Palm 1.1ml 1:20 w/v  
 Penicillium notatum 1.1mL 1:10 w/v  
 Phoma herbarum 1.1mL 1:10 w/v  
 Plantain (English), Ribwort 1.1mL 1:20 w/v  
 Rough Marshelder mix (BPT) 1.1mL 1:20 w/v  
 Russian Thistle 1.1mL 1:20 w/v  
 Ryegrass 1.1mL 100,000 BAU/mL  
 Sagebrush, Mugwort 1.1mL 1:20 w/v  
 Sheep Sorrel 1.1mL 1:20 w/v  
 Sycamore, American 1.1mL 1:20 w/v  
 Timothy grass 1.1mL 100,000 BAU/mL  
 Trichoderma viride 1.1mL 1:10 w/v  
 Walnut, Black 1.1mL 1:20 w/v

This list is not comprehensive in nature, and due to known cross reactivity of specific allergens to certain related genus and families of grasses, trees, molds and other allergenic sources, patients can be treated by Allerdent for multiple environmental non-food based allergies identified, using only a few related serum antigenic extracts, instead of multiple extracts. If needed, on the basis of a newly identified allergen associated with allergies or asthma worldwide, another FDA approved serum extract may be added for use with Allerdent. The rationale regarding cross reactivity and the antigenic environmental issues are mentioned as below.

#### 4. Allergen Cross Reactivity

It is very important to have a basic understanding of cross-reactivity when it comes to allergens. Cross-reactivity basically means that two or more different plants possess the same or very similar proteins that elicit the same allergic response in susceptible individuals. Generally speaking, the more closely related two plants are, the greater the cross-reactivity. For example, all Oak trees belong to the Genus family of Quercus; Red Oak is Quercus (Genus) rubra (specie), White Oak is Quercus alba. There are 60 Oaks native to North America and others that have been introduced. Allergy testing in the US typically uses one or two Oaks and an allergy to any of the other 58 Oaks will show up with that one or two Oaks tested. Additionally, there are only about 4- 5 Oak trees that are licensed as allergenic extracts, yet treatment with one Oak tree pollen has proven successful for all Oaks. This is important because many of the specific plants in the Pediatric Allergy Solutions and Optimum Allergy Solutions (PAS/OAS) testing battery at the species level are not the same plants as found in Saudi Arabia and in other areas of the world. However, they are very close relatives and will demonstrate cross-reactivity.

#### 5. Significant Aeroallergens in Saudi Arabia and Worldwide

In population-based skin testing, weeds were the most important plant aeroallergens on evaluation of the clinical data provided, which compared to the US, where grass is the most important aeroallergens (16,17,18). In terms of prevalence of test reactivity, here are the aeroallergens that have demonstrated reactivity in patient population studies of Saudi Arabia:

Saudi Arabia Allergen	PAS Allergen (Latin Name)	PAS Allergen (Common Name)
<b>Chenopodium murale</b>	Chenopodium album	Lambsquarters
<b>Salsola imbricate</b>	Salsola kali	Russian Thistle
<b>Rumex vesicarius</b>	Rumex acetosella	Sheep Sorrel
<b>Atriplex nummularia</b>	Chenopodium album*	Lambsquarters*
<b>Amaranthus viridis</b>	Amaranthus retroflexus	Rough Pigweed
<b>Artemesia monsperma</b>	Artemesia vulgaris Artemesia tridentate	Mugwort Sagebrush
<b>Plantago boissieri</b>	Plantago lanceolata	English Plantain
<b>Prosopsis juliflora</b>	See discussion	
<b>Ricinus communis</b>	See discussion	
<b>Cynodon dactylon</b>	Cynodon dactylon	Bermuda grass
<b>Lolium perenne</b>	Lolium perenne	Perennial Ryegrass
<b>Phleum pretense</b>	Phleum pretense	Timothy grass
<b>Phoenix dactylifera</b>	Arecastrum romanz.**	Queen Palm**
<b>Morus alba</b>	Morus rubra	Red Mulberry
<b>Olea europa</b>	Fraxinus americana Ligustrum vulgare	White Ash Privet
<b>Fraxinus excelsior</b>	Fraxinus americana	White Ash
<b>Cupressus spp</b>	Juniperus ashei	Mountain Cedar
<b>Ulocladium</b>	Alternaria***	Alternaria***

Penicillium	Penicillium	Penicillium
Aspergillus	Aspergillus	Aspergillus
Cladosporium	Cladosporium	Cladosporium
Chaetomium	No substitute	No substitute
Dermatophagoides pter.	Dermatohpagoides pter.	Dust Mite, Dpt
Dermatophagoides far.	Dermatophagoides far.	Dust mite, Df
Blatta orientalis	Mix	Cockroach mix
Periplaneta americana	Mix	Cockroach mix
Blatella germanica	Mix	Cockroach mix
Cat hair	Cat Hair	Cat Hair

\*= Atriplex species have demonstrated cross-reactivity with Lambsquarters using both in vivo and in vitro methods.

\*\*= Phoenix dactylifera, being in the same Family as Queen Palm, has demonstrated some cross-reactivity.

\*\*\*= Ulocladium is a very close relative to Alternaria, and extensive cross-reactivity has been demonstrated.

## 6. Discussion of Results

The PAS/OAS testing battery is quite extensive and, aside from Prosopsis and Riccinus, appears to provide excellent coverage of known aeroallergens in Saudi Arabia. **The ability of the current PAS/OAS fingerstick 180 allergen molecular proteomic assay panel to cover specific IgE associated aeroallergens provided is greater than 95%, when cross reactivity due to familiar antigenic similarity between families is considered.**

The ability to obtain the appropriate FDA approved serum antigenic extract to be used for compounding within Allerdent, once the exact environmental allergens are determined to be causing the specific IgE related increase associated with that allergen for patients worldwide would be very easy to accomplish. Allerdent is not manufactured with any non-FDA approved serum antigenic extract source, as this would potentially compromise its clinical effectiveness.

All clinical studies about the effectiveness of Allerdent were performed with FDA approved serum antigenic extracts (7,9). Allerdent's very high adherence rates and subsequently high curability rates of allergies and asthma, in comparison to standard treatments associated with SLIT and OMIT would have a very high likelihood of causing a substantial and significant decrease in health care expenses all areas of the world, including the United States with our higher rates of allergy and secondary asthma, with an associated decrease in healthcare costs for all treated patients with allergies and asthma within the world.

Allerdent's high compliance rate would be expected to result in substantially improved treatment specifically in the outpatient sector, due to its safety and ease of use as an activity of daily living, brushing your teeth, only two minutes daily.

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