

# ALK PRODUCT CATALOG



WORLD LEADER IN ALLERGY  
IMMUNOTHERAPY

SINCE 1923

2021



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A couple is walking on a dirt path through a lush green forest. A large, leafy tree dominates the upper half of the frame, its branches spreading out. The couple, a man and a woman, are in the lower third of the image, walking towards the camera. The man is wearing a dark jacket and a scarf, and the woman is wearing a dark jacket and a scarf. They are holding hands. The background is a dense forest with many trees and green foliage. The overall scene is peaceful and natural.

**ALK** is a global pharmaceutical company focusing on **allergy treatment, prevention, and diagnosis.**



ALK is a global allergy solutions company, with a wide range of allergy treatments, products and services that meet the unique needs of allergy sufferers, their families and healthcare professionals.

ALK is committed to helping as many people with allergy as possible, which means providing your practice with quality supplies and services to help your business thrive and provide your patients with educational materials to support immunotherapy awareness and improve compliance.

From our extensive selection of allergy extracts, skin testing devices, unique products, and patient resources, we are committed to helping allergic patients.

## ALK ALSO OFFERS THESE PRODUCTS:

### PRE-PEN® (benzylpenicilloyl polylysine injection USP) Penicillin Allergy Testing

FDA approved for the assessment of sensitization to penicillin (benzylpenicillin or penicillin G) in patients suspected to have a clinical penicillin hypersensitivity.

### OTIPRIO® (ciprofloxacin otic suspension)

The first and only single-dose ciprofloxacin otic suspension administered by a healthcare professional.

### Center-AI® (allergenic extracts, alum precipitated)

Center-AI is the only alum precipitated extract offered in the United States.

### Histatrol® (histamine phosphate)

Positive Skin Test Control.

### ODACTRA® (House Dust Mite [*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*] Allergen Extract Tablet for Sublingual Use 12 SQ-HDM)

The first and only FDA-approved sublingual tablet for house dust mite-induced allergic rhinitis, with or without conjunctivitis.

### GRASTEK® (Timothy Grass Pollen Allergen Extract Tablet for Sublingual Use 2800 BAU)

The first FDA-approved sublingual tablet indicated for allergic rhinitis with or without conjunctivitis due to timothy grass or cross-reactive grass pollen.

### RAGWITEK® (Short Ragweed Pollen Allergen Extract Tablet for Sublingual Use 12 Amb a 1-U)

The first and only FDA-approved sublingual tablet to treat ragweed pollen allergies.

Please see full prescribing information including boxed warning for ODACTRA®, GRASTEK®, and RAGWITEK® starting on page 48 for full safety information.

## PRE-PEN® (benzylpenicilloyl polylysine injection USP)

PRE-PEN® is FDA approved for the assessment of sensitization to penicillin (benzylpenicillin or penicillin G) in patients suspected to have a clinical penicillin hypersensitivity.

PRE-PEN® (benzylpenicilloyl polylysine injection USP) is manufactured by AllerQuest, LLC, and distributed exclusively by ALK.

PRE-PEN® (benzylpenicilloyl polylysine injection USP) is a clear, colorless, sterile solution supplied in 0.25 mL sealed glass ampules. Each ampule is sufficient to evaluate one patient by skin prick (percutaneous) test and duplicate intradermal (intracutaneous) tests.

## PRE-PEN® (benzylpenicilloyl polylysine injection USP)

Item#	NDC #	Description	Vial Size	Concentration
PRPE	49471-001-05	PRE-PEN® (benzylpenicilloyl polylysine injection USP) <i>PRE-PEN® is sold in boxes of 5 ampules; each ampule is intended for single patient use only.</i>	5 x 0.25 mL	6.0 x 10 <sup>-5</sup> M

## Diagnostic Supplies

Item#	Description	Qty	Diagnostic
DILU15	Aqueous Negative Control	5 mL Multi-Dose	Intradermal Testing
NSP100	Normal Saline with Phenol (NSP) 100ml	1 20 mm x 52 mm vial	Skin Prick Testing
HIST14	Histatrol® (histamine phosphate), 1.0 mg/mL	5 mL Dropper	Skin Prick Testing
DT2D	Duotip-Test® II Devices	Box of 400	Skin Prick Testing
1058155	Duotip-Test® II, 5 device pack	50 packs	Skin Prick Testing
1059360	Penicillin Skin Testing Supply Kit Each kit contains: <ul style="list-style-type: none"><li>• Duotip-Test® II devices (5 pack)</li><li>• Pre-printed syringe labels</li><li>• Testing preparation instruction card</li><li>• Alcohol swabs &amp; ruler</li></ul>	Box of 5	Supply kit does not contain PRE-PEN® ampules
1040012	Skin Test Reaction Guide (3 - 9 mm)	Pack of 50 guides	Skin Prick Testing

**Note:** Penicillin G is also required for penicillin allergy skin testing and is available from your pharmacy or healthcare wholesaler. The recommended strength for skin testing per the Drug Allergy Practice Parameters is 10,000 units/mL.\*\*

See the Syringe section on page 31 for a syringe product list. Availability may vary.

### INDICATION

PRE-PEN is indicated for the assessment of sensitization to penicillin (benzylpenicillin or penicillin G) in patients suspected to have clinical penicillin hypersensitivity. A negative skin test to PRE-PEN is associated with an incidence of immediate allergic reactions of less than 5% after the administration of therapeutic penicillin, whereas the incidence may be more than 50% in a history-positive patient with a positive skin test to PRE-PEN. These allergic reactions are predominantly dermatologic. Whether a negative skin test to PRE-PEN predicts a lower risk of anaphylaxis is not established. Similarly, when deciding the risk of proposed penicillin treatment, there are not enough data at present to permit relative weighing in individual cases of a history of clinical penicillin hypersensitivity as compared to positive skin tests to PRE-PEN and/or minor penicillin determinants.

### IMPORTANT SAFETY INFORMATION

The risk of sensitization to repeated skin testing with PRE-PEN is not established. Rarely, a systemic allergic reaction including anaphylaxis (see below) may follow a skin test with PRE-PEN. To decrease the risk of a systemic allergic reaction, puncture skin testing should be performed first. Intradermal skin testing should be performed only if the puncture test is entirely negative.

PRE-PEN is contraindicated in those patients who have exhibited either a systemic or marked local reaction to its previous administration. Patients known to be extremely hypersensitive to penicillin should not be skin tested.

No reagent, test, or combination of tests will completely assure that a reaction to penicillin therapy will not occur. The value of the PRE-PEN skin test alone as a means of assessing the risk of administering therapeutic penicillin (when penicillin is the preferred drug of choice) in the following situations is not established:

- Adult patients who give no history of clinical penicillin hypersensitivity.
- Pediatric patients.

In addition, the clinical value of PRE-PEN where exposure to penicillin is suspected as a cause of a current drug reaction or in patients who are undergoing routine allergy evaluation is not known. Likewise, the clinical value of PRE-PEN skin tests alone in determining the risk of administering semisynthetic penicillins (phenoxymethyl penicillin, ampicillin, carbenicillin, dicloxacillin, methicillin, nafcillin, oxacillin, amoxicillin), cephalosporin-derived antibiotics, and penem antibiotics is not known.

In addition to the results of the PRE-PEN skin test, the decision to administer or not administer penicillin should take into account individual patient factors. Healthcare professionals should keep in mind the following:

- A serious allergic reaction to therapeutic penicillin may occur in a patient with a negative skin test to PRE-PEN.
- It is possible for a patient to have an anaphylactic reaction to therapeutic penicillin in the presence of a negative PRE-PEN skin test and a negative history of clinical penicillin hypersensitivity.
- If penicillin is the drug of choice for a life-threatening infection, successful desensitization with therapeutic penicillin may be possible irrespective of a positive skin test and/or a positive history of clinical penicillin hypersensitivity.

Occasionally, patients may develop an intense local inflammatory response at the skin test site. Rarely, patients will develop a systemic allergic reaction, manifested by generalized erythema, pruritus, angioedema, urticaria, dyspnea, hypotension, and anaphylaxis. The usual methods of treating a skin test antigen-induced reaction—the applications of a venous occlusion tourniquet proximal to the skin test site and administration of epinephrine are recommended. The patient should be kept under observation for several hours.

Pregnancy Category C: Animal reproduction studies have not been conducted with PRE-PEN. It is not known whether PRE-PEN can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. The hazards of skin testing in such patients should be weighed against the hazard of penicillin therapy without skin testing.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit [www.fda.gov/medwatch](http://www.fda.gov/medwatch) or call 1-800-FDA-1088.

Please see full Prescribing Information on page 40, for additional Important Safety Information.

\*\*Solensky et al., Drug Allergy: An Updated Practice Parameter. The Annals of Allergy, Asthma & Immunology. Volume 105. October 2010.

**PRE-PEN®**  
(benzylpenicilloyl polylysine injection USP)  
Skin Test Antigen

OTIPRIO® (ciprofloxacin otic suspension) 6% the first and only single-dose ciprofloxacin otic suspension administered by a healthcare professional

OTIPRIO is available to order at the following wholesalers/distributors:

NDC: 69251-201-01

UPC: 3-69251-20101-8

Unit Quantity: One (1) box contains one single-patient use 2 mL vial.



Wholesaler/Distributor	Item Order #	Contact Information
ASD Specialty Healthcare*	46146	Tel #: 1-800-746-6273 Fax #: 1-800-547-9413 Email: asd.customerservice@asdhealthcare.com
Besse Medical	46146	Tel #: 1-800-543-2111 Fax #: 1-800-543-8695 Web: www.besse.com
Cardinal Health Specialty Distribution†	5216924	Tel #: 1-866-677-4844 Fax #: 1-888-345-4916 Web: specialtyonline.cardinalhealth.com orderexpress.cardinalhealth.com
Henry Schein	124-8971	Tel #: 1-800-772-4346 Fax #: 1-800-329-9109 Web: www.henryschein.com/medical
McKesson Plasma and Biologics	3518339	Tel #: 1-877-625-2566 Fax #: 1-888-752-7626 Web: connect.mckesson.com
McKesson Medical Surgical	1083735	Tel #: 1-800-571-2100 Web: mms.mckesson.com

\* For customers of AmerisourceBergen Corporation full-line wholesale division, OTIPRIO is available through ASD Healthcare and can be ordered using the PassPort ordering platform through AmerisourceBergen. The PassPort Item Number for OTIPRIO is 10162548.

† For customers of Cardinal Health full-line wholesale division, OTIPRIO is available for purchase through Cardinal Health Specialty Distribution.

Visit OTIPRIO.com or contact your local sales consultant to learn more

## INDICATIONS AND USAGE

OTIPRIO® (ciprofloxacin otic suspension) 6% is a fluoroquinolone antibacterial indicated for:

- The treatment of pediatric patients (6 months of age and older) with bilateral otitis media with effusion undergoing tympanostomy tube placement
- The treatment of acute otitis externa in patients 6 months of age and older due to *Pseudomonas aeruginosa* and *Staphylococcus aureus*

## IMPORTANT SAFETY INFORMATION

### CONTRAINDICATIONS

OTIPRIO (ciprofloxacin otic suspension) 6% is contraindicated in patients with a history of hypersensitivity to ciprofloxacin, to other quinolones, or to any of the components of OTIPRIO.

### WARNINGS AND PRECAUTIONS

**Potential for Microbial Overgrowth:** OTIPRIO may result in overgrowth of non-susceptible bacteria and fungi. If such infections occur, institute alternative therapy.

### ADVERSE REACTIONS

*Bilateral otitis media with effusion clinical trials:* Adverse reactions (incidence at least 3%) with OTIPRIO vs sham were: nasopharyngitis (5% vs 4%), irritability (5% vs 3%), and rhinorrhea (3% vs 2%). *Acute otitis externa clinical trial:* Adverse reactions (incidence at least 2%) with OTIPRIO vs sham were: ear pruritus (2% vs 2%), headache (2% vs 1%), otitis media (2% vs 1%), and ear discomfort (2% vs 0%).

### USE IN SPECIFIC POPULATIONS

**Pediatric Use:** The safety and effectiveness of OTIPRIO in infants below six months of age have not been established for the treatment of pediatric patients with bilateral otitis media with effusion undergoing tympanostomy tube placement and acute otitis externa.

For more detailed information, please read the full Prescribing Information on page 57.

OTIPRIO® is a registered trademark of Otonomy, Inc.

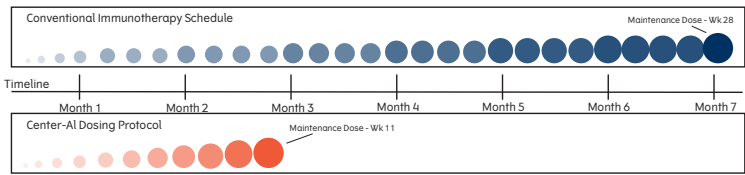


# Center-Al® (allergenic extracts, alum precipitated)

Center-Al® (allergenic extracts, alum precipitated) has been shown in studies to be an alternative treatment option for patients versus conventional aqueous extracts. The alum promotes slower absorption of allergen upon subcutaneous injection leading to prolonged antigenic stimulus and fewer reactions.<sup>4</sup> Center-Al is the only alum precipitated extract offered in the United States.

**Reduced Incidence of Reactions:** Clinical studies have shown that alum precipitated extracts result in fewer systemic reactions than aqueous extracts at comparable doses.<sup>1,2</sup>

**Dosing Protocol:** The product specifications recommend an 11 week build-up to reach maintenance which is quicker than most conventional immunotherapy schedules where the average build-up is 28 weeks or more.<sup>4</sup>



## SPECIES LIST FOR CENTER-AL®

Trees	Weeds	Grasses
Acacia	Cocklebur	Bahia
Alder, White	Lamb's Quarters	Bermuda
Ash, White	Mugwort	Johnson
Box Elder	Pigweed, Rough	Orchard
Birch, Black	Plantain, English	Rye, Perennial
Elm, American	Ragweed, Short	Timothy
Hickory, Shagbark	Ragweed, Western	
Maple, Sugar	Russian Thistle	
Mulberry, Red	Sheep Sorrel	
Oak, White		
Olive Tree		
Poplar, White		
Sycamore, American		
Walnut, Black		

### Clinical Evidence

In multiple studies, this product has shown clinical improvement with reduced adverse reactions compared to conventional aqueous extracts.<sup>1,2,3</sup>

### WARNING

This allergenic extract is intended for use by physicians who are experienced in the administration of allergenic extracts for immunotherapy and the emergency care of anaphylaxis, or for use under the guidance of an allergy specialist. These allergenic extracts are not directly interchangeable with allergenic extracts of the same labeled potency from different manufacturers. The patient must be re-evaluated with the newly selected extract. Patients being switched from other types of extracts such as aqueous extracts, glycerinated extract, or alum precipitated extracts from other suppliers to this allergenic extract should be started as though they were coming under treatment for the first time. Patients should be instructed to recognize adverse reaction symptoms and cautioned to contact the physician's office if reaction symptoms occur. As with all allergenic extracts, severe systemic reactions may occur. In certain individuals, these life-threatening reactions may be fatal. Patients should be observed for 20 to 30 minutes following treatment, and emergency measures, as well as personnel trained in their use, should be immediately available in the event of a life-threatening reaction. Sensitive patients may experience severe anaphylactic reactions resulting in respiratory obstruction, shock, coma and/or death. Patients with unstable asthma or steroid dependent asthmatics and patients with underlying cardiovascular disease are at greater risk to a fatal outcome from a systemic allergic reaction. If treated, these high risk patients should be started at lower (more conservative) doses and be progressed more slowly to a maintenance dose. Usually this is a lower dose than for those patients without these predispositions. (See DOSAGE AND ADMINISTRATION) This product should not be injected intravenously. Deep subcutaneous routes have proven to be safe. See the warnings, precautions, adverse reactions and overdose sections below. Patients receiving beta-blockers may not be responsive to epinephrine or inhaled bronchodilators. Respiratory obstruction not responding to parenteral or inhaled bronchodilators may require theophylline, oxygen, intubation and the use of life support systems. Parenteral fluid and/or plasma expanders may be utilized for treatment of shock. Adrenocorticosteroids may be administered parenterally or intravenously.

See full prescribing information provided on page 38 for complete warnings and indications.

1. Ransom, J.H, et. al. Ann. Allergy 29:635, 1971. 2. Nelson, H.S., et. al. Ann. Allergy 45:333, 1980. 3. Norman, P.S., et.al. J. Allergy Clin. Immunol. 50:31, 1972. 4. Center-Al® (allergenic extract, alum precipitated) Package Insert; 168G; Oct 2008.



# SUBLINGUAL IMMUNOTHERAPY TABLETS

RAGWITEK®  
GRASTEK®  
ODACTRA®

ODACTRA® is the first and only FDA-approved sublingual tablet for house dust mite–induced allergic rhinitis, with or without conjunctivitis.

ODACTRA® is available at pharmacies in 30 tablet packs. 5 tablet starter packs are available from your ALK Allergy Consultant.

Go to [ODACTRAHCP.com](http://ODACTRAHCP.com) to:

- Order Starter Packs for your office
- Obtain prior authorization support
- See the clinical data behind ODACTRA®
- Contact a representative for more information
- Access Savings Cards for your patients

Patients can go to [ODACTRA.com](http://ODACTRA.com) to learn more and obtain a savings offer.

ODACTRA is an allergen extract indicated as immunotherapy for house dust mite (HDM)-induced allergic rhinitis, with or without conjunctivitis, confirmed by in vitro testing for IgE antibodies to *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* house dust mites, or skin testing to licensed house dust mite allergen extracts. ODACTRA is approved for use in adults 18 through 65 years of age.

ODACTRA is not indicated for the immediate relief of allergic symptoms.

### Important Safety Information About ODACTRA

#### WARNING: SEVERE ALLERGIC REACTIONS

- ODACTRA can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction.
- Do not administer ODACTRA to patients with severe, unstable or uncontrolled asthma.
- Observe patients in the office for at least 30 minutes following the initial dose.
- Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use.
- ODACTRA may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction.
- ODACTRA may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers.

Please see full prescribing information on page 48.



GRASTEK® is the first and only FDA-approved sublingual tablet indicated for allergic rhinitis with or without conjunctivitis due to timothy grass or cross-reactive grass pollen.

GRASTEK® is indicated for children as young as 5 years.

GRASTEK® is available at pharmacies in 30 tablet packs. 5 tablet starter packs are available from your ALK Allergy Consultant.

Patients can go to [GRASTEK.com](http://GRASTEK.com) to learn more and obtain a savings offer.

GRASTEK is an allergen extract indicated as immunotherapy for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for Timothy grass or cross-reactive grass pollens. GRASTEK is approved for use in persons 5 through 65 years of age.

GRASTEK is not indicated for the immediate relief of allergic symptoms.

#### Selected Important Safety Information About GRASTEK

##### WARNING: SEVERE ALLERGIC REACTIONS

- GRASTEK can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction.
- Do not administer GRASTEK to patients with severe, unstable or uncontrolled asthma.
- Observe patients in the office for at least 30 minutes following the initial dose.
- Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use.
- GRASTEK may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction.
- GRASTEK may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers.

Please see full prescribing information on page 51.





**RAGWITEK®** is the first and only FDA-approved sublingual tablet to treat ragweed pollen allergies.

**RAGWITEK®** is available at pharmacies in 30 tablet packs. 5 tablet starter packs are available from your ALK Allergy Consultant.

Patients can go to [RAGWITEK.com](https://www.ragwitek.com) to learn more and obtain a savings offer.

RAGWITEK is an allergen extract indicated as immunotherapy for the treatment of short ragweed pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies for short ragweed pollens. RAGWITEK is approved for use in adults 18 through 65 years of age.

RAGWITEK is not indicated for the immediate relief of allergic symptoms.

#### Selected Important Safety Information About RAGWITEK

##### WARNING: SEVERE ALLERGIC REACTIONS

- RAGWITEK can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction.
- Do not administer RAGWITEK to patients with severe, unstable or uncontrolled asthma.
- Observe patients in the office for at least 30 minutes following the initial dose.
- Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use.
- RAGWITEK may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction.
- RAGWITEK may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers.

Please see full prescribing information on page 54.



**RAGWITEK®**  
Short Ragweed Pollen Allergen Extract  
Tablet for Sublingual Use 12 Amb a 1-U

# EXTRACTS

POLLEN  
POLLEN MIXES  
MOLD & FUNGI  
MOLD MIXES  
SMUT  
INSECTS  
EPIDERMAL  
FOODS

# POLLENS

Name <i>Latin Name</i>	Item #	Allergen Type	Premium 1 • Premium 2 ★	Skin Prick Diagnostic	Included in Mixes <sup>^</sup>	Formulation			
						Aqueous 1:10 w/v	Glycerin 1:20 w/v	Aqueous 40,000 PNU	Center-Al® (alum)
Acacia <i>Acacia dealbata</i>	ACAC	Tree	•	•			•		•
Alder, White <i>Alnus rhombifolia</i>	ALDE	Tree		•	•	•	•		•
Alfalfa <i>Medicago sativa</i>	ALFA	Cul. Crop	★	•			•		
Ash, Arizona (Velvet) <i>Fraxinus velutina</i>	ARAS	Tree	•			•			
Ash, White <i>Fraxinus americana</i>	ASH-	Tree		•	•	•	•	•	•
Bahia Grass <i>Paspalum notatum</i>	BAHI	Grass	•	•		•	•		•
Bayberry (Wax Myrtle) <i>Morella cerifera</i>	BAYB	Tree	•	•		•	•		
Beech, American <i>Fagus grandifolia</i>	BEEC	Tree	•	•		•	•		
Bermuda <i>Cynodon dactylon</i>	BERM	Grass			•				•
Birch, Black <i>Betula lenta</i>	BLBI	Tree		•	•	•			•
Birch, Red <i>Betula nigra</i>	REBI	Tree		•	•	•	•		
Birch, White <i>Betula verrucosa</i>	WHBI	Tree		•	•	•	•		
Box Elder <i>Acer negundo</i>	BOEL	Tree		•	•	•	•		•
Brome <i>Bromus inermis</i>	BROM	Grass	•	•	•		•		
Carelessweed <i>Amaranthus palmeri</i>	CARE	Weed		•		Available in Aqueous 1: 20 w/v and Glycerin 1:40 w/v			
Cedar, Mountain <i>Juniperus ashei</i>	MOCE	Tree		•		•	•		
Cedar, Red <i>Juniperus virginiana</i>	RECE	Tree		•		•	•		
Cocklebur <i>Xanthium strumarium</i>	COCK	Weed	•	•	•	•	•	•	•
Corn Pollen <i>Zea mays</i>	CORN	Cul. Crop		•			•		
Cottonwood, Eastern <i>Populus deltoides</i>	COWO	Tree		•	•	•	•		
Cottonwood, Western <i>Populus deltoides ssp. monilifera</i>	WECO	Tree	•	•		•	•		
Cypress, Arizona <i>Cupressus arizonica</i>	ARCY	Tree		•			•		
Cypress, Bald <i>Taxodium distichum</i>	BACY	Tree	•	•			•		
Dandelion <i>Taraxacum officinale</i>	DAND	Weed		•			•		
Dock, Yellow <i>Rumex crispus</i>	YEDO	Weed	•	•	•	•	•		

Product availability is subject to change without notice.

<sup>^</sup>Please see the full list of stock mixes & full list of Standardized products on page 22.

\* Center-Al products are available in 10,000 or 20,000 PNU.

Premium products carry a surcharge and will vary by premium level. Level 2 premium products carry a larger surcharge than level 1.



# POLLENS

Name <i>Latin Name</i>	Item #	Allergen Type	Premium 1 • Premium 2 ★	Skin Prick Diagnostic	Included in Mixes^	Formulation			
						Aqueous 1:10 w/v	Glycerin 1:20 w/v	Aqueous 40,000 PNU	Center-Al® (alum)
Dog Fennel <i>Eupatorium capillifolium</i>	DOFE	Weed	•	•			•		
Elm, American <i>Ulmus americana</i>	ELM-	Tree		•	•	•	•	•	•
Elm, Cedar <i>Ulmus crassifolia</i>	CEEL	Tree	★	•		•	•		
Elm, Chinese <i>Ulmus pumila</i>	CHEL	Tree	•	•			•		
Eucalyptus <i>Eucalyptus globulus</i>	EUCA	Tree	•	•		•	•		
Goldenrod <i>Solidago canadensis</i>	GOLD	Weed	•	•			•		
Hackberry <i>Celtis occidentalis</i>	HACK	Tree	•	•		•	•		
Hickory, Shagbark <i>Carya ovata</i>	HICK	Tree	•	•	•	•	•		•
Johnson Grass <i>Sorghum halepense</i>	JOHN	Grass		•	•	•	•	•	•
Juniper, Western <i>Juniperus occidentalis</i>	WEJU	Tree		•		•	•		
Kochia <i>Kochia scoparia</i>	KOCH	Weed		•	•	•	•	•	
Lamb's Quarters <i>Chenopodium album</i>	LAQU	Weed		•	•	•	•	•	•
Lenscale <i>Atriplex lentiformis</i>	LENS	Weed					•		
Maple, Red <i>Acer rubrum</i>	REMA	Tree		•	•		•		
Maple, Sugar <i>Acer saccharum</i>	MAPL	Tree	•	•	•	•	•	•	•
Marsh Elder, Burweed <i>Iva xanthifolia</i>	BUMA	Weed	•	•		•	•		
Marsh Elder, Rough <i>Iva annua</i>	ROMA	Weed		•		•	•	•	
Melaleuca <i>Melaleuca quinquenervia</i>	MELA	Tree	•	•			•		
Mesquite <i>Prosopis juliflora</i>	MESQ	Tree	•	•		•	•		
Mugwort <i>Artemisia vulgaris</i>	MUGW	Weed	•	•	•	•	•		•
Mulberry, Red <i>Morus rubra</i>	REMU	Tree		•		•	•		•
Mulberry, White <i>Morus alba</i>	WHMU	Tree		•		•	•		
Nettle <i>Urtica dioica</i>	NETT	Weed		•			•		
Oak, Red <i>Quercus rubra</i>	REOA	Tree		•	•		•		
Oak, Virginia Live <i>Quercus virginiana</i>	VILI	Tree		•	•	•	•		
Oak, White <i>Quercus alba</i>	OAK-	Tree		•	•	•	•	•	•
Olive Tree <i>Olea europaea</i>	OLIV	Tree		•			•		•
Orchard <i>Dactylis glomerata</i>	ORCH	Grass			•				•

# POLLENS

						Formulation			
Name <i>Latin Name</i>	Item #	Allergen Type	Premium 1 • Premium 2 ★	Skin Prick Diagnostic	Included in Mixes <sup>^</sup>	Aqueous 1:10 w/v	Glycerin 1:20 w/v	Aqueous 40,000 PNU	Center-AI® (alum)
Palm, Queen <i>Arecastrum romanzoffiana</i>	QUPA	Tree		•		•	•		
Pecan Pollen <i>Carya illinoensis</i>	PEPO	Tree		•	•	•	•		
Pepper Tree, California <i>Schinus molle</i>	CAPE	Tree	•	•			•		
Pigweed, Rough <i>Amaranthus retroflexus</i>	ROPI	Weed		•	•	•	•		•
Pigweed, Spiny <i>Amaranthus spinosus</i>	SPPI	Weed	•	•		•	•		
Pine, Australian <i>Casuarina equisetifolia</i>	AUPI	Tree	•	•		•	•		
Pine, Yellow <i>Pinus echinata</i>	YEPI	Tree		•			•		
Pine, White <i>Pinus strobus</i>	WHPI	Tree		•		•	•		
Plantain, English <i>Plantago lanceolata</i>	ENPL	Weed		•	•	•	•	•	•
Poplar, White <i>Populus alba</i>	POPL	Tree		•	•	•	•		•
Privet <i>Ligustrum vulgare</i>	PRIV	Tree	•	•		•	•		
Quack Grass <i>Elymus repens</i>	QUGR	Grass	•			•			
Ragweed, False <i>Ambrosia acanthicarpa</i>	FARA	Weed	•	•	•		•		
Ragweed, Short <i>Ambrosia artemisiifolia</i>	SHRA	Weed		•	•	•	•		•
Ragweed, Tall <i>Ambrosia trifida</i>	TARA	Weed		•	•	•	•		
Ragweed, Western <i>Ambrosia psilostachya</i>	WERA	Weed		•	•	•	•		•
Russian Thistle <i>Salsola kali</i>	RUTH	Weed	•	•	•	•	•		•
Rye, Perennial <i>Lolium perenne</i>	PERY	Grass			•				•
Sagebrush <i>Artemisia tridentata</i>	SAGE	Weed		•	•	•	•		
Sheep Sorrel <i>Rumex acetosella</i>	SHSO	Weed		•	•	•	•		•
Sweet Gum <i>Liquidambar styraciflua</i>	SWGU	Tree		•		•	•		
Sycamore, American <i>Platanus occidentalis</i>	SYCA	Tree		•	•	•	•		•
Timothy <i>Phleum pratense</i>	TIMO	Grass			•				•
Walnut, Black <i>Juglans nigra</i>	BLWA	Tree		•	•	•	•		•
Water Hemp, Western <i>Amaranthus tuberculatus</i>	WEWA	Weed	•	•		Available in Glycerin 1:40 w/v			
Willow, Black <i>Salix nigra</i>	BLWI	Tree	•	•	•	•	•		

Product availability is subject to change without notice.

<sup>^</sup>Please see the full list of stock mixes & full list of Standardized products on page 22.

\* Center-AI products are available in 10,000 or 20,000 PNU.

Premium products carry a surcharge and will vary by premium level. Level 2 premium products carry a larger surcharge than level 1.

# POLLEN MIXES

Name (Mix Components)	Item #	Allergen Type	Skin Prick Diagnostic	Non-Standardized**				
				Aqueous 1:10 w/v	Glycerin 1:20 w/v	Aqueous 20,000	Aqueous 40,000	Center-Al® (alum)
4 Weed Mix (Cocklebur, Rough Pigweed, English Plantain, Lamb's Quarters)	4WEE	Weed	•		•		•	•
Mixed Ragweed (Tall, Short)	MIRA	Weed	•	•	•	•	•	•
Western Weed Mix (Kochia, Sagebrush, Western Ragweed/False Ragweed, Russian Thistle)	WEWE	Weed						•
Sorrel/Dock Mix (Sheep Sorrel & Yellow Dock)	SODO	Weed	•		•			
Weed Mix 7B (Cocklebur, English Plantain, Lamb's Quarters, Mugwort, Rough Pigweed, Sheep Sorrel, Yellow Dock)	WE7B	Weed			•			
Weeds, Mixed (Cocklebur, Rough Marsh Elder, English Plantain, Lamb's Quarters)	MIWE	Weed	•		•			
5 Grass Mix (Timothy, Orchard, June, Redtop, Sweet Vernal)	5GRA	Grass						•
6 Grass Mix (Timothy, Orchard, June, Redtop, Meadow Fescue, Perennial Rye)	6GRA	Grass						•
7 Grass Mix (Timothy, Orchard, June, Redtop, Meadow Fescue, Perennial Rye, Sweet Vernal)	7GRA	Grass						•
8 Southern Grass Mix (Bermuda, Johnson, 6 grass mix)	8SGR	Grass						•
9 Southern Grass Mix (Bermuda, Johnson, 7 grass mix)	9SGR	Grass						•
Standardized Grasses, Midwest Mix (20% June, 20% Orchard, 20% Redtop, 40% Timothy)	STMW	Grass		Available in Glycerin 100,000 BAU				
9 Tree Mix (Alder, White Ash, Black Birch, American Elm, Shagbark Hickory, Maple (Sugar), White Oak, White Poplar, American Sycamore)	9TRE	Tree	•	•	•		•	•
10 Tree Mix (White Ash, Red Birch, Box Elder, Eastern Cottonwood, American Elm, Shagbark Hickory, Red Oak, American Sycamore, Black Walnut, Black Willow)	10TR	Tree			•			
Birch Mix (Red Birch, White Birch)	BIMI	Tree	•		•			
Hickory/Pecan Mix (Shagbark Hickory/Pecan Pollen)	HIPE	Tree	•	•	•			
Maple Mix (Red Maple, Box Elder)	MAMI	Tree	•		•			
Maple/Box Elder Mix (Sugar Maple, Box Elder)	MABO	Tree	•					
Oak Mix (Virginia Live, Red, White)	OAMI	Tree	•		•			

\*Center-Al products are available in 10,000 or 20,000 PNU.

\*\*Standardized Products on page 22.

Premium products carry a surcharge and will vary by premium level. Level 2 premium products carry a larger surcharge than level 1.

Product availability is subject to change without notice. Mixes are equal parts unless otherwise specified.



## MOLDS & FUNGI

Name (Alternate Name/previous nomenclature)	Item #	Skin Prick Diagnostic	Formulation	
			Aqueous (1:10 w/v)*	Glycerin (1:20 w/v)*
<i>Alternaria alternata</i> ( <i>Alternaria alternata</i> / <i>Alternaria tenuis</i> )	ALTE	•	•	•
<i>Aspergillus fumigatus</i>	ASFU	•	•	•
<i>Aureobasidium pullulans</i> ( <i>Pullularia pullulans</i> )	AURE	•	•	•
<i>Bipolaris sorokiniana</i> ( <i>Bipolaris sorokiniana</i> or <i>Helminthosporium sativum</i> / <i>Drechslera sorokiniana</i> )	BIPO	•	•	•
<i>Botrytis cinerea</i>	BOTR	•	•	•
<i>Candida albicans</i>	CAAL	•	•	•
<i>Cladosporium cladosporioides</i> ( <i>Hormodendrum cladosporioides</i> )	CLCL	•	•	•
<i>Epicoccum nigrum</i> ( <i>Epicoccum purpurascens</i> )	EPIC	•	•	•
<i>Gibberella pulicaris</i> ( <i>Fusarium roseum</i> )	GIBB	•	•	•
<i>Mucor plumbeus</i>	MUCO	•	•	•
<i>Penicillium notatum</i>	PENO	•	•	•
<i>Rhodotorula mucilaginosa</i> ( <i>Rhodotorula rubra</i> )	RHOD	•	•	•
<i>Saccharomyces cerevisiae</i> (Yeast)	SACC	•		•
<i>Sarocladium strictum</i> ( <i>Sarocladium strictum</i> / <i>Acremonium strictum</i> )	SARO	•	•	•
<i>Trichophyton mentagrophytes</i>	TRME	•	•	•

## MOLD MIXES

Name (Mix Components)	Item #	Skin Prick Diagnostic	Formulation	
			Aqueous (1:10 w/v)*	Glycerin (1:20 w/v)*
Mold Mix A ( <i>Alternaria</i> , <i>Aspergillus</i> , <i>Cladosporium</i> , <i>Penicillium</i> )	MOMA	•	•	•
Mold Mix B ( <i>Epicoccum</i> , <i>Gibberella</i> , <i>Mucor</i> )	MOMB	•	•	•

## SMUT

Name Latin Name	Item #	Allergen Type	Premium	Skin Prick Diagnostic	Formulation		
					Glycerin 1:10 w/v	Glycerin 1:20 w/v	Aqueous 1:10 w/v
Corn Smut <i>Ustilago maydis</i>	COSM	Smut	•			•	

\*The PNU value for aqueous mold extracts can be found on the vial labels, while PNU values for glycerinated mold extracts can be obtained by contacting Sales Support at 1-800-325-7354.

For additional information please contact Medical Scientific Affairs (1-855-782-9323 or [science@alk.net](mailto:science@alk.net)).

# INSECTS

Name <i>Latin Name/(Mix Comp.)</i>	Item #	Allergen Type	Premium 1	Skin Prick Diagnostic	Formulation		
					Aqueous 1:10 w/v	Glycerin 1:20 w/v	Glycerin 1:100 w/v
Ant, Fire <i>Solenopsis invicta</i>	FIAN	Insect	•	•	•	•	
Cockroach, American <i>Periplaneta americana</i>	AMCO	Insect	•	•		•	
Cockroach, German <i>Blattella germanica</i>	GECO	Insect	•	•		•	
Cockroach, Mixed (American, German)	MICO	Insect	•	•		•	
Mosquito <i>Culex pipiens</i>	MOSQ	Insect	•	•			•

# EPIDERMAL

Name <i>Latin Name/(Mix Comp.)</i>	Item #	Allergen Type	Premium 1 • Premium 2 ★	Skin Prick Diagnostic	Formulation				
					Glycerin 1:10 w/v	Glycerin 1:20 w/v	Aqueous 1:10 w/v	Aqueous 10,000 PNU	Aqueous 20,000 PNU
Cattle Epithelium <i>Bos taurus</i>	COEP	Epidermal	•	•		•			
Dog Epithelium <i>Canis lupus familiaris</i>	DOEP	Epidermal		•	•	•	•	•	•
Feather, Mixed (Chicken, Duck, Goose)	MIFE	Epidermal		•	•	•			
Guinea Pig Epithelium <i>Cavia porcellus</i>	GUIN	Epidermal	★	•		•			
Horse Epithelium <i>Equus caballus</i>	HOEP	Epidermal	•	•	•	•			
Mouse Epithelium <i>Mus musculus</i>	MOEP	Epidermal	★	•		•			
Rabbit Epithelium <i>Oryctolagus cuniculus</i>	RABB	Epidermal	•	•	•	•			

Premium products carry a surcharge and will vary by premium level. Level 2 premium products carry a larger surcharge than level 1. Product availability is subject to change without notice.

# FOODS

Name <i>Latin Name</i>	Item #	Diagnostic Only	
		Glycerin 1:10 w/v	Glycerin 1:100 w/v
Almond <i>Prunus dulcis</i>	ALMO	•	
Apple <i>Malus domestica</i>	APPL	•	
Apricot <i>Prunus armeniaca</i>	APRI	•	
Asparagus <i>Asparagus officinalis</i>	ASPA	•	
Avocado <i>Persea americana</i>	AVOC	•	
Banana <i>Musa sapientum</i>	BANA	•	
Barley <i>Hordeum vulgare</i>	BARL	•	
Bean, Kidney <i>Phaseolus vulgaris</i>	KIBE	•	
Bean, String Green <i>Phaseolus vulgaris</i>	STRI	•	
Beef <i>Bos taurus</i>	BEEF	•	
Brazil Nut <i>Bertholletia excelsa</i>	BRNU	•	
Broccoli <i>Brassica oleracea</i> var. <i>botrytis</i>	BROC	•	
Buckwheat <i>Fagopyrum esculentum</i>	BUCK	•	
Cabbage <i>Brassica oleracea</i> var. <i>capitata</i>	CABB	•	
Cantaloupe <i>Cucumis melo</i> <i>cantalupensis</i>	CANT	•	
Carrot <i>Daucus carota</i>	CARR	•	
Casein <i>Bos taurus</i>	CASE		•
Celery <i>Apium graveolens</i>	CELE	•	
Cherry <i>Prunus avium</i>	CHER	•	
Chicken <i>Gallus gallus</i>	CHIC	•	
Cinnamon <i>Cinnamomum verum</i>	CINN	•	
Clam <i>Mercenaria mercenaria</i>	CLAM	•	
Cocoa Bean (Chocolate) <i>Theobroma cacao</i>	COBE	•	
Coconut <i>Cocos nucifera</i>	COCO	•	
Codfish <i>Gadus morhua</i>	CODF	•	
Coffee <i>Coffea arabica</i>	COFF	•	
Corn, Sweet <i>Zea mays</i>	SWCO	•	
Crab Meat, King Crab <i>Paralithodes</i> <i>camtschatica</i>	CRAB	•	

All food products come in 5 mL dropper vials.

Name <i>Latin Name/(Mix Comp.)</i>	Item #	Diagnostic Only	
		Glycerin 1:10 w/v	Glycerin 1:100 w/v
Cucumber <i>Cucumis sativus</i>	CUCU	•	
Egg, Whole (Chicken) <i>Gallus gallus</i>	EGG-		•
Egg, White (Chicken) <i>Gallus gallus</i>	EGWH		•
Egg, Yolk (Chicken) <i>Gallus gallus</i>	EGYO		•
Fish Mix (Flounder, Codfish, Halibut)	MIFI	•	
Flounder <i>Pleuronectes glacialis</i>	FLOU	•	
Garlic <i>Allium sativum</i>	GARL	•	
Grapes, White Seedless <i>Vitis vinifera</i>	VITI	•	
Grapefruit <i>Citrus X paradisi</i>	GRAP	•	
Halibut <i>Hippoglossus</i> <i>hippoglossus</i>	HALI	•	
Honeydew <i>Cucumis melo</i>	HONE	•	
Lamb <i>Ovis aries</i>	LAMB	•	
Lemon <i>Citrus X limon</i>	LEMO	•	
Lettuce <i>Lactuca sativa</i>	LETT	•	
Lima Bean <i>Phaseolus lunatus</i>	LIBE	•	
Lobster <i>Homarus americanus</i>	LOBS	•	
Milk, Goat <i>Capra aegagrus hircus</i>	GOMI	•	
Milk, Whole Cow's <i>Bos taurus</i>	COMI	•	
Mushroom <i>Agaricus campestris</i>	MUSH	•	
Mustard <i>Sinapis alba</i>	MUST	•	
Oat Grain <i>Avena sativa</i>	OAGR	•	
Olive <i>Olea europaea</i>	OLIF	•	
Onion <i>Allium cepa</i>	ONIO	•	
Orange <i>Citrus X sinensis</i>	ORAN	•	
Oyster <i>Crassostrea virginica</i>	OYST	•	
Pea, Green (English) <i>Pisum sativum</i>	GRPE	•	
Peach <i>Prunus persica</i>	PEAC	•	
Peanut <i>Arachis hypogaea</i>	PEAN	•	
Pear <i>Pyrus communis</i>	PEAR	•	
Pecan <i>Carya illinoensis</i>	PENU	•	

# FOODS

Name <i>Latin Name / (Mix Comp.)</i>	Item #	Diagnostic Only	
		Glycerin 1:10 w/v	Glycerin 1:100 w/v
Pepper, Bell (Green) <i>Capsium annuum</i>	BEPE	•	
Pepper, Black <i>Piper nigrum</i>	BLPE	•	
Pineapple <i>Ananas comosus</i>	PINE	•	
Pistachio Nut <i>Pistacia vera</i>	PINU	•	
Plum <i>Prunus domestica</i>	PLUM	•	
Pork <i>Sus scrofa</i>	PORK	•	
Potato, Sweet <i>Ipomoea batatas</i>	SWPO	•	
Potato, White <i>Solanum tuberosum</i>	WPOT	•	
Rice <i>Oryza sativa</i>	RICE	•	
Rye Grain <i>Secale cereale</i>	RYGR	•	
Salmon <i>Salmo salar</i>	SALM	•	
Sesame Seed <i>Sesamum indicum</i>	SESE	•	
Shellfish, Mixed (Crab, Shrimp, Lobster, Oyster)	MISH	•	
Shrimp <i>Crangon crangon</i>	SHRI	•	
Soybean <i>Glycine max</i>	SOYB	•	
Spinach <i>Spinacia oleracea</i>	SPIN	•	
Squash, Zucchini <i>Cucurbita pepo</i>	SQUA	•	
Strawberry <i>Fragaria X ananassa</i>	STRA	•	
Tea <i>Thea sinensis</i>	THSI	•	
Tomato <i>Solanum lycopersicum</i>	TOMA	•	
Tuna <i>Thunnus thynnus</i>	TUNA	•	
Turkey Meat <i>Meleagris gallopavo</i>	TURK	•	
Vanilla <i>Vanilla planifolia</i>	VANI	•	
Walnut, English <i>Juglans regia</i>	ENWF	•	
Watermelon <i>Citrullus lanatus</i>	WATE	•	
Wheat Grain <i>Triticum aestivum</i>	WHGR	•	

All food products come in 5 mL dropper vials.

# STANDARDIZED EXTRACTS

POLLEN  
POLLEN MIXES  
EPIDERMAL  
MITES



## POLLEN

Name <i>Latin Name</i>	Item #	Allergen Type	Premium 1 •	Skin Prick Diagnostic	Included in Mixes	Formulation			
						Standardized 10,000 BAU	Standardized 100,000 BAU	Aqueous 1:10 w/v	Glycerin 1:20 w/v
Bermuda <i>Cynodon dactylon</i>	STBE	Grass		•		•			
June (Kentucky Blue) <i>Poa pratensis</i>	STJU	Grass		•	•		•		
Meadow Fescue <i>Festuca pratensis</i>	STMF	Grass		•	•		•		
Orchard <i>Dactylis glomerata</i>	STOR	Grass		•	•		•		
Ragweed, Short <i>Ambrosia artemisiifolia</i>	SHRA	Weed		•	•			•	•
Redtop <i>Agrostis alba</i>	STRT	Grass		•	•		•		
Rye, Perennial <i>Lolium perenne</i>	STPR	Grass		•	•		•		
Sweet Vernal <i>Anthoxanthum odoratum</i>	STSV	Grass	•	•	•		•		
Timothy <i>Phleum pratense</i>	STTI	Grass		•	•		•		

## POLLEN MIXES

Name <i>(Mix Components)</i>	Item #	Allergen Type	Skin Prick Diagnostic	Standardized
				Glycerin 100,000 BAU
Standard Grass Mix #4-S <i>(June, Orchard, Red Top, Timothy)</i>	GR4S	Grass	•	•
5 Standard Grass Mix <i>(Timothy, Orchard, June, Redtop, Sweet Vernal)</i>	ST5G	Grass	•	•
6 Standard Grass Mix <i>(Timothy, Orchard, June, Redtop, Meadow Fescue, Perennial Rye)</i>	ST6G	Grass	•	•
7 Standard Grass Mix <i>(Timothy, Orchard, June, Redtop, Meadow Fescue, Perennial Rye, Sweet Vernal)</i>	ST7G	Grass	•	•
Standardized Grasses, Midwest Mix <i>(20% June, 20% Orchard, 20% Redtop, 40% Timothy)</i>	STMW	Grass		•

## EPIDERMAL

Name <i>Latin Name</i>	Item #	Allergen Type	Skin Prick Diagnostic	Standardized
				Glycerin 10,000 BAU
Cat Hair <i>Felis catus</i>	STCH	Epidermal	•	•

## MITES

Name <i>Latin Name/ (Mix Comp.)</i>	Item #	Allergen Type	Skin Prick Diagnostic	Formulation	
				Standardized	Glycerin 10,000 AU
Dust Mite <i>D. farinae</i>	STDF	Mite	•	•	•
Dust Mite <i>D. pteronyssinus</i>	STDP	Mite	•	•	•
Mite, Mixed <i>(D. farinae &amp; D. pteronyssinus)</i>	STMM	Mite	•	•	•

# ANCILLARY SUPPLIES & DIAGNOSTICS

DILUENTS

STERILE EMPTY VIALS

NON STERILE VIALS & MISC

DIAGNOSTIC CONTROLS, DEVICES, WELLS & TRAYS

SYRINGES

TRAYS

# DILUENTS

Some Ancillary products are available with different color vial seals (noted below). Actual color selection may vary by item. Contact Sales Support for specific product availability.

Colors available: R = red, Y = gold, G = green, O = orange, P = pink, V = purple, B = blue.

The last letter of the part number where color options are available determines the seal color.  
For instance: HSA4020S is HSA 4.0 mL with a Silver seal; HSA4020R is HSA 4.0 ml with a Red seal.

## Normal Saline with Phenol (NSP)

Item#	Volume	Vial Size	Quantity
NSP2020S	2.0 mL	20 mm x 22 mm	25
NSP4020S	4.0 mL	20 mm x 22 mm <i>*Various Colors Available</i>	25
NSP4520S	4.5 mL	20 mm x 22 mm <i>*Various Colors Available</i>	25
NSP8020S	8.0 mL	20 mm x 22 mm	25
NSP9020S	9.0 mL	20 mm x 22 mm <i>*Various Colors Available</i>	25
NSP30	30 mL	20 mm x 29 mm (Tall)	1
NSP50	50 mL	20 mm x 40 mm	1
NSP100	100 mL	20 mm x 52 mm	1

## 50% Glycerin

Item#	Volume	Vial Size	Quantity
GLY4020	4.0 mL	20 mm x 22 mm	25
GLY8020	8.0 mL	20 mm x 22 mm	25
GLY100	100 mL	20 mm x 52 mm	1

## Albumin Saline with Phenol (HSA)

Item#	Volume	Vial Size	Quantity
HSA1813	1.8 mL	13 mm x 14 mm (2-13 Vial)	100
HSA1820	1.8 mL	20 mm x 22 mm (5-20 Vial)	100
HSA1820SINGLE	1.8 mL	20 mm x 22 mm (5-20 Vial)	1
HSA4020S	4.0 mL	20 mm x 22 mm <i>*Various Colors Available</i>	25
HSA4520S	4.5 mL	20 mm x 22 mm <i>*Various Colors Available</i>	25
HSA8020S	8.0 mL	20 mm x 22 mm	25
HSA9020S	9.0 mL	20 mm x 22 mm <i>*Various Colors Available</i>	25
HSA30	30 mL	20 mm x 36.5 mm	1
HSA100	100 mL	20 mm x 52 mm	1

# STERILE EMPTY VIALS (SEV)

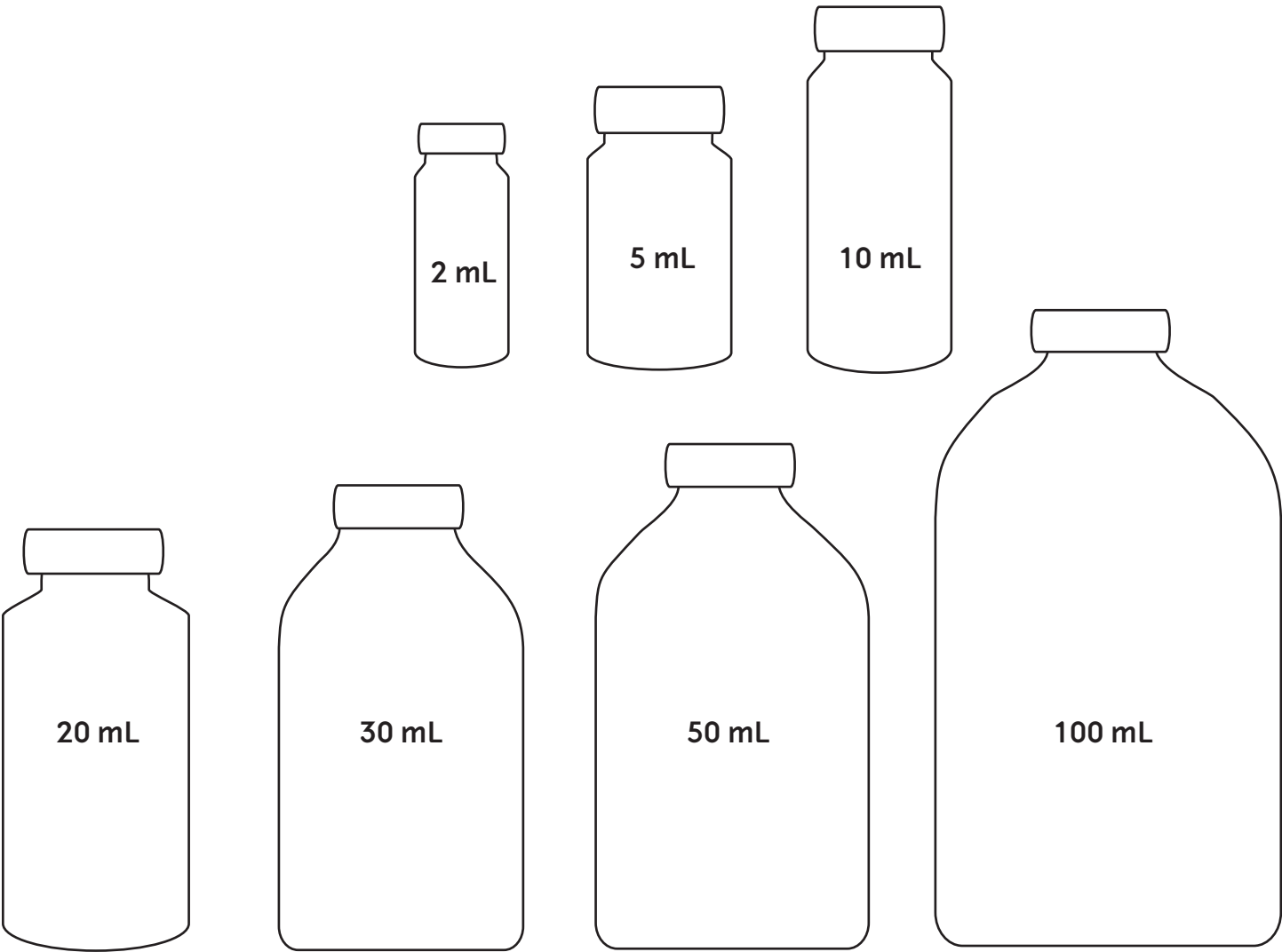
Item#	Volume	Vial Size	Quantity
SEV213	2.0 mL	14 mm x 13 mm	100
SEV520S	5.0 mL	20 mm x 22 mm <i>*Various Colors Available</i>	25
SEV1020S	10 mL	20 mm x 22 mm <i>*Various Colors Available</i>	25
SEV20	20 mL	20 mm x 30 mm	10
SEV30	30 mL	20 mm x 36.5 mm	25
SEV50	50 mL	20 mm x 40 mm	25
SEV100	100mL	20 mm x 52 mm	25



ITEM #SEV1020S  
10 ML 20 MM X 22 MM

ITEM #SEV100  
100 ML 20 MM X 52 MM

## SEV SIZE CHART



SEV and AMBER SEV sizes are the same, included here and on page 27.

## AMBER STERILE EMPTY VIALS (SEV)

Item#	Volume	Vial Size	Quantity
SEV213S-AMB	2.0 mL	14 mm x 12 mm	100
SEV520S-AMB	5.0 mL	20 mm x 22 mm	25
SEV1020S-AMB	10 mL	20 mm x 22 mm	25
SEV30-AMB	30 mL	20 mm x 36.5 mm	25
SEV50-AMB	50 mL	20 mm x 40 mm	25
SEV100-AMB	100 mL	20 mm x 52 mm	25



ITEM #SEV100-AMB  
100 ML 20 MM X 52 MM

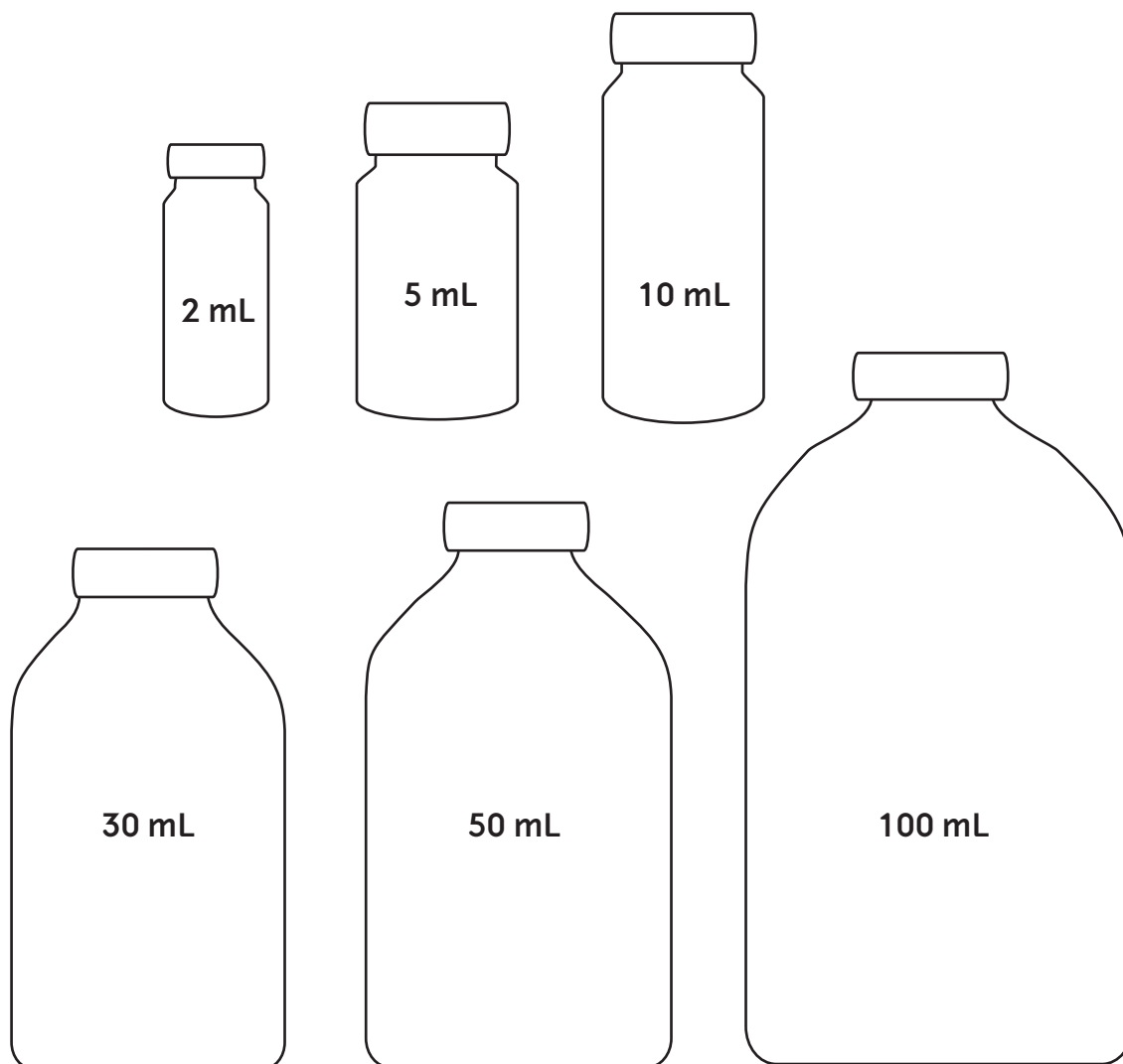


ITEM #SEV1020S-AMB  
10 ML 20 MM X 22 MM



ITEM #SEV213-AMB  
2 ML 14 MM X 12 MM

## AMBER SEV SIZE CHART



AMBER SEV and SEV sizes are the same, included here and on page 26.



# NON-STERILE VIALS AND MISC.

## Labels

Item#	Description
80467	Titration Labels
80230	Vial Labels, Roll of 1,000 Blue
80232	Vial Labels, Roll of 1,000 Yellow
80235	Vial Labels, Roll of 1,000 Green
80250	Vial Labels, Roll of 1,000 Red
LABELS-2	Vial Labels, Roll of 1,000 White



ITEMS #80230, #80232, #80235, #80250  
VIAL LABELS

## Non-sterile Vials & Dropper Tips

Item#	Description	Quantity
80138	4 mL Glass Dropper Tip	144
80139	4 mL Glass Screw Top Bottle	144
80151	5 mL Glass Dropper Tip	144
80152	5 mL Glass Screw Top Bottle	144
80142	7/10 mL Plastic Tip	144
80143	7/10 mL Plastic Cap	144
80144	7 mL Plastic Bottle	144
80157	10 mL Plastic Bottle	144
80148	10 mL Glass Dropper Tip	144
80149	10 mL Glass Screw Top Bottle	144
80153	15 mL Glass Dropper Tip	144
80154	15 mL Glass Screw Top Bottle	144



ITEM #80143  
7/10 ML PLASTIC CAP



ITEM #80138  
4 ML GLASS DROPPER TIP

ITEM #80151  
5 ML GLASS DROPPER TIP



ITEM #80154  
15 ML GLASS DROPPER VIAL



ITEM #80149  
10 ML GLASS DROPPER VIAL



ITEM #80152  
5 ML GLASS DROPPER VIAL



ITEM #80139  
4 ML GLASS DROPPER VIAL



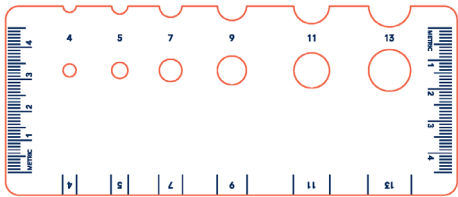
ITEM #80153  
15 ML GLASS DROPPER TIP

ITEM #80148  
10 ML GLASS DROPPER TIP

# NON-STERILE VIALS AND MISC.

## Information Sheets & Misc Items

Item#	Description
80475	Reaction Guides, Pack of 50
80474	Cold Packs
80472	Patient History Forms, Order Forms
06XB399999	Mailing Boxes, 6 x 10 mL (for 20 mm base)
04XB399999	Mailing Boxes, 4 x 10 mL (for 20 mm base)
BOXX399999	Boxes, 100 X 10 mL, with partitions (for 20 mm base)



ITEM #80475  
REACTION GUIDES

ITEM #06XB399999  
MAILING BOXES 6 X 10 ML



ITEM #04XB399999  
MAILING BOXES 4 X 10 ML

## Colored Caps for Vials (13 mm)

Item#	Color	Quantity
80405	Dark Blue	100
80415	Green	100
80425	Orange	100
80430	Pink	100
80435	Purple	100
80440	Red	100
80455	Yellow	100

## Colored Caps for Vials (20 mm)

Item#	Color	Quantity
80432	Dark Blue	144
80416	Green	144
80426	Orange	144
80431	Pink	144
80457	Purple	144
80441	Red	144
80456	Yellow	144



ITEMS #80405, #80415, #80425, #80430, #80435, #80440, #80455  
COLORED CAPS FOR VIALS 13 MM

# DIAGNOSTIC CONTROLS, DEVICES, WELLS & TRAYS

The Multi-Test® and Multi-Test® PC are indicated for the percutaneous administration of diagnostic allergenic extracts. These medical devices are sterile, disposable, multiple test head applicators used to administer skin test substances. When used to apply allergenic extracts it provides, a quick, convenient, and standardized procedure. Multi-Test PC is the latest addition to the Multi-Test family.

Duotip-Test® II is a sterile, disposable, plastic bifurcated needle used to administer skin test substances. When employed with allergenic extracts, it provides a quick, convenient, and standardized procedure that is well accepted by patients. Before using Duotip-Test II, or any testing device, the administrator must carefully study the package inserts accompanying allergenic extracts and control solutions.

## Diagnostic Controls

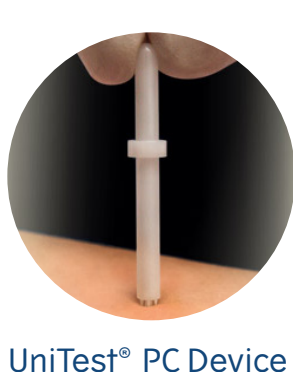
Item#	Description	Vial Size	Diagnostic
DILU15	Aqueous Control	5 mL Multi-Dose	Intradermal Testing
DILU14	Glycerin Control 50%	5 mL Dropper	Scratch Testing
HIST15*	Histatrol® (histamine phosphate), 0.1 mg/mL	5 mL Multi-Dose	Intradermal Testing
HIST14*	Histatrol® (histamine phosphate), 1.0 mg/mL	5 mL Dropper	Scratch Testing

Note: The term "scratch testing" is a common term that generally refers to percutaneous skin testing.

\*For intradermal skin testing, the product is a sterile solution that contains 0.1 mg/mL histamine base (0.275 mg/mL histamine phosphate). For percutaneous skin testing, the product is a sterile solution that contains 1 mg/mL histamine base (2.75 mg/mL histamine phosphate).

## Skin Testing Systems

Item#	Description
MUDB	Multi-Test II Devices, Box of 6
MUDE	Multi-Test II Devices, Bulk Cases of 600 (12 Trays of 50)
MTPB	Multi-Test PC Devices, Box of 6
MTPC	Multi-Test PC Devices, Bulk Cases of 600 (12 Trays of 50)
MUPK	Multi-Test II Devices, Promotional Starter Kit (5 boxes of devices, 1 Dipwell® tray)
MUTC	Multi-Test II Devices, Dipwell Tray with Lid, Capped Wells
MUTP	Multi-Test II Devices, Trial Pack (25 boxes of devices, 2 Dipwell trays)
MUTT	Multi-Test II Devices, Tote Tray (stackable)
UTPC	UniTest PC Devices, Box of 400
DT2D	Duotip-Test II Devices, Box of 400
DT2KP	Duotip-Test II Devices, Promotional Starter Kit (1 box of devices, 1 Dipwell tray, 1 pack of wells, recording forms, tray labels)
DT2K3	Duotip-Test II Devices, Starter Kit (3 boxes of devices, 2 Dipwell trays, 2 packs of wells, recording forms, tray labels)
DT2T	Duotip-Test II Devices, Dipwell Tray (40 wells)
DT2W	Duotip-Test II Devices, Wells (Pack of 40)



# SYRINGES

## Safety Syringes

Item#	Volume	Needle Size	Description	Quantity	Manufact	Manufact Part #	Manufact Packaging
SYR80407	1.0 mL	25 G x 5/8"	Safety Glide Reg. Bevel	400	BD	305903	8 boxes of 50 (individually wrapped)
SYR80395	1.0 mL	26 G x 3/8"	Safety Glide ID Bevel	1,000	BD	305951	40 trays of 25
SYR80394	1.0 mL	27 G x 1/2"	Safety Glide Reg. Bevel	1,000	BD	305950	40 trays of 25
SYR80428	1.0 mL	27 G x 1/2"	Safety Allergy Tray	1,000	SOL-M	181027T	40 trays of 25

## Standard Syringes

Item#	Volume	Needle Size	Description	Quantity	Manufact	Manufact Part #	Manufact Packaging
SYR80345	0.5 mL	27 G x 1/2"	Reg. Bevel	1,000	BD	305535	40 trays of 25
SYR80365	0.5 mL	27 G x 3/8"	ID Bevel	1,000	BD	305536	40 trays of 25
SYR80355	1.0 mL	26 G x 1/2"	ID Bevel	1,000	BD	305538	40 trays of 25
SYR80350	1.0 mL	26 G x 1/2"	Reg. Bevel	1,000	BD	305537	40 trays of 25
SYR80360	1.0 mL	26 G x 3/8"	ID Bevel	1,000	BD	305539	40 trays of 25
SYR80370	1.0 mL	27 G x 1/2"	Reg. Bevel	1,000	BD	305540	40 trays of 25
SYR80427	1.0 mL	27 G x 1/2"	Non-Safety Allergy Tray	1,000	SOL-M	181027T	40 trays of 25
SYR80375	1.0 mL	27 G x 3/8"	ID Bevel	1,000	BD	305541	40 trays of 25
SYR80340	1.0 mL	27 G x 3/8"	Reg. Bevel	1,000	BD	305542	40 trays of 25
SYR80405	1.0 mL	28 G x 1/2"	Monoject Perm. Attached Reg. Bevel	1,000	Kendall	501236	40 trays of 25
SYR80378	5.0 mL	22 G x 1"	Luer-Lock Reg. Bevel	400	BD	309630	4 boxes of 100 (individually wrapped)
SYR80349	10.0 mL	20 G x 1"	Luer-Lock Reg. Bevel	400	BD	309644	4 boxes of 100 (individually wrapped)

## Mixing Syringes

Item#	Volume	Needle Size	Description	Quantity	Manufact	Manufact Part #	Manufact Packaging
SYR80429	1.0 mL	23 G x 1/2"	Mixing Tray	1,000	SOL-M	181023T	40 trays of 25

Note - Syringes available may vary and are not exclusive to the types listed above, please call Sales Support for more information.

# TRAYS

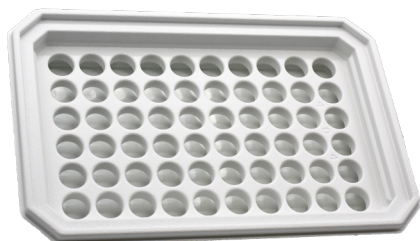
Item#	Description	Dimensions in inches (L x W x H)
80300	Vial Trays for 18 mm and 22 mm base vials, 48 holes (6x8)	10" x 7 1/4" x 1"
80301	Vial Trays for 18 mm and 22 mm base vials, 60 holes (6x10)	12" x 7 1/4" x 1"
80322	Rachman Tray, Large #202, 13 mm base vials, 84 holes	
80323	Rachman Tray, Large #303, 13 mm base vials, 70 holes	
80324	Rachman Tray, Large #404, 22 mm base vials, 60 holes	
80328	Rachman Tray, Large #808, 18 holes	
80185	Lucite Tray, 22 mm base vials, 5 - 10 mL, 60 holes	11" x 7" x 1/2"
80329	Syringe Tray (18 places)	
80290	Rondo Tray, 13 mm base vials, 6 holes	
80291	Rondo Box Only, 13 mm base vials, 6 holes	
80296	Rondo Box Only, 13 mm base vials, 10 holes	



ITEM #80322  
RACHMAN TRAY, LARGE #202



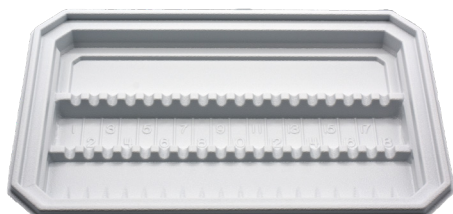
ITEM #80323  
RACHMAN TRAY, LARGE #303



ITEM #80324  
RACHMAN TRAY, LARGE #404



ITEM #80328  
RACHMAN TRAY, LARGE #808



ITEM #80329  
SYRINGE TRAY, 18 PLACE



ITEM # 80300 & #80301  
VIAL TRAYS FOR 18 MM AND 22 MM BASE VIALS, 48 & 60



# PACKAGE INSERTS

All package inserts are current at the time of printing, but are subject to change.  
Contact ALK at 800-325-7354 with any questions.

ALLERGENIC EXTRACTS,  
FOR DIAGNOSTIC USE ONLY  
DIRECTIONS FOR USE

WARNING

This product is intended for use by physicians who are experienced in the administration of allergenic extracts and the emergency care of anaphylaxis, or for use under the guidance of an allergy specialist.

As with all allergenic extracts, severe systemic reactions may occur. In certain individuals these life-threatening reactions may result in death. Fatalities associated with skin testing have been reported. Patients should be observed for at least 20 - 30 minutes following testing. Emergency measures and adequately trained personnel should be immediately available in the event of a life-threatening reaction.

Patients with unstable asthma or steroid dependent asthmatics and patients with underlying cardiovascular disease are at greater risk to a fatal outcome from a systemic allergic reaction.

Sensitive patients may experience severe anaphylactic reactions resulting in respiratory obstruction, shock, coma and/or death. Adverse events are to be reported to MedWatch (1-800-FDA-1088), Adverse Event Reporting, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852-9787. This product should not be injected intravenously. Patients receiving beta blockers may not be responsive to epinephrine or inhaled bronchodilators. Respiratory obstruction not responding to parenteral or inhaled bronchodilators may require theophylline, oxygen, intubation and the use of life support systems. Parenteral fluid and/or plasma expanders may be utilized for the treatment of shock. Adrenocorticosteroids may be administered parenterally or intravenously. Refer to WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections below.

Port Washington, NY 11050

US Government License No. 1256

DESCRIPTION

Sterile diagnostic extracts are supplied in either phenol-saline diluent for Intradermal Testing or in diluent containing glycerin 50% (v/v) for Percutaneous Testing and phenol 0.4% (preservative). Inactive ingredients may include: sodium chloride for isotonicity, glycerin, and sodium bicarbonate as a buffer.

Pollens are individually extracted from pure pollen extracted in a phenol-preserved sodium bicarbonate solution. Short Ragweed and Mixed (Tall and Short) Ragweed extracts are standardized by Antigen E content and so labeled. The Antigen E content of extracts containing Short Ragweed at a concentration more dilute than a weight/volume ratio of 1:10 are obtained by calculating the Antigen E content based on the assay value of more concentrated extract. Pollen extracts are filtered aseptically and after final packaging, they are tested for sterility and safety. Molds are individually extracted from pure powdered inactivated mold source material extracted in phenol preserved saline. Mold extracts are filtered aseptically and after final packaging are tested for sterility and safety. Molds (fungi) are present in all inhabited places at all seasons of the year; they are so ubiquitous that they are prevalent at times when common allergic pollens and other inhalants are not. In the home and surroundings, molds are found in upholstered furniture, mattresses, drapes, cellar and storage room dust, woollens, leather goods, fruits, meats, cheeses, garden soil and on plants. Spores, mycelial fragments and mold residues are thus inhaled, contacted and ingested continuously.

Foods, miscellaneous inhalants and epidermals are individually extracted in phenol preserved saline or glycerin, filtered aseptically and after final packaging are tested for sterility and safety.

CLINICAL PHARMACOLOGY

Diagnostically (for skin testing) the allergen combines with IgE antibodies fixed to mast cells in the skin. This complexing causes an increase in cellular permeability and degranulation of the mast cells releasing chemical mediators. These mediators (such as histamine) are responsible for a local inflammatory response of wheal and erythema typical of a positive skin test reaction and also, the symptoms commonly associated with allergic disease.<sup>1</sup> The more mediator release, the larger the reaction (wheal and erythema).

INDICATIONS AND USAGE

These products are for diagnostic use only. Diagnostic allergenic extracts are indicated for use in skin testing to establish the clinical relevance of specific allergens to which the patient has been exposed. By measuring skin test response the physician may assess the degree of sensitivity that patients have to the allergens. For extracts standardized in AU and BAU, see individual directions for use. Allergenic extracts for diagnostic use only of coffee, mosquito, cottonseed, and flaxseed have not been shown by adequate data to be safe and effective for therapeutic use.

CONTRAINDICATIONS

Patients on beta blockers can be non-responsive to beta agonists that may be required to reverse a systemic reaction (also, see boxed WARNING statement and ADVERSE

REACTIONS). The physician should carefully weigh the benefit derived from skin testing vs. the risk to the patient should a systemic reaction arise.

Patients with unstable asthma or steroid dependent asthmatics and patients with underlying cardiovascular disease are at greater risk to a fatal outcome from a systemic allergic reaction<sup>2,3</sup>. See also PRECAUTIONS and ADVERSE REACTIONS.

WARNING

Patients should always be observed for at least 20 - 30 minutes after skin testing. In the event of a marked systemic reaction such as urticaria, angioedema, wheezing, dyspnea, respiratory obstruction, hypotension, coma and death (see ADVERSE REACTIONS), applications of a tourniquet above the injection site and administration of 0.2 mL to 1 mL (0.01 mg/kg) of epinephrine injection (1:1,000) are recommended. Maximal recommended dose for children between 2 and 12 years of age is 0.5 mL. The tourniquet is then gradually released at 15 minute intervals. Patients under treatment with beta blockers may be refractory to the usual dose of epinephrine.

Volume expanders and vasopressor agents may be required to reverse hypotension, inhalation bronchodilators and parenteral aminophylline may be required to reverse bronchospasm. In case of respiratory obstruction, oxygen and intubation may be necessary. Life-threatening reactions unresponsive to the above may require cardiopulmonary resuscitation.

PRECAUTIONS

INFORMATION FOR PATIENTS:

Patients should be instructed to describe any active allergic symptoms such as rhinitis, wheezing, dyspnea, etc. prior to testing. Also, see ADVERSE REACTIONS and WARNINGS Sections.

Patients should always be observed 20 to 30 minutes after testing.

General:

- In the presence of active symptoms such as rhinitis, wheezing, dyspnea, etc., the indications for skin testing must be weighed carefully against the risk of temporarily aggravating the symptoms by the testing itself. Objective assessment of pulmonary function such as Peak Expiratory Flow Rate (PEFR) before allergen administration and prior to discharge may be useful in unstable asthmatics to reduce the chances of exacerbation of the patient's asthma. Patients should be instructed to describe any active allergic symptoms as described above prior to skin testing and encouraged to report any late reactions from this testing. Also, see ADVERSE REACTIONS and WARNING sections.
- Store allergenic extracts between 2°-8°C at all times, even during use.
- Care must be taken to avoid drawing blood.
  - For percutaneous testing, if blood is observed, immediately wipe the allergen from the site.
  - For intradermal skin testing, pull gently on the syringe plunger and note if any blood enters the syringe. If blood is obtained, reposition the needle and repeat before injecting (see DOSAGE AND ADMINISTRATION).
- Allergenic extracts become less potent with age. Allergenic extracts containing glycerin 50% v/v are relatively stable. Non-glycerinated aqueous extracts, particularly dilute forms as used for intradermal skin testing, have been shown to be extremely unstable. Until such time as stability studies are complete with dilute allergens, new intradermal strength materials should be prepared every few weeks.
- Use standard aseptic precautions if making dilutions from stock concentrates to intradermal strength.
- For intradermal testing: Extracts in glycerin 50% v/v must be diluted with a non-glycerinated diluent and must be diluted at least 25-fold to less than 2% glycerin by volume, as glycerin above this level can cause false positive intradermal skin test results.

**Pregnancy - Category C:** Animal reproduction studies have not been conducted with allergenic extracts. It is also not known whether allergenic extracts can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

Controlled studies of hyposensitization with moderate to high doses of allergenic extracts during conception and all trimesters of pregnancy have failed to demonstrate any risk to the fetus or to the mother<sup>4</sup>. However, on the basis of histamine's known ability to contract the uterine muscle, the release of significant amounts of histamine from allergen exposure to skin test overdose should be avoided on theoretical grounds. Therefore, allergenic extracts should be used cautiously in a pregnant woman and only if clearly needed.

**Pediatric Use:** Allergenic extracts for diagnostic use have been given safely in infants and young children. Infants have lower skin test reactivity to histamine, as well as common allergens. Skin test reactivity gradually increases to age 6 and plateaus to age 60. Therefore, small skin test reactions should be anticipated in children under age 6.

**Geriatric Use:** Skin test reactivity gradually decreases after age 60. Therefore, smaller skin test reactions should be anticipated in adults over age 60.

**Nursing Mothers:** It is not known if allergens administered subcutaneously appear in human milk. Because many drugs are excreted in human milk, caution should be exercised when allergenic extracts are administered to a nursing woman.

**Carcinogenesis, mutagenesis, impairment of fertility:** Studies in animals have not been performed.

Drug Interactions:

Drugs can interfere with the performance of skin tests<sup>5</sup>.

Antihistamines: Response to mediator (histamine) released by allergens is suppressed by antihistamines. The length of suppression varies and is dependent on individual patient, type of antihistamine and length of time the patient has been on antihistamines. The duration of this suppression may be as little as 24 hours (chlorpheniramine), and can be as long as 40 days (astemizole).

Tricyclic Antidepressants: These exert a potent and sustained decrease of skin reactivity to histamine which may last for a few weeks.

Beta<sub>2</sub> Agonists: Oral terbutaline and parenteral ephedrine, in general, have been shown to decrease allergen induced wheal.

Dopamine: Intravenous infusion of dopamine may inhibit skin test responses.

Beta Blocking Agents: Propranolol can significantly increase skin test reactivity.

Other Drugs: Short acting steroids, inhaled beta<sub>2</sub> agonists, theophylline and cromolyn do not seem to affect skin test response.

ADVERSE REACTIONS

Fatalities from skin testing in the United States have been extensively reviewed by Lockey.<sup>2</sup> Six fatalities were associated with intradermal testing without previous percutaneous testing and one was associated with a combination of percutaneous (scratch) and intradermal skin testing. With careful attention to dosage and administration, fatal reactions occur infrequently, but it must be remembered that allergenic extracts are highly potent to sensitive individuals and overdose could result in anaphylactic symptoms. Therefore it is imperative that physicians administering allergenic extracts for skin testing understand, and be prepared for the treatment of severe reactions.

**Local:** Immediate wheal and erythema reactions are to be expected; but if very large, may be the first manifestation of a systemic reaction. In such cases, immediately wipe the test site(s) with sterile gauze or cotton to remove excess allergen.

**Systemic Reactions:** Systemic reactions are characterized by one or more of the following symptoms: sneezing, mild to severe generalized urticaria, itching (other than at the skin test site), extensive or generalized edema, wheezing, asthma, dyspnea, cyanosis, hypotension, syncope, and upper airway obstruction. Symptoms may progress to shock and death. Patients should always be observed for at least 20 - 30 minutes after testing.

Volume expanders and vasopressor agents may be required to reverse hypotension. Inhalational bronchodilators and parenteral aminophylline may be required to reverse bronchospasm. Severe airway obstruction unresponsive to bronchodilator may require tracheal intubation and use of oxygen. In the event of a marked systemic reaction, application of a tourniquet above the injection site and the administration of 0.2 mL to 1.0 mL of epinephrine injection (1:1,000) is recommended. Maximum recommended dose for children between 2 and 12 years of age is 0.3 mL. The tourniquet should not be left in place without loosening for 90 seconds every 15 minutes.

Adverse events should be reported via MedWatch (1-800-FDA-1088), Adverse Event Reporting, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852-9787.

OVERDOSAGE

Signs and symptoms of overdose are typically large local and systemic reactions. For management of overdose reactions, refer to the ADVERSE REACTIONS section above.

DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Skin test techniques for immediate (Type I) hypersensitivity testing fall into two major categories: percutaneous, and intracutaneous.

**Percutaneous techniques:** For percutaneous testing, in general, skin is scratched, punctured or pricked just before the allergen is applied or through a drop of test allergen. There are several devices available for this technique. Refer to the manufacturer or distributor's circular for specific directions for their use.

In General:

- It is recommended that the test areas should be placed no

closer than 4 - 5 cm apart to avoid interference of reactions when several tests are applied.

2. Skin test areas should be cleansed with alcohol and air dried.
3. Preferably, the allergen should be placed on the volar surface of the forearm, upper arm, or the patient's back. The patient should be placed in a comfortable position prior to testing.
4. For scratch testing, a sharp, clean, sterile instrument is used to abrade the skin, but not to draw blood. Each scratch should be about 2 - 4 mm in length. A small drop of extract is placed on the surface of the skin.
5. Prick testing: For prick testing, a sharp, sterile instrument is used to puncture the skin slightly, applying it at a 15 - 20° angle to the skin. The instrument is gently raised, "tenting" the skin until it pops out, generally pricking through the drop of allergen. Do not draw blood.
6. For puncture testing, a sharp, clean, sterile instrument must be used. Puncture the skin, through the drop of allergen, perpendicular to the skin. Do not draw blood.

For all of the above techniques, a separate instrument must be used for each patient; if the instrument is to be used to pass through the allergen, to avoid cross-contamination, a separate instrument is to be used for each allergen. The test should be read in 15 minutes, measuring both wheal size and erythema.

**Intracutaneous (intradermal) testing:** General: Intradermal testing is more sensitive than percutaneous testing and its specificity is dependent on dose. Intradermal testing is not intended as an initial screen unless used in highly dilute solutions. Intradermal testing is usually reserved for allergens that have demonstrated either negative or equivocal percutaneous skin test response in the face of positive or unclear history.

Intradermal testing of one allergen in several serial dilutions (beginning with the weakest to the more concentrated dilutions) may also be useful in assessing degree of patient sensitivity for the establishment of a safe starting dose for immunotherapy.

Bulk extracts must be diluted for intradermal testing. Use of Sterile Diluent for Allergenic Extracts or Sterile Diluent for Allergenic Extracts Normal Saline with HSA (albumin saline) is recommended. Dilutions should be made with sterile disposable syringes using aseptic technique. Commonly 10 fold dilutions are used to achieve a desired concentration for intradermal testing and continuation of immunotherapy. For example, transferring 0.5 mL of a 10,000 PNU/mL extract into 4.5 mL of diluent will yield 5 mL of extract at 1,000 PNU/mL. For weight volume products, a 1:100 w/v dilution may be prepared from a 1:10 w/v by transferring 0.5 mL of the 1:10 w/v to 4.5 mL of diluent. Prepare as many additional serial dilutions as necessary to reach the appropriate concentration. As a general rule intradermal strength should begin at no higher than 1/100 to 1/1000 of the percutaneous strength that resulted in a negative skin test reaction.

1. It is recommended that the test areas should be spaced no less than 5 cm apart to avoid interference with adjacent allergen or control.
2. Skin should be cleansed with alcohol and air dried.
3. A sterile 1 mL or 1/2 mL syringe with a 26 - 30 gauge needle should be used. A separate sterile syringe should be used for each extract and each patient.
4. Care should be taken to eliminate air bubbles from the syringe prior to injecting the test dose. It is suggested that not more than 6 - 10 allergens of each different type be used at any one time. Very sensitive patients may show rapid response.
5. The skin is held tensely, and the needle is inserted almost parallel to the skin, beveled side up far enough to cover the beveled portion. Slowly inject sufficient extract to make a small bleb of approximately 5 mm in diameter (0.01 - 0.02 mL).
6. Read the test results in 15 minutes.

Selection of the proper strength for intracutaneous testing: A general rule for the prevention of untoward reactions, particularly in extremely sensitive patients, is to screen by percutaneous methods initially, and begin intradermal testing at a strength not more than 1/100 of a negative or equivocal percutaneous reaction.

**Controls:** In both percutaneous and intracutaneous tests, a negative control test with diluent alone should be performed because some patients exhibit dermatographia, and/or other non-specific irritant responses.

As a positive control in the evaluation of allergenic skin testing,

histamine 1 mg/mL (histamine base) should be used for percutaneous testing, and histamine 0.1 mg/mL (histamine base) should be used for intradermal testing.

**Interpretation of results:** Patient's response is graded on the basis of the size of erythema or wheal.<sup>6</sup> General guidelines follow for percutaneous testing, different devices and/or techniques influence the size of the reaction, therefore it is important to refer to the device manufacturer's or distributor's instructions when grading reactions.

**Percutaneous (prick or scratch) test:**

- 0 No reaction or less than control.
- + Erythema greater than control, smaller than a nickel (21 mm diameter).
- ++ Erythema greater than a nickel in diameter, no wheal.
- +++ Wheal and erythema without pseudopods.
- ++++ Wheal and erythema with pseudopods.

**Intradermal test:**

- 0 No reaction or less than negative control.
- + 3-4 mm wheal with erythema, or erythema alone larger than a nickel (21 mm diameter).
- ++ 4-8 mm wheal and erythema, without pseudopods.
- +++ Over 8 mm wheal and erythema without pseudopods.
- ++++ Wheal and erythema with pseudopods.

**HOW SUPPLIED**

**For scratch and prick testing:** 5 mL dropper applicator vials in 50% v/v glycerin or 10mL stoppered vial in 50% v/v glycerin. Available individually and in a complete set of the most common allergens. Available in either Protein Nitrogen Units (PNU/mL) or weight to volume (w/v).

**For intracutaneous testing:** 5 mL sterile vials, aqueous based, individually and in a complete set of the most common allergens. Available in either Protein Nitrogen Units (PNU/mL) or weight to volume (w/v).

**Histatrol®** Positive skin test control - histamine. 1 mg/mL and 0.1 mg/mL histamine base.

**See Product Catalog for specific diagnostic concentrations available.**

**STORAGE**

To maintain stability of allergenic extracts, proper storage conditions are essential. Bulk concentrates and diluted extracts are to be stored at 2° to 8°C even during use. Bulk or diluted extracts are not to be frozen. Do not use after the expiration date shown on the vial label.

**REFERENCES**

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2. Lockey, R.F., et al. Fatalities from immunotherapy (IT) and skin testing (ST). J. Allergy Clin. Immunol. 1987: 79: 660.
3. Reid, M.J. et al. Survey of fatalities from skin testing and immunotherapy. 1985-1989. J. Allergy Clin Immunol. 1993; 92:6.
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DIRECTIONS FOR USE OF  
THERAPEUTIC ALLERGENIC EXTRACTS

**WARNING**

This product is intended for use by physicians who are experienced in the administration of allergenic extracts and the emergency care of anaphylaxis or for use under the guidance of an allergy specialist. Patients should be instructed to recognize adverse reaction symptoms and cautioned to contact the physician's office if reaction symptoms occur. As with all allergenic extracts, severe systemic reactions may occur. In certain individuals, these reactions may rarely result in death. Patients should be observed for 20 to 30 minutes following treatment, and emergency measures, as well as personnel trained in their use, should be immediately available in the event of a life-threatening reaction. Patients with unstable asthma or steroid dependent asthmatics and patients with underlying cardiovascular disease are at greater risk. Adverse events are to be reported to Med Watch (1-800-FDA-1088), Adverse Event Reporting, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852-9787.

This product should not be injected intravenously. Deep subcutaneous routes have proven to be safe. Patients receiving beta-blockers may not be responsive to epinephrine or inhaled bronchodilators. Respiratory obstruction not responding to parenteral or inhaled bronchodilators may require theophylline, oxygen, intubation and the use of life support systems. Parenteral fluid and/or plasma expanders may be utilized for the treatment of shock. Adrenocorticosteroids may be administered parenterally or intravenously. Refer to WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections below.

Port Washington, NY 11050

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**DESCRIPTION**

Sterile therapeutic extracts are supplied in either Phenol Saline Diluent or in Diluent containing Glycerin 50% (v/v) for subcutaneous injection. Inactive ingredients may include: Sodium Chloride for isotonicity, Glycerin, and Sodium Bicarbonate as buffering agents. These products are compounded and diluted on a w/v or PNU basis. Pollens are individually extracted from pure pollen extracted in a phenol-preserved sodium bicarbonate solution. Short Ragweed and Mixed (Tall and Short) Ragweed extracts are standardized by Antigen E content and so labeled. The Antigen E content of extracts containing Short Ragweed at a concentration more dilute than a weight/volume ratio of 1:10 are obtained by calculating the Antigen E content based on the assay value of more concentrated extract. Pollen extracts are filtered aseptically and, after final packaging, they are tested for sterility and safety. Molds are individually extracted from pure powdered inactivated mold source material extracted in phenol preserved saline. Mold extracts are filtered aseptically and after final packaging are tested for sterility and safety. Molds are present in all inhabited places at all seasons of the year; they are so ubiquitous that they are prevalent at times when common allergic pollens and other inhalants are not. In the home and surroundings, molds are found in upholstered furniture, mattresses, drapes, cellar and storage room dust, woolens, leather goods, fruits, meats, cheeses, garden soil and on plants. Spores, mycelial fragments and mold residues are thus inhaled, contacted and ingested continuously.

Miscellaneous inhalants and epidermals are individually extracted in phenol preserved saline, filtered aseptically and after final packaging are tested for sterility and safety.

**CLINICAL PHARMACOLOGY**

The treatment consists of the subcutaneous injection of gradually increasing doses of the allergens to which the patient is allergic. It has been demonstrated that this method of treatment induces an increased tolerance to the allergens responsible for the symptoms on subsequent exposure. The exact relationships between allergen, skin-sensitizing antibody (IgE) and the blocking antibody (IgG) have not been precisely established. Clinically confirmed immunological studies have adduced evidence of the efficacy of hyposensitization therapy.

Numerous controlled studies have demonstrated the clinical efficacy of immunotherapy with cat, dust mites and some pollen extracts. Nevertheless, responses are variable, and in a few studies patients reported no appreciable benefit.

Extracts containing Short Ragweed pollen bear a labeled potency declaration in terms of Antigen E content. Numerous studies have confirmed Antigen E (AgE) as the major antigen associated with Short Ragweed pollinosis.<sup>1</sup> Therefore, it is essential that the physician be aware of AgE content of allergenic extract administered for hyposensitization therapy.

Some studies have indicated that for most patients a cumulative Antigen E dosage of less than 0.1 unit is not immunizing (sufficient to stimulate specific IgG antibodies).<sup>2</sup> This, however, does not suggest that 0.1 unit is a maximum tolerated dose. Most moderately sensitive patients may tolerate a dosage of ten to fifty times greater. If results with this product are unsatisfactory with exquisitely sensitive patients who cannot tolerate an immunizing dose, the physician should consider alternative therapy.

One well-controlled study demonstrated that standard immunotherapy (gradually increasing doses of antigen given subcutaneously to a maximum tolerated peak dose) using crude ragweed extract of known

Antigen E potency, was significantly superior to placebo and low dose immunotherapy (0.1 units AgE cumulative dose) in amelioration of symptoms associated with ragweed hay fever. These patients received a cumulative dose of 18-350 units Antigen E (median = 84.9 units). The maximum single dose ranged from 3.7 to 46.8 units (median = 11.1 units) prior to the ragweed hay fever season.<sup>10</sup>

Patients for this study were sensitive to Ragweed Antigen E, as determined by intradermal skin testing at a dose of 0.01 units AgE/mL. A series of 24 weekly injections were administered. Forty-seven percent of the patients experienced at least one systemic reaction with an average of 1.2 systemic reactions per patient. None of the patients were able to achieve the expected maximum dose (90 units of Antigen E) in the 24 weekly injection dosage schedule.

**INDICATIONS AND USAGE**

Hyposensitization (injection) therapy is a treatment for patients exhibiting allergic reactions to seasonal pollens, dust, molds, animal danders, various other inhalants, and in situations where the offending allergen cannot be avoided.

Prior to initiation of therapy, the clinical sensitivity should be established by careful evaluation of the patient's history confirmed by diagnostic skin testing. Hyposensitization should not be prescribed for sensitivities to allergens which can easily be avoided.

**CONTRAINDICATIONS**

A patient should not be immunized with preparations of allergens to which the patient has not demonstrated symptoms, IgE antibodies, positive skin tests, or properly controlled challenge testing. In most cases, immunotherapy is not indicated for those allergens that can be eliminated or minimized by environmental control.

Patients on beta-blockers are not candidates for immunotherapy, as they can be non-responsive to beta-agonists that may be required to reverse a systemic reaction (also see WARNINGS AND ADVERSE REACTIONS).

In the presence of active symptoms such as rhinitis, wheezing, dyspnea, etc., the indication of immunotherapy must be weighed carefully against the risk of temporarily aggravating the symptoms by the injection itself.

Also, there is some evidence, although inconclusive, that routine immunizations may exacerbate autoimmune diseases.<sup>3,4,5</sup> Hyposensitization should be given cautiously to patients with this predisposition. Patients with severe cardiorespiratory symptoms are at an additional risk during a systemic reaction. The physician must weigh risk to benefit in these cases.

**WARNINGS**

Patients should always be observed for at least 20-30 minutes after any injection. In the event of a marked systemic reaction, application of a tourniquet above the injection site and administration of 0.2 mL to 1 mL (0.01 mg/kg) of Epinephrine Injection (1:1,000) is recommended. Maximal recommended dose for children between 2 and 12 years is 0.5 mL. The tourniquet is then gradually released at 15 minute intervals. Patients under treatment with beta-blockers may be refractory to the usual dose of epinephrine.

Volume expanders and vasopressor agents may be required to reverse hypotension. Inhalation bronchodilators and parenteral aminophylline may be required to reverse bronchospasm. In cases of respiratory obstruction, oxygen and intubation may be necessary. Life-threatening reaction unresponsive to the above may require cardiopulmonary resuscitation.

**DO NOT GIVE INTRAVENOUSLY**

After inserting the needle, but before injecting the dose, pull plunger of the syringe slightly. If blood returns in the syringe, discard the syringe and contents and repeat injection at another site.

Bulk concentrated extracts must be diluted for initial therapy.

Withhold allergenic extracts temporarily or reduce the dose in patients with any one of the following conditions:

- Severe rhinitis or asthma symptoms;
- Infection or flu accompanied by fever;
- Exposure to excessive amounts of clinically relevant allergen prior to therapy.

Patients with unstable asthma or steroid dependent asthmatics and patients with underlying cardiovascular disease are at greater risk. See **PRECAUTIONS AND ADVERSE REACTIONS**.

**TRANSFER OF PATIENTS**

From pyridine extracted alum complexed allergenic extracts to aqueous extracts and glycerinated: In order to avoid untoward reaction, it is recommended that therapy be initiated as though patients were previously untreated. The first dose should be related to the patient's sensitivity, determined by history and confirmed by skin testing.

From unstandardized aqueous extracts to standardized aqueous extracts and glycerinated: The physician should establish the potency relationship, perhaps by comparative skin testing at equal concentration, prior to injecting the first standardized dose.

From aqueous alum precipitated or modified extracts to aqueous extracts and glycerinated: Since this subject has not been studied,

it is recommended that therapy be initiated as if the patient were not previously treated.

**PRECAUTIONS**

**INFORMATION TO PATIENTS:**

Patients should be instructed to describe any active allergic symptoms such as rhinitis, wheezing, dyspnea, etc. prior to injection including any late reactions from previous administration. Patients should be instructed to remain in the office for 20 to 30 minutes after injection to monitor for adverse reactions. Also, see **ADVERSE REACTIONS** and **WARNINGS** Sections.

If the protective action of allergenic extract injections is considered essential for the patient's welfare, appropriate symptomatic therapy with antihistaminic, adrenergic or other drugs might be needed either prior to or in conjunction with the allergenic extract injections.

**GENERAL:**

1. Objective assessment of pulmonary function such as Peak Expiratory Flow Rate (PEFR) before allergen administration may be useful in unstable asthmatic to reduce the chances of exacerbation of the patient's asthma.
2. Store allergenic extracts between 2° and 8°C at all times, even during use.
3. Injections are to be given subcutaneously with the usual sterile precautions using a tuberculin syringe.
4. Care must be taken to avoid injecting into a blood vessel. Pull gently on syringe plunger to determine if a blood vessel has been entered (See **WARNINGS**).
5. Allergenic extracts slowly become less potent with age. During the course of treatment, it may be necessary to continue therapy with a vial of extract bearing a later expiration date. The initial dose of the extract bearing the later expiration date should be lowered to a safe, non-reaction eliciting level which can be confirmed by comparative skin testing using end-point titration.
6. Use standard aseptic precautions when making dilutions. The first dose of the new extract should be reduced to at least 25% of the amount of the dosage from the previous extract.
7. Extracts in 50% glycerin can cause discomfort at the site of the injection.

**PREGNANCY - CATEGORY C:** Animal reproduction studies have not been conducted with allergenic extracts. It is also not known whether allergenic extracts can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

Controlled studies of hyposensitization with moderate to high doses of allergenic extracts during conception and all trimesters of pregnancy have failed to demonstrate any risk to the fetus or to the mother. However, on the basis of histamine's known ability to contract uterine muscle, the release of significant amounts of histamine from allergen exposure or hyposensitization overdose should be avoided on theoretical grounds. Therefore, allergenic extracts should be used cautiously in a pregnant woman and only if clearly needed.

**PEDIATRIC USE:** Children can receive the same dose as adults, however, to minimize the discomfort associated with dose volume it may be advisable to reduce the volume of the dose by one-half and administer the injection at two different sites.

**NURSING MOTHERS:** It is not known if allergens administered subcutaneously appear in human milk. Because many drugs are excreted in human milk, caution should be exercised when allergenic extracts are administered to a nursing woman.

**CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:** Studies in animals have not been performed.

**DRUG INTERACTIONS:** Drugs can interfere with the performance of skin tests.<sup>6</sup>

Antihistamines: Response to mediator (histamine) released by allergens is suppressed by antihistamines. The length of suppression varies and is dependent on individual patient, type of antihistamine and length of time the patient has been on antihistamines. The duration of this suppression may be as little as 24 hours (chlorpheniramine), and can be as long as 40 days (astemizole).

Tricyclic Antidepressants: These exert a potent and sustained decrease of skin reactivity to histamine which may last for a few weeks.

Beta2 Agonists: Oral terbutaline and parenteral ephedrine, in general, have been shown to decrease allergen induced wheal. Dopamine: Intravenous infusion of dopamine may inhibit skin test responses.

Beta Blocking Agents: Propranolol can significantly increase skin test reactivity (See **WARNINGS**).

Other Drugs: Short acting steroids, inhaled beta<sub>2</sub> agonists, theophylline and cromolyn do not seem to affect skin test response.

**ADVERSE REACTIONS**

Anaphylaxis and deaths following the injection of mite and other extracts have been reported by The British Committee on Safety in Medicine.<sup>7</sup> Fatalities from immunotherapy in the United States since 1945 have been extensively reviewed by Lockey, R. F., et al<sup>8</sup> and more



recently by Reid, M. J. et al.<sup>9</sup>

With careful attention to dosage and administration, such reactions occur infrequently, but it must be remembered that allergenic extracts are highly potent to sensitive individuals and OVERDOSE could result in anaphylactic symptoms. Therefore, it is imperative that physicians administering allergenic extracts understand and be prepared for the treatment of severe reactions.

**Local:** Reactions at the site of injection may be immediate or delayed. Immediate wheal and erythema reactions are ordinarily of little consequence; but if very large, may be the first manifestation of a systemic reaction. If large local reactions occur, the patient should be observed for systemic symptoms for which treatment is outlined below.

Delayed reactions start several hours after injection with local edema, erythema, itching or pain. They are usually at their peak at 24 hours and usually require no treatment. Antihistamine drugs may be administered orally.

The next therapeutic dose should be reduced to the dose which did not elicit a reaction, and subsequent doses increased more slowly; i.e., use of intermediate dilutions.

**Systemic:** Systemic reactions are characterized by one or more of the following symptoms: Sneezing, mild to severe generalized urticaria, itching other than at the injection site, extensive or generalized edema, wheezing, asthma, dyspnea, cyanosis, tachycardia, lacrimation, marked perspiration, cough, hypotension, syncope and upper airway obstruction. Symptoms may progress to shock and death. Patients should always be observed for at least 20 to 30 minutes after any injection. Volume expanders and vasopressor agents may be required to reverse hypotension. Inhalational bronchodilators and parenteral aminophylline may be required to reverse bronchospasm. Severe airway obstruction, unresponsive to bronchodilator, may require tracheal intubation and use of oxygen. In the event of a marked systemic reaction, application of a tourniquet above the injection site and the administration of 0.2 mL to 1 mL of Epinephrine Injection (1:1,000) are recommended. Maximal recommended dose for children under 2 years of age is 0.3 mL. Maximal recommended dose for children between 2 and 12 years of age is 0.5 mL. The tourniquet should not be left in place without loosening for 90 seconds every 15 minutes.

The next therapeutic injection of extract should be reduced to the dose which did not elicit a reaction, and subsequent doses increased more slowly; i.e., use of intermediate dilutions.

#### OVERDOSAGE

Signs and symptoms of overdose are typically local and systemic reactions. For a description and management of overdose reactions, refer to "Adverse Reaction" section above.

#### DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

When diluting bulk extracts, use of Sterile Diluent for Allergenic Extracts or Sterile Diluent for Allergenic Extracts Normal Saline with HSA (albumin saline) is recommended. Dilutions should be made with sterile disposable syringes using aseptic technique. Commonly, 10 fold dilutions are used to achieve a desired concentration for initiation and continuation of immunotherapy. For example, transferring 0.5 mL of a 10,000 PNU/mL extract into 4.5 mL of diluent will yield 5 mL of extract at 1,000 PNU/mL. For weight volume products, a 1:100 w/v dilution may be prepared from a 1:10 w/v by transferring 0.5 mL of the 1:10 w/v to 4.5 mL of diluent. Prepare as many additional serial dilutions as necessary to reach the appropriate concentration.

Starting dose for immunotherapy is related directly to a patient's sensitivity as determined by carefully executed skin testing. Degree of sensitivity can be established by determination of D50.11 A general rule is to begin at 1/10 of the dose that produces sum of erythema of 50 mm (approximately a 2+ positive skin test reaction).

For example, if a patient exhibits a 2+ intradermal reaction to 1 AU/mL, the first dose should be no higher than 0.05 mL of 0.1 AU/mL. Dosage may be increased by 0.05 mL each time until 0.5 mL is reached, at which time the next 10-fold more concentrated dilution can be used, beginning with 0.05 mL, if no untoward reaction is observed.

Interval between doses in the early stages of immunotherapy is no more than once to twice a week, and may gradually be increased to once every two weeks. Generally, maintenance injections may be given as infrequently as once every two weeks to once a month.

Injections are given subcutaneously, preferably in the arm. It is advantageous to give injections in alternate arms and routinely in the same area. In some patients, a local tolerance to the allergen may develop thus preventing a possible severe local reaction.

Formal stability studies for diluted and undiluted forms of unstandardized extracts have not been performed; therefore, it is recommended that minimal amounts of the concentrate be diluted so that the diluted product is used up within a relatively short period of time; i.e., preferably not more than four weeks.

#### PRE-SEASONAL METHOD OF TREATMENT

Treatment of hay fever by the pre-seasonal method should be started

6-10 weeks prior to the usual onset of symptoms. Therapy should be started early enough to permit a graduated series of doses at 2-7 day intervals. It is recommended that the larger doses be spaced 5-7 days apart.

Some physicians continue therapy into or through the season by repeating a reduced or MAINTENANCE dose at weekly or biweekly intervals. If during the season, hay fever symptoms develop, relief may be provided by giving supplemental treatment. If the last dose was well-tolerated and not more than 2 weeks has elapsed since it was given, this dose may be given again and repeated every 4 to 7 days.

#### PERENNIAL TREATMENT

The patient's tolerance to the offending pollen or pollens is first established by the injection of a series of graduated doses as outlined in the PRE-SEASONAL METHOD, not necessarily given pre-seasonally, since perennial therapy may be begun at any time. After completion of the ascending series of injections, from 1/4 to 1/2 of the highest well-tolerated dose is continued at 2 to 3 week intervals throughout the year. Shortly before the usual onset of symptoms (4 to 5 weeks prior to the season) the interval between injections is shortened and the dosage is gradually increased, according to the Pre-Seasonal schedule, until maximum well-tolerated dose is again attained. This top dose should be reached just before the usual onset of symptoms at which time the treatment is discontinued. If patient's symptoms persist, therapy may be continued at a reduced dosage level, usually 1/4 to 1/2 of the top dose.

#### DOSAGE ADJUSTMENTS

For Products Containing Short Ragweed.

In transferring patients from unstandardized to standardized product, the physician should establish the potency relationships, perhaps by comparative skin testing, prior to injecting the first standardized dose.

AgE is important in adjusting dosage of Short Ragweed extracts to accurately transfer a patient from older extracts to fresher material. In such cases, the dosage of AgE should be considered in addition to the W/V dilution or protein nitrogen units. Antigen E concentration continuously declines in Short Ragweed Pollen extracts at a rate that varies with the formulation of the product. Aqueous extracts retain Antigen E potency less effectively than glycerin 50% (v/v) extracts. These differences are reflected in the expiration date declared on the vial. The continuous decline should be considered. Also, where ragweed is a component of an allergen mixture, clinical response to the other components must be considered in adjustment of dosage based on AgE content alone. The usual course of immunotherapy is three to five years.

**Caution:** A small percent of individuals allergic to Short Ragweed are more sensitive to minor antigens such as Ra3 Ra5 than AgE. There is no correlation between the amount of these antigens and either AgE or PNU content.

**NOTE:** For extracts of Short Ragweed or equal part mixture of Short and Tall Ragweed refer to AgE dosage schedule. The AgE content for those products is indicated on the vial label. The physician may use the formula below to determine the AgE dosage for each injection.

AgE dosage can be monitored by using the following formula: W/V compounded products:

Labeled AgE X Dose (mL) = dose in AgE PNU compounded products:

Labeled AgE/mL X dose in PNU = dose in AgE Labeled PNU/mL

#### HOW SUPPLIED

1. Concentrate in multiple dose vials:

10 mL and 50 mL, single antigens or specified mixtures, potency expressed in PNU/mL (up to and including 100,000 PNU/mL) or W/V (up to and including 1:10 W/V), aqueous or in 50% glycerin, to be diluted prior to use. 1:10 w/v short ragweed extracts contain  $\geq$  300 units/mL of AgE.

2. Sterile Diluent for Allergenic Extracts (Phenol Saline) is supplied in vials of 4.5 mL, 9.0 mL, 30 mL and 100 mL.

**STORAGE:** To maintain stability of allergenic extracts, proper storage conditions are essential. Bulk concentrates and diluted extracts are to be stored at 2° to 8° C even during use. Bulk or diluted extracts are not to be frozen. Do not use after the expiration date shown on the vial label.

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DIRECTIONS FOR USE OF CENTER - AL® THERAPEUTIC  
ALLERGENIC EXTRACTS ALUM PRECIPITATED  
OF

POLLENS, MOLDS,  
INHALANTS AND EPIDERMALS

DOSAGE BASED ON  
PROTEIN NITROGEN CONTENT

**WARNING**

This allergenic extract is intended for use by physicians who are experienced in the administration of allergenic extracts for immunotherapy and the emergency care of anaphylaxis, or for use under the guidance of an allergy specialist. These allergenic extracts are not directly interchangeable with allergenic extracts of the same labeled potency from different manufacturers. The patient must be re-evaluated with the newly selected extract. Patients being switched from other types of extracts such as aqueous extracts, glycerinated extract, or alum precipitated extracts from other suppliers to this allergenic extract should be started as though they were coming under treatment for the first time. Patients should be instructed to recognize adverse reaction symptoms and cautioned to contact the physician's office if reaction symptoms occur. **As with all allergenic extracts, severe systemic reactions may occur. In certain individuals, these life-threatening reactions may be fatal.** Patients should be observed for 20 to 30 minutes following treatment, and emergency measures, as well as personnel trained in their use, should be immediately available in the event of a life-threatening reaction.

Sensitive patients may experience severe anaphylactic reactions resulting in respiratory obstruction, shock, coma and/or death. Patients with unstable asthma or steroid dependent asthmatics and patients with underlying cardiovascular disease are at greater risk to a fatal outcome from a systemic allergic reaction. If treated, these high risk patients should be started at lower (more conservative) doses and be progressed more slowly to a maintenance dose. Usually this is a lower dose than for those patients without these predispositions. (See **DOSAGE AND ADMINISTRATION**)

This product should not be injected intravenously. Deep subcutaneous routes have proven to be safe. See the warnings, precautions, adverse reactions and overdose sections below.

Patients receiving beta-blockers may not be responsive to epinephrine or inhaled bronchodilators. Respiratory obstruction not responding to parenteral or inhaled bronchodilators may require theophylline, oxygen, intubation and the use of life support systems. Parenteral fluid and/or plasma expanders may be utilized for treatment of shock. Adrenocorticosteroids may be administered parenterally or intravenously. Refer to the warnings, precautions and adverse reaction sections below.

**DESCRIPTION**

Center-Al® (Allergenic extracts, Alum Precipitated) is prepared from aqueous allergenic extracts by the formation of an aluminum hydroxide precipitated complex. It is supplied as a sterile suspension in multiple dose vials for subcutaneous injection. 0.4% Phenol is added as a preservative.

This product is compounded and diluted on a PNU basis. Extracts containing Short Ragweed Pollen also bear a labeled potency declaration in terms of Antigen E content.

**CLINICAL PHARMACOLOGY**

Numerous studies have confirmed Antigen E (AgE) as the major antigen associated with Short Ragweed pollinosis. In a well controlled study, purified Antigen E was significantly superior to placebo in amelioration of symptoms associated with Short Ragweed pollinosis.<sup>1</sup> Therefore, it is essential that the physician be aware of AgE content of allergenic extracts administered for hyposensitization therapy.

Some studies have indicated that for most patients a cumulative Antigen E dosage of less than 0.1 unit is not immunizing (sufficient to stimulate specific IgG antibodies).<sup>2</sup> This, however, does not suggest that a 0.1 unit is a maximum tolerated dose. Most moderately sensitive patients may tolerate a dosage ten to fifty times greater. For exquisitely sensitive patients who cannot tolerate an immunizing dose of this preparation, the physician should consider immunotherapy with alternatives to conventional aqueous allergenic extract.

Alum precipitated bacterial and viral vaccines and alum precipitated toxoids have been effectively and routinely used in immunization injections for many years. The explanation usually given for the effect of such preparations is that the physical chemical absorption of an antigen onto an alum complex results in a slower release of the antigen with a consequent prolongation of the antigenic stimulus.

The treatment consists of the subcutaneous injection of gradually increasing doses of the allergens to which the patient is allergic. It has been demonstrated that this method of treatment induces an increased tolerance to the allergens responsible for the symptoms on subsequent exposure. Although the exact relationships between allergen, skin-sensitizing antibody (IgE) and the blocking antibody (IgG) have not been precisely established, clinically confirmed immunological studies have demonstrated the safety of Center-Al extracts and effectiveness in terms of symptom reduction and IgG response consistent with dose administered.<sup>3</sup>

In a controlled study with Center-Al Ragweed given pre-seasonally, patients were selected and matched by histamine release to Antigen E and assigned to treatment groups: Aqueous, Center-Al, and Placebo<sup>3</sup>. All patients were highly sensitive to Ragweed Antigen E, reacting to <0.001 mcg Antigen E/mL as determined by intradermal skin testing. These patients received a pre-seasonal course of immunotherapy and

achieved a mean cumulative dose of 52 units of Antigen E (27,365 PNU) in 13 to 19 injections. Starting doses in these patients were 10 PNU or approximately 0.02 units of AgE. This dosage was found to be significantly superior to Placebo as measured by symptom scores during the ragweed pollen season.

Although maximum tolerated doses for **Center-Al** expressed in AgE content have not specifically been studied, one investigator reported maximum tolerated doses with **Center-Al** ragweed at 2,000-5,000 PNU (4-10 units of Antigen E) with previously untreated patients.<sup>9</sup> At least three investigators using mixed (tall and short) ragweed extracts demonstrated a maximum tolerated peak dose of 2,000 to 10,000 PNU in 10-13 injections in moderately sensitive patients.<sup>6,10-12</sup> This was achieved by roughly doubling the dose in each successive injection at low dosages (<1,000 PNU) and if well tolerated, increasing the dosage approximately 50% until maximum tolerated dose for each patient was achieved.

Reaction rates for these patients were significantly lower than patients treated with aqueous extracts with the same or more conservative dosage regimen.<sup>3,7,8,11</sup>

**INDICATIONS AND USAGE**

Hyposensitization (injection) therapy is a treatment for patients exhibiting allergic reactions to seasonal pollens, dust mites, molds, animal danders, and various other inhalants, in situations where the offending allergen cannot be avoided.

Prior to the initiation of therapy, clinical sensitivity should be established by careful evaluation of the patient's history confirmed by diagnostic skin testing. Hyposensitization should not be prescribed for sensitivities to allergens which can be easily avoided.

**CONTRAINDICATIONS**

A patient should not be immunized against a substance which the patient has not demonstrated symptoms and/or tissue-fixed IgE antibodies as demonstrated by skin testing. Immunotherapy should not be attempted in patients with active asthma, severe respiratory obstruction, or cardiovascular disease.

There is some evidence, although inconclusive, that routine immunizations may exacerbate autoimmune diseases. Hyposensitization should be given cautiously to patients with this predisposition. The physician must weigh risk to benefit in these rare cases.

Patients with Alzheimer's disease, Down's syndrome and renal insufficiency are theoretically at risk from aluminum intake, including alum precipitated allergenic extracts.

**WARNINGS**

Patients should always be observed for at least 20-30 minutes after any injection. In the event of a marked systemic reaction, application of a tourniquet above the injection site and administration of 0.2 mL to 1.0 mL of Epinephrine injection (1:1,000) are recommended. Maximal recommended dose for children under 2 years of age is 0.3 mL. Maximal recommended dose for children between 2 and 12 years of age is 0.5 mL. The tourniquet is then gradually released. Patients under treatment with beta-blockers may be refractory to the usual dose of epinephrine.

**PRECAUTIONS**

**Information For Patients:** Patients should be instructed to describe any active allergic symptoms such as rhinitis, wheezing, dyspnea, etc. prior to injection including any late reactions from previous administration. Patients should be instructed to remain in the office for 20 to 30 minutes after injection to monitor for adverse reactions. Also, see **ADVERSE REACTIONS** and **WARNINGS** sections.

**General:**

1. **Center-Al** Allergenic Extracts, Alum Precipitated, are not to be used for intradermal testing.
2. Store at temperatures 2° and 8°C at all times, even during use.
3. DO NOT FREEZE. Freezing may cause agglomeration.
4. Shake vial thoroughly to disperse suspension prior to removal of the dose to be administered.
5. A separate sterile syringe and needle should be used for each individual patient, to prevent transmission of homologous serum hepatitis and other infectious agents from one person to another.
6. Injections are to be administered subcutaneously with the usual sterile precautions, preferably in the upper outer aspects of the arm, using a sterile tuberculin-type syringe and 25 or 26 gauge needle, 1/2 to 1/4 in length.
7. Avoid injecting intravenously. Pull back gently on syringe plunger and note if blood enters the syringe. If blood should enter the syringe, withdraw the needle and reinsert at another site, repeating the same precaution.
8. Allergenic extracts slowly become less potent with age. During the course of treatment, it may be necessary to continue therapy with a vial of extract bearing a later expiration date. The initial dose of the extract bearing the later expiration date should be lowered to a safe non-reaction-eliciting level, usually reducing the dosage of the first injection of the new vial 50-75% of the previous well tolerated dose of the older vial.
9. Subcutaneous nodules may develop at injection sites. The incidence of nodules increases with higher dosage of individual products and with extemporaneous mixtures at lower dosage. No single dose should provide more than 5,000 PNU whether as single allergen or mixture nor should it exceed 0.5 mL in volume.

If nodules occur, the highest single dose administered should be limited to a maximum of 0.2 mL (2,000 PNU).

**DRUG INTERACTIONS:**

**Center-Al** Allergenic Extracts, Alum Precipitated, are not to be mixed with any non-alum containing allergen(s) or with other types of alum precipitated products. Such mixing may free the alum-absorbed allergens.

**Center-Al** Allergenic Extracts, Alum Precipitated, should be diluted only with Sterile Diluent for Allergenic Extracts (Phenol-Saline) containing 0.9% Sodium Chloride, 0.4% Phenol. Use of other types of diluents may result in re-solution of some of the alum-complexed allergen thereby resulting in release of free aqueous extracts.

Patients receiving beta-blockers may not be responsive to epinephrine or an inhaled bronchodilator.

**PREGNANCY - CATEGORY C:** Animal reproduction studies have not been conducted with **Center-Al** (Allergenic Extracts, Alum Precipitated). It is also not known whether **Center-Al** can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

Controlled studies of hyposensitization with moderate to high doses of allergenic extracts during conception and all trimesters of pregnancy have failed to demonstrate any risk to the fetus or to the mother. However, on the basis of histamine's known ability to contract the uterine muscle, the release of significant amounts of histamine from allergen exposure or hyposensitization overdose should be avoided on theoretical grounds. Therefore, allergenic extracts should be used cautiously in a pregnant woman and only if clearly needed.

**PEDIATRIC USE:** Children can receive the same dose as adults, however, to minimize discomfort associated with dose volume it may be advisable to reduce the volume of the dose by one-half and administer the injection at two different sites.

**NURSING MOTHERS:** It is not known if allergens administered subcutaneously appear in human milk. Because many drugs are excreted in human milk, caution should be exercised when allergenic extracts are administered to a nursing woman.

**CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:** Studies in animals have not been performed.

**ADVERSE REACTIONS**

**Local:** Reactions at the site of injection may be immediate or delayed. Immediate wheal and erythema reactions are ordinarily of little consequence, but if very large may be the first manifestation of a systemic reaction. If large local reactions occur, the patient should be observed for systemic symptoms for which treatment is outlined below.

Delayed reactions start several hours after injection with local edema, erythema, itching or pain. They are usually at their peak at 24 hours and usually require no treatment. Antihistamine drugs may be administered orally.

The next therapeutic dose should be reduced to the dose which did not elicit a reaction, and subsequent doses increased more slowly, i.e., use of intermediate dilutions.

**Systemic:** It should be noted that anaphylaxis and deaths following the injection of mite and other extracts, including pollen extracts, have been reported by The British Committee on Safety in Medicine.<sup>13</sup> Fatalities from immunotherapy in the United States since 1945 have been extensively reviewed by Lockey, R.F., et al.<sup>14</sup> and also more recently by Reid, M.J., et al.<sup>15</sup> With careful attention to dosage and administration, such reactions occur infrequently, but it must be remembered that allergenic extracts are highly potent to sensitive individuals and OVERDOSE could result in anaphylactic symptoms. Therefore, it is imperative that physicians administering allergenic extracts understand and be prepared for the treatment of severe reactions.

Systemic reactions are characterized by one or more of the following symptoms: sneezing, mild to severe generalized urticaria, itching other than at the injection site, extensive or generalized edema, wheezing, asthma, dyspnea, cyanosis, tachycardia, lacrimation, marked perspiration, cough, hypotension, syncope and upper airway obstruction. Symptoms may progress to shock and death. Patients should always be observed for at least 20-30 minutes after any injection.

Volume expanders and vasopressor agents may be required to reverse hypotension. Inhalational bronchodilator and parenteral aminophylline may be required to reverse bronchospasm. Severe airway obstruction, unresponsive to bronchodilator, may require tracheal intubation.

In the event of a marked systemic reaction, application of a tourniquet above the injection site and administration of 0.2 mL to 1.0 mL of Epinephrine Injection (1:1,000) are recommended. Maximal recommended dose for children under 2 years of age is 0.3 mL. Maximal recommended dose for children between 2 and 12 years of age is 0.5 mL. The tourniquet is then gradually released.

The next therapeutic injection of extract should be reduced to the dose which did not elicit a reaction, and subsequent doses increased more slowly, i.e., use of intermediate dilutions.

Adverse Events should be reported via MedWatch (1-800-FDA-1088), Adverse Event Reporting, Food & Drug Administration, 5600 Fishers Lane, Rockville, MD 20852-9787.

## DOSAGE AND ADMINISTRATION

The starting dose for immunotherapy is related directly to a patient's sensitivity as determined by carefully executed percutaneous (prick/puncture) and intracutaneous (intradermal) skin testing with non-alum adsorbed allergenic extract. A general rule is to begin at 1/10 of the intradermal dose that produces sum of erythema of 50 mm (approximately a 2+ positive skin test reaction). Patient's response to skin testing is graded on the basis of the size of the erythema and wheal. Refer to the diagnostic allergenic extract package enclosure for specific information.

### TRANSFER OF PATIENTS FROM OTHER AQUEOUS EXTRACTS TO CENTER-AL EXTRACTS

Patients may be transferred from other aqueous allergens to **Center-AI** Alum Precipitated Extracts during treatment. To avoid untoward reactions, it may be necessary to initiate treatment as though the patient were previously untreated. In transferring from standardized extracts, the more rapid rate of decline in activity of aqueous extract relative to alum precipitated extract must be considered in cautiously transferring patients to alum precipitated extract.

Caution should be observed since the **Center-AI** preparation may be more potent than the aqueous product.

### TRANSFER OF PATIENTS FROM OTHER ALUM-COMPLEXED EXTRACTS TO CENTER-AL EXTRACTS

Patients may be transferred from other alum-complexed allergenic extracts to **Center-AI** Alum Precipitated extracts. In order to avoid untoward reactions, it is recommended that previous therapy be disregarded and therapy with **Center-AI** be initiated as though the patient were previously untreated. The first dose of **Center-AI** should be related to the patient's sensitivity, determined by history and confirmed by skin testing. CAUTION: **Center-AI** Alum Precipitated extracts should not be mixed with other alum precipitated or aqueous extracts.

### PRE-SEASONAL AND PERENNIAL METHOD OF TREATMENT

The use of **Center-AI** Allergenic extract, Alum Precipitated, in the treatment of patients by the pre-seasonal method should be started 10 to 12 weeks prior to the usual onset of symptoms. Therapy should be initiated early enough to permit a graduated series of doses at weekly intervals. It is recommended that the larger doses be spaced 2 to 3 weeks apart and that the top dose be reached prior to the season.

Increased tolerance acquired through hyposensitization can vary from a few to several months. To assure prolongation of this acquired tolerance, perennial or year-round treatment is recommended.

Some physicians continue therapy into or through the season by repeating a reduced MAINTENANCE dose at 4 to 6 week intervals.

### SUGGESTED DOSAGE SCHEDULE

A treatment schedule is related directly to the patient's degree of sensitivity, determined initially by clinical history and skin testing, and continuously by response to therapeutic doses. Thus, an individual treatment schedule for each patient must be established during the course of therapy. Maximum protection can be obtained with a dosage kept constantly below the patient's limit of tolerance. Every precaution should be taken to avoid a systemic or generalized reaction which in addition to being dangerous, may depress rather than increase the patient's tolerance.

### FOR ALL PREPARATIONS (EXCEPT SHORT RAGWEED AND MIXED SHORT AND TALL RAGWEED)

Labeled Antigen E content of extracts containing Short Ragweed at a weight/volume concentration more dilute than 1:10 may have been obtained by calculation from the Antigen E assay value of a more concentrated extract that was analyzed, officially released by the Office of Biologics, and subsequently diluted.

Below is listed a suggested dosage schedule for Pre-Seasonal Treatment. A column has been left blank for AgE dosage of short ragweed containing extracts.

**Note:** For extracts of short ragweed or equal part mixture of Short and Tall Ragweed refer to AgE dosage schedule. The AgE content for those products is indicated on the vial label. The physician may use the formula below to determine the AgE dosage for each injection.

AgE dosage can be monitored by using the formula:

$$\frac{\text{Labeled AgE}}{\text{Labeled PNU/mL}} \times \text{X dose in PNU} = \text{dose in AgE}$$

**Note:** Suggested dosage schedules which follow have not been subjected to adequate and well controlled trials to establish their safety and efficacy.

Dose No.	Vial Strength	Volume Injected	PNU Per Dose	AgE Dose
1	100 PNU/mL	0.1 mL	10	
2	100 PNU/mL	0.2 mL	20	
3	100 PNU/mL	0.5 mL	50	
4	1,000 PNU/mL	0.1 mL	100	
5	1,000 PNU/mL	0.25 mL	250	
6	1,000 PNU/mL	0.5 mL	500	
7	10,000 PNU/mL	0.1 mL	1,000	
8	10,000 PNU/mL	0.2 mL	2,000	
9	10,000 PNU/mL	0.3 mL	3,000	
10	10,000 PNU/mL	0.4 mL	4,000	
11	10,000 PNU/mL	0.5 mL	5,000	

## MAINTENANCE DOSE:

10,000 PNU/mL      0.5 mL      5,000

NO SINGLE DOSE SHOULD EXCEED 5,000 PNU. For continuing therapy with extracts containing Short Ragweed, see following section on Dosage Adjustments.

### SHORT RAGWEED EQUAL PARTS MIXES OF SHORT AND TALL RAGWEED (DOSAGE BASED ON ANTIGEN CONTENT)

Suggested dosage schedule for Short Ragweed and Equal Part Mixture of Short and Tall Ragweed:

Dose No	AgE Units/mL	Volume Injected	AgE Per Dose
1	0.4	0.1	0.04
2	0.4	0.2	0.08
3	0.4	0.5	0.2
4	4	0.1	0.4
5	4	0.25	1.0
6	4	0.5	2.0
7	40	0.1	4.0
8	40	0.2	8.0
9	40	0.3	12
10	40	0.4	16
11	40	0.5	20

### MAINTENANCE DOSE:

40      0.5      20  
80      0.25      20

NO SINGLE DOSE SHOULD EXCEED 20 UNITS

### DOSAGE ADJUSTMENTS (FOR PRODUCTS CONTAINING SHORT RAGWEED)

AgE is important in adjusting dosage of Short Ragweed extracts to accurately transfer a patient from older extracts to fresher material. In such cases, the dosage of AgE should be considered in addition to the protein nitrogen units. Antigen E concentration continuously declines in Short Ragweed Pollen extracts at a rate that varies with the formulation of the product. Aqueous extracts retain Antigen E potency less effectively than 50% glycerinated or Alum Precipitated extracts. Antigen E is most stable in freeze-dried extracts. These differences are reflected in the expiration date declared on the vial label. The continuous decline should be considered. Also, where Ragweed is a component of an allergen mixture, clinical response to the other components must be considered in adjustment of dosage based on AgE content alone.

CAUTION: A small percent of individuals allergic to Short Ragweed are more sensitive to minor antigens such as Ra3 and Ra5 than AgE. There is no correlation between the amount of these antigens and either AgE or PNU content.

### HOW SUPPLIED

Therapeutic **Center-AI** Allergenic Extracts, Alum Precipitated, are supplied in 10 mL and 30 mL vials, in concentrations of 10,000 PNU/mL and 20,000 PNU/mL. Prescription treatment sets for individual patients are also available. **Center-AI** must be stored continuously at 2° to 8°C. DO NOT FREEZE. Diluent: Sterile Diluent for allergenic extracts (Phenol-Saline) is provided in vials of 4.5 mL, 9.0 mL, and 30 mL.

**STORAGE:** To maintain stability of allergenic extracts, proper storage conditions are essential. Bulk concentrates and diluted extracts are to be stored at 2° to 8°C even during use. Bulk or diluted extracts are not to be frozen. Do not use after the expiration date shown on the vial label.

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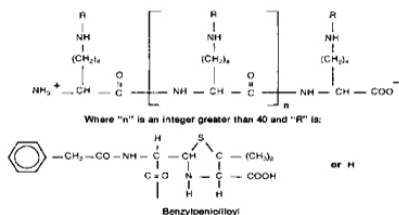
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**PRE-PEN®**  
benzylpenicilloyl polylysine injection, solution  
**Skin Test Antigen**

**DESCRIPTION:**

PRE-PEN® (benzylpenicilloyl polylysine injection USP) is a sterile solution of benzylpenicilloyl polylysine in a concentration of 6.0 X 10-5 M (benzylpenicilloyl) in 0.01 M phosphate buffer and 0.15 M sodium chloride. The benzylpenicilloyl polylysine in PRE-PEN is a derivative of poly-L-lysine, where the epsilon amino groups are substituted with benzylpenicilloyl groups (50-70%) forming benzylpenicilloyl alpha amide. Each single dose ampule contains 0.25 mL of PRE-PEN.

PRE-PEN has the following structure:



**CLINICAL PHARMACOLOGY:**

PRE-PEN is a skin test antigen reagent that reacts specifically with benzylpenicilloyl IgE antibodies initiating the release of chemical mediators which produce an immediate wheal and flare reaction at a skin test site. All individuals exhibiting a positive skin test to PRE-PEN possess IgE against the benzylpenicilloyl structural group which is a hapten. A hapten is a low molecular weight chemical that conjugates with a carrier (e.g. poly-L-lysine) resulting in the formation of an antigen with the hapten's specificity. The benzylpenicilloyl hapten is the major antigenic determinant in penicillin-allergic individuals. However, many individuals reacting positively to PRE-PEN will not develop a systemic allergic reaction on subsequent exposure to therapeutic penicillin, especially among those who have not reacted to penicillins in the past. Thus, the PRE-PEN skin test determines the presence of penicilloyl IgE antibodies which are necessary but not sufficient for acute allergic reactions due to the major penicilloyl determinant.

Non-benzylpenicilloyl haptens are designated as minor determinants, since they less frequently elicit an immune response in penicillin treated individuals. The minor determinants may nevertheless be associated with significant clinical hypersensitivity. PRE-PEN does not react with IgE antibodies directed against non-benzylpenicilloyl haptens.

**INDICATIONS AND USAGE:**

PRE-PEN is indicated for the assessment of sensitization to penicillin (benzylpenicillin or penicillin G) in patients suspected to have clinical penicillin hypersensitivity. A negative skin test to PRE-PEN is associated with an incidence of immediate allergic reactions of less than 5% after the administration of therapeutic penicillin, whereas the incidence may be more than 50% in a history-positive patient with a positive skin test to PRE-PEN. These allergic reactions are predominantly dermatologic. Whether a negative skin test to PRE-PEN predicts a lower risk of anaphylaxis is not established. Similarly, when deciding the risk of proposed penicillin treatment, there are not enough data at present to permit relative weighing in individual cases of a history of clinical penicillin hypersensitivity as compared to positive skin tests to PRE-PEN and/or minor penicillin determinants.

**CONTRAINDICATIONS:**

PRE-PEN is contraindicated in those patients who have exhibited either a systemic or marked local reaction to its previous administration. Patients known to be extremely hypersensitive to penicillin should not be skin tested.

**WARNINGS:**

The risk of sensitization to repeated skin testing with PRE-PEN is not established. Rarely, a systemic allergic reaction including anaphylaxis (see below) may follow a skin test with PRE-PEN. To decrease the risk of a systemic allergic reaction, puncture skin testing should be performed first. Intradermal skin testing should be performed only if the puncture test is entirely negative.

**PRECAUTIONS:**

**General:**

No reagent, test, or combination of tests will completely assure that a reaction to penicillin therapy will not occur.

The value of the PRE-PEN skin test alone as a means of assessing the risk of administering therapeutic penicillin (when penicillin is the preferred drug of choice) in the following situations is not established:

1. Adult patients who give no history of clinical penicillin hypersensitivity.
2. Pediatric patients.

In addition, the clinical value of PRE-PEN where exposure to penicillin is suspected as a cause of a current drug reaction or in patients who are undergoing routine allergy evaluation is not known. Likewise, the clinical value of PRE-PEN skin tests alone in determining the risk of administering semi-synthetic penicillins (phenoxymethyl penicillin, ampicillin, carbenicillin, dicloxacillin, methicillin, nafcillin, oxacillin, amoxicillin), cephalosporin-derived antibiotics, and penem antibiotics is not known.

In addition to the results of the PRE-PEN skin test, the decision to administer or not administer penicillin should take into account individual patient factors. Healthcare professionals should keep in mind the following:

1. A serious allergic reaction to therapeutic penicillin may occur in a patient with a negative skin test to PRE-PEN.
2. It is possible for a patient to have an anaphylactic reaction to therapeutic penicillin in the presence of a negative PRE-PEN skin test and a negative history of clinical penicillin hypersensitivity.
3. If penicillin is the drug of choice for a life-threatening infection, successful desensitization with therapeutic penicillin may be possible irrespective of a positive skin test and/or a positive history of clinical penicillin hypersensitivity.

**Pregnancy – Pregnancy Category C:**

Animal reproduction studies have not been conducted with PRE-PEN. It is not known whether PRE-PEN can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. The hazards of skin testing in such patients should be weighed against the hazard of penicillin therapy without skin testing.

**ADVERSE REACTIONS:**

Occasionally, patients may develop an intense local inflammatory response at the skin test site. Rarely, patients will develop a systemic allergic reaction, manifested by generalized erythema, pruritus, angioedema, urticaria, dyspnea, hypotension, and anaphylaxis. The usual methods of treating a skin test antigen-induced reaction — the applications of a venous occlusion tourniquet proximal to the skin test site and administration of epinephrine are recommended. The patient should be kept under observation for several hours.

**DOSAGE AND ADMINISTRATION:**

**SKIN TESTING DOSAGE AND TECHNIQUE**

Skin testing responses can be attenuated by interfering drugs (e.g. H1-antihistamines and vasopressors). Skin testing should be delayed until the effects of such drugs have dissipated, or a separate skin test with histamine can be used to evaluate persistent antihistaminic effects in vivo. Due to the risk of potential systemic allergic reactions, skin testing should be performed in an appropriate healthcare setting under direct medical supervision.

**Puncture Testing:**

Skin testing is usually performed on the inner volar aspect of the forearm. The skin test antigen should always be applied first by the puncture technique. After preparing the skin surface, apply a small drop of PRE-PEN solution using a sterile 22-28 gauge needle. The same needle can then be used to make a single shallow puncture of the epidermis through the drop of PRE-PEN. Very little pressure is required to break the epidermal continuity. Observe for the appearance of a wheal, erythema, and the occurrence of itching at the test site during the succeeding 15 minutes at which time the solution over the puncture site is wiped off. A positive reaction consists of the development within 10 minutes of a pale wheal, sometimes with pseudopods, surrounding the puncture site and varying in diameter from 5 to 15 mm (or more). This wheal may be surrounded by a variable diameter of erythema, and accompanied by a variable degree of itching. The most sensitive individuals develop itching quickly, and the wheal and erythema are prompt in their appearance. As soon as a positive response as defined above is clearly evident, the solution over the scratch should be immediately wiped off. If the puncture test is either negative or equivocally positive (less than 5 mm wheal with little or no erythema and no itching), an intradermal test may be performed.

**The Intradermal Test:**

Using a 0.5 to 1.0 cc syringe with a 3/8" to 5/8" long, 26 to 30 gauge, short bevel needle, withdraw the contents of the ampule. Prepare with an alcohol swab a skin test area on the upper, outer arm, sufficiently below the deltoid muscle to permit proximal application of a tourniquet later, if necessary. Be sure to eject all air from the syringe through the needle, then insert the needle, bevel up immediately below the skin surface. Inject an amount of PRE-PEN sufficient to raise a small intradermal bleb of about 3mm in diameter, in duplicate at least 2cm apart. Using a separate syringe and needle, inject a like amount of saline or allergen diluting solution as a control at least 5 cm removed from the antigen test sites. Most skin reactions will develop within 5-15 minutes and response to the skin test is read at 20 minutes as follows:

*Negative response* — no increase in size of original bleb and no greater reaction than the control site.

*Ambiguous response* — wheal only slightly larger than initial injection bleb, with or without accompanying erythematous flare and slightly larger than the control site; OR discordance between duplicates.

*Positive response* — itching and significant increase in size of original blebs to at least 5mm. Wheal may exceed 20 mm in diameter and exhibit pseudopods.

If the control site exhibits a wheal greater than 2-3 mm, repeat the test, and if the same reaction is observed, a physician experienced with allergy skin testing should be consulted.

**HOW SUPPLIED: NDC 49471-001-05**

PRE-PEN® (benzylpenicilloyl polylysine injection USP) is a clear, colorless, sterile solution supplied in ampules containing 0.25 mL.

Box of 5 single dose ampules. Ampules are opened by snapping the neck of the ampule using two forefingers of each hand. Visually inspect for glass shards before use. Each ampule is for single patient use only. Discard any unused portion.

PRE-PEN is optimally stored under refrigeration (2-8 °C). PRE-PEN subjected to ambient temperatures for more than 24 hours should be discarded. As with all parenteral drug products, PRE-PEN should be inspected visually for particulate matter and discoloration prior to administration.

**Rx only**

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Directions for Use of  
Positive Skin Test Control – Histamine  
HISTATROL®

Histamine Base 1 mg/mL  
(Histamine Phosphate 2.75 mg/mL)  
in Glycerin 50% (v/v)  
For Percutaneous Testing

Histamine Base 0.1 mg/mL  
(Histamine Phosphate 0.275 mg/mL)  
For Intracutaneous (Intradermal) Testing

## DESCRIPTION

The chemical formula for Histamine Phosphate is C<sub>5</sub>H<sub>9</sub>N<sub>3</sub>·2H<sub>3</sub>PO<sub>4</sub>; its molecular weight is 307.14. For prick, puncture or scratch testing, the product is a sterile solution that contains 1 mg/mL histamine base (2.75 mg/mL Histamine Phosphate) in Water for Injection; it also contains Glycerin 50% (v/v) as viscosity agent and Phenol 0.4% as preservative. For intracutaneous (intradermal) skin testing, the product is a sterile solution that contains 0.1 mg/mL histamine base (0.275 mg/mL Histamine Phosphate) in Water for Injection and Phenol 0.4% as preservative. The product should be stored refrigerated and protected from light.

## CLINICAL PHARMACOLOGY

Histamine acts as a potent vasodilator when released from mast cells during an allergic reaction. It is largely responsible for the immediate skin test reaction of a sensitive patient when challenged with an offending allergen. The effect of added Glycerin (50% v/v) to 1 mg/mL histamine base was studied by puncture testing using a bifurcated needle in twelve volunteer subjects. The mean sum of cross-diameters of the wheals was 13.25 mm (range 10-15 mm) for the non-glycerinated, and 12.54 mm (range 9-15 mm) for the glycerinated formulation. Sum of cross-diameters of erythema was 52.88 mm (range 23-92 mm) for the non-glycerinated, and 54.42 mm (range 19-87 mm) for the glycerinated formulation. These differences are not statistically significant.

## INDICATIONS AND USAGE

For use as a positive control in evaluation of allergenic (immediate hypersensitivity or "Type I") skin testing.

## CONTRAINDICATIONS

Histamine should not be injected into individuals with hypotension, severe hypertension, severe cardiac, pulmonary, or renal disease. Not to be used for diagnosis of pheochromocytoma or to test the ability of the gastric mucosa to secrete hydrochloric acid.

## WARNINGS

Care must be taken in intracutaneous testing to avoid injection into a venule or capillary. Pull back gently on the syringe plunger and note if blood is drawn. If blood is drawn, withdraw needle and inject into another skin site. Small doses by any route of administration may precipitate asthma in patients with bronchial hyperactivity. This product is not intended for inhalation, or subcutaneous injection. The utmost caution is advised in using histamine in such patients and in those with a history of bronchial asthma.

## PRECAUTIONS

### General

A separate sterile needle or other percutaneous testing device should be used for each individual patient to prevent transmission of hepatitis and other infectious agents from one person to another.

Epinephrine Injection (1:1,000) and injectable antihistamines should be available for immediate use in the event the patient exhibits a severe response. A tourniquet can be applied above the test site to slow absorption if a severe response occurs.

### Drug Interactions

Drugs can interfere with the performance of skin tests in general, and specifically with histamine.1

Antihistamines: Response to histamine is suppressed by antihistamines. The length of suppression varies, and is dependent on individual patient, type of antihistamine and length of time the patient has been on antihistamines. The duration of this suppression may be as little as 24 hours (chlorpheniramine), and can be as long as 40 days (astemizole).

Tricyclic Antidepressants: These exert a potent and sustained decrease of skin reactivity to histamine, which may last for a few weeks. Beta2 Agonists: Oral terbutaline and parenteral epinephrine, in general, have been shown to decrease allergen induced wheal. Theoretically, this may also reduce whealing capacity to histamine.

Dopamine: Intravenous infusion of dopamine has been shown to inhibit skin test responses to histamine.

Beta Blocking Agents: Propranolol can significantly increase skin test reactivity, including histamine.

Other Drugs: Short acting steroids, inhaled beta agonists, theophylline and cromolyn do not seem to affect skin test response.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Animal studies have not been conducted with Histamine.

## Nursing Mothers

It is not known if Histamine administered percutaneously or intracutaneously appears in human milk. Because many drugs are excreted in human milk, caution should be exercised when histamine is administered to a nursing woman.

## Pregnancy Category C

It is not known whether Histamine can cause fetal harm when administered during pregnancy or whether it can affect reproduction capacity. Histamine should be given during pregnancy only if clearly needed.

There are no adequate and well-controlled studies during pregnancy. However, based on histamine's known ability to contract uterine muscle, exposure or repeated doses should be avoided. HISTATROL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus or mother.

## Pediatric Use

Histamine solutions for percutaneous testing have been given safely in infants and young children.2,3,4,5 Neonates and infants have lower skin test reactivity to histamines as well as common allergens.3,4,5,6 About 20% of infants less than six months of age have been observed to have a negative reaction to histamine hydrochloride (1 mg/mL of salt).4 Skin test reactivity gradually increases to age six and plateaus to age sixty.2,3 Therefore, small skin test reactions should be anticipated in children under age six.

## ADVERSE REACTIONS

### Local:

Reactions such as wheal, erythema and localized pruritus are to be expected, but if very large (i.e. greater than 4+ as described dosage and administration) may be the first manifestation of a systemic reaction.

Systemic: Following the injection of large doses of histamine, systemic reactions may include flushing, dizziness, headache, bronchial constriction, urticaria, asthma, marked hypertension or hypotension, abdominal cramps, vomiting, metallic taste, and local or generalized allergic manifestations (see also OVERDOSAGE).

## OVERDOSAGE

A large subcutaneous dose of Histamine Phosphate may cause severe occipital headache, blurred vision, angular pain, a rapid drop in blood pressure, and cyanosis of the face. Overdosage may cause severe symptoms including vasomotor collapse, shock, and even death. Epinephrine Injection 0.01 mg/kg to a maximum of 1.0 mg given subcutaneously or intramuscularly should be used in case of emergency due to severe reactions (see Precautions). An antihistamine preparation may be given intramuscularly to ameliorate systemic reaction to overdose.

## DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

### For Prick, Puncture and Scratch Testing

Histamine base 1 mg/mL (Histamine Phosphate 2.75 mg/mL) should be used to give a reaction. (Refer to Interpretation Section.) Prick, Puncture or Scratch Test Techniques

1. The skin in the test area should be cleansed with alcohol and air dried.
2. The histamine control skin test solution should be placed at the same site with the other skin test antigens, either on the patient's back or on the volar surface of the forearm. The patient should be placed in a comfortable position before the testing is begun.
3. For the prick test, a sharp needle is used to puncture the skin, but not to draw blood. If the scratch test is used, carefully break or scratch the skin with a sterile scarifier. Do not draw blood. Each scratch should be about 2 mm - 4 mm in length.
4. A small drop of the histamine base 1 mg/mL (Histamine Phosphate 2.75 mg/mL) is placed on the abraded skin site no closer than 4 or 5 cm from an adjacent test site. Some physicians prefer to place the solution on the test area and then prick through the drop with a sharp needle.
5. Use a separate sterile scarifier or needle for each patient.

6. The test should be read at 15 minutes; if a large wheal reaction occurs before that time the test site should be wiped free of histamine.

### Interpretation

The patient's response is based on the size of: erythema (degree of redness) and/or size of wheal (smooth, slightly elevated area) which appear after 10 minutes. For percutaneous testing, different devices and/or techniques influence the size of the reaction. Therefore, it is important to refer to the device manufacturer's or distributor's instructions when grading reactions. For prick, puncture and scratch testing, histamine base 1 mg/mL (Histamine Phosphate 2.75 mg/mL) should be used to give a positive reaction. In a large population, the NHANES II survey reports a mean diameter (average of length and width) wheal of 4.4 mm ± 1.65 mm (± standard deviation) and a mean erythema of 18.4 mm ± 8.55 mm (± standard deviation) when

using 25 gauge B-D needle by prick puncture (Pepys) technique.7 All positive reactions should be interpreted against an appropriate negative control.

### For Intradermal Skin Testing

Histamine base 0.1 mg/mL (Histamine Phosphate 0.275 mg/mL) or 0.01 mg/mL should be used to give a reaction. (Refer to Interpretation Section.)

### Intracutaneous (Intradermal) Test Techniques

1. The skin should be cleansed with alcohol and air dried.
2. A sterile one milliliter tuberculin syringe with 26 or 27 gauge needle should be used. A single sterile syringe should be used for each solution to assure sterility. Only the histamine base 0.1 mg/mL (Histamine Phosphate, 0.275 mg/mL) or greater dilution solution should be used.
3. The histamine base skin test solution should be injected at the same site with the other skin test allergens, either on the patient's back or on the arm. The patient should be placed in a comfortable position before the testing is begun.
4. The skin is held tense and the needle is inserted almost parallel to the skin, bevel side up, far enough to cover the beveled portion. Slowly inject 0.01 mL or 0.02 mL, making a small bleb approximately 3 mm - 5 mm in diameter.
5. The test should be read in 15 minutes.

### Interpretation

The patient's response is based on the size of: erythema (degree of redness) and/or size of wheal (smooth, slightly elevated area) which appear after 10 minutes. For intradermal skin testing, histamine base 0.1 mg/mL (Histamine Phosphate 0.275 mg/mL) or 0.01 mg/mL should be used to give a positive reaction. The available 0.1 mg/mL concentration must be diluted ten-fold to achieve this dose. All positive reactions should be interpreted against an appropriate negative control. In two successive years of testing, the Committee on Standardization of the American College of Allergy reported positive reactions at histamine base doses of 0.01 mg/mL and higher. Mean sum of wheal diameters was approximately 14 mm ± 4.8 mm and sum of erythema diameter was approximately 52 mm ± 21.6 mm following 0.01 mL intradermal doses of 0.01 mg/mL histamine base. When 0.01 mL of 0.1 mg/mL histamine base was injected, the sum of cross-diameters of wheal ranged from 15-20 mm and the sum of cross-diameters of erythema ranged from 60-80 mm.8

## HOW SUPPLIED

Multidose vials containing 5 mL histamine base, 1 mg/mL (Histamine Phosphate 2.75 mg/mL) in Glycerin 50% (v/v) for prick, puncture, or scratch testing. Multidose vials containing 5 mL histamine base, 0.1 mg/mL (Histamine Phosphate 0.275 mg/mL) in aqueous solution for intradermal testing. Store at 2° - 8°C.

## REFERENCES

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DIRECTIONS FOR USE OF ALLERGENIC EXTRACTS  
STANDARDIZED GRASS POLLENS

**WARNING**

Standardized allergenic extract is intended for use by physicians who are experienced in the administration of standardized (BAU/mL) allergenic extracts for immunotherapy and the emergency care of anaphylaxis, or for use under the guidance of an allergy specialist. **Standardized allergenic extracts are not directly interchangeable with allergenic extracts of the same labeled potency from different manufacturers.** The initial dose of standardized extract must be based on skin testing as described in the warnings, dosage and administration section of this insert.

Patients should be instructed to recognize adverse reaction symptoms and cautioned to contact the physician's office if reaction symptoms occur. **As with all allergenic extracts, severe systemic reactions may occur. In certain individuals, these life-threatening reactions may be fatal.**

Patients should be observed for at least 20 - 30 minutes following treatment, and emergency measures, as well as personnel trained in their use, should be immediately available in the event of a life-threatening reaction. Patients with unstable asthma or steroid dependent asthmatics and patients with underlying cardiovascular disease are at greater risk to a fatal outcome from a systemic allergic reaction.

This product should not be injected intravenously. It is intended for percutaneous and subcutaneous use. See the warnings, precautions, adverse reactions and overdosage sections below.

Patients receiving beta-blockers may not be responsive to epinephrine or inhaled bronchodilators. Respiratory obstruction not responding to parenteral or inhaled bronchodilators may require theophylline, oxygen, intubation and the use of life support systems. Parenteral fluid and/or plasma expanders may be utilized for treatment of shock. Adrenocorticosteroids may be administered parenterally or intravenously. Refer to the warnings, precautions and adverse reaction sections below.

Sensitive patients may experience severe anaphylactic reactions resulting in respiratory obstruction, shock, coma and/or death. Adverse events are to be reported to MedWatch (1-800-FDA-1088), Adverse Experience Reporting, HFM-210 Center for Biologics Evaluation & Research, Food & Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

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**DESCRIPTION**

Standardized allergenic extract of grass pollens from Timothy (Phleum pratense), Orchard (Dactylis glomerata), June (Poa pratensis), Red Top (Agrostis alba), Sweet Vernal (Anthoxanthum odoratum), Meadow Fescue (Festuca elatior), Perennial Rye (Lolium perenne), Bermuda Grass (Cynodon dactylon), in the accompanying vial are sterile, and contain glycerin 50% v/v and phenol 0.4% (preservative). Inert ingredients may include sodium chloride for isotonicity and sodium bicarbonate buffer.

Glycerinated pollen extracts, for subcutaneous injection for immunotherapy and/or percutaneous or intracutaneous testing (see Dosage and Administration section), are prepared from defatted dried pollen extracted in glycerinated Coca's Fluid, filtered aseptically, and dispensed into multiple dose vials. These are subsequently tested for sterility, safety, and potency.

For ease in use and for lot-to-lot consistency, the potency is expressed in Bioequivalent Allergy Units (BAUs) per milliliter. A value of 10,000 BAU/mL is assigned to the CBER reference standard that can be diluted 1:0.5 million to produce intradermal SE (sum of Erythema) of 50 mm in highly puncture reactive subjects<sup>1</sup>. A value of 100,000 BAU/mL is assigned to the CBER reference standard that can be diluted 1:5 million to produce intradermal SE (sum of Erythema) of 50 mm in highly puncture reactive subjects. The relative potency of each lot of standardized extract has been compared to the official CBER reference standard by an acceptable assay such as ELISA Inhibition.<sup>2</sup> When the potency is equivalent by ELISA Inhibition to the reference, the product is assigned 10,000 BAU/mL or 100,000 BAU/mL. Standardized grass pollen extracts, except for Bermuda, have potency designations of either 10,000 BAU/mL or 100,000 BAU/mL. Bermuda grass pollen extract is only available with a 10,000 BAU/mL potency designation.

In the ELISA Inhibition assay, a competitive binding assay, the wells of microtiter plates are coated using a characterized allergenic extract. Allergic sera is added to each well. The binding of IgE specific for the coating allergen is inhibited by concentrations of a test sample of an extract of the same allergen. The amount of IgE bound to the solid phase allergen (and subsequently the degree of inhibition) is determined using enzyme-labeled anti-human IgE antibodies and the appropriate substrate. The potency relative to a reference is determined using a parallel line bioassay method.

**CLINICAL PHARMACOLOGY**

Diagnostically (for skin testing) the allergen combines with IgE antibodies fixed to mast cells in the skin.<sup>3</sup> This complexing causes an increase in cellular permeability and degranulation of the mast cells releasing chemical mediators. These mediators (such as histamine) are responsible for a local inflammatory response of wheal and erythema typical of a positive skin test reaction and also, the symptoms commonly associated with allergic disease. The more mediator released, the larger the reaction (wheal and erythema).

Treatment consists of the subcutaneous injection of gradually increasing doses of the allergens to which the patient is allergic. It has been demonstrated that this method of treatment induces an increased tolerance to the allergens responsible for the symptoms on subsequent exposure. Although the exact relationships between allergen, skin-sensitizing antibody (IgE) and the blocking antibody (IgG) have not been

precisely established, clinically confirmed immunological studies have adduced evidence of the efficacy of hyposensitization therapy.

Numerous controlled studies have demonstrated the clinical efficacy of immunotherapy with cat, dust mites and some pollen, including grass pollen extracts.<sup>4</sup> Nevertheless, responses are variable, and in a few studies patients reported no appreciable benefit.

Puncture test data with 10,000 BAU/mL Grass Pollen Extract CBER reference preparations, in 15 grass allergic patients yielded the following sizes of wheal and erythema ( $\Sigma$  = sum of longest diameter and orthogonal cross diameter).<sup>5</sup>

A. Puncture bifurcated needle data with 10,000 BAU/mL CBER Reference Grass Pollen Extracts.

Reference	FDA		Erythema (mm)		Wheal (mm)	
Pollen	Lot #	N	Mean	Range	Mean	Range
Bermuda	E4-Ber	15	90.3	43-123	15.7	7-31
June	E3-Jkb	15	77.3	47-107	15.9	6-28
Meadow Fescue	E4-MF	15	81.1	57-115	11.9	7-22
Orchard	E4-Or	15	84.3	57-111	14.1	9-19
Perennial Rye	E10-Rye	15	92.3	73-135	17.5	6-36
Red Top	E4-Rt	15	77.1	42-98	14.1	8-19
Sweet Vernal	E4-SV	15	81.2	28-123	15.7	8-30
Timothy	E6-Ti	15	88.3	51-109	16.9	8-40

The intradermal dose (BAU50) of the CBER (FDA) Grass Pollen Extract Reference Preparation required producing a 50 mm Sum of Erythema was calculated based on titration in sensitive individuals.

B. Intradermal Dose of CBER Reference Grass Pollen Extracts for 50mm Sum of Erythema Diameter (BAU50)<sup>5</sup>.

Reference	FDA	BAU 50/mL	
Pollen	Lot #	Mean	Range
Bermuda	E4-Ber	0.02	0.4-0.0003
June	E3-Jkb	0.02	0.1-0.004
Meadow Fescue	E4-MF	0.02	0.9-0.002
Orchard	E4-Or	0.02	1.9-0.002
Perennial Rye	E10-Rye	0.02	0.7-0.002
Red Top	E4-Rt	0.02	0.8-0.004
Sweet Vernal	E4-SV	0.02	1.0-0.002
Timothy	E6-Ti	0.02	0.6-0.002

**INDICATIONS AND USAGE**

Indicated use of allergenic extracts is for the diagnosis and treatment (hyposensitization therapy) of patients who experience allergic symptoms due to exposure to grass pollen and who exhibit type I skin sensitivity when tested to those specific allergens.

Hyposensitization (injection) therapy is a treatment for patients exhibiting allergic reactions to seasonal pollens, dust mites, molds, animal danders, and various other inhalants in situations where the offending allergen cannot be avoided.

For previously untreated patients, prior to the initiation of therapy, clinical sensitivity to the standardized grass pollen extract should be established by careful evaluation of the patient's history confirmed by diagnostic skin testing. Hyposensitization should not be prescribed for sensitivities to allergens which can easily be avoided.

10,000 BAU/mL extracts are indicated for percutaneous testing. If negative, the 100,000 BAU/mL dose may be used. Availability of 10,000 and 100,000 BAU/mL dosages facilitate safe switching. Patients who tolerate dilutions prepared from the 10,000 BAU/mL dosage and require a higher dose may be treated with dilutions prepared from the 100,000 BAU/mL dosage.

100,000 BAU/mL concentrations may be especially useful when patients are hyposensitized to numerous allergens. Mixing of allergenic extracts dilutes the potency of each constituent. Using higher concentrations such as 100,000 BAU/mL allows for dilution with other extracts without sacrificing immunizing properties. **CAUTION:** The final potency of each individual component in a patient mixture should never exceed 10,000 BAU/mL. See also, **DOSEAGE AND ADMINISTRATION** section for discussion of mixture labeling.

**CONTRAINDICATIONS**

A patient should not be immunized with preparations of allergens to which the patient has not demonstrated symptoms, IgE antibodies, positive skin tests, or properly controlled challenge testing. In most cases, immunotherapy is not indicated for those allergens that can be eliminated or minimized by environmental control.

Patients on beta-blockers are not candidates for immunotherapy, as they can be non-responsive to beta-agonists that may be required to reverse a systemic reaction (also see **WARNINGS** and **ADVERSE REACTIONS**). In the presence of active symptoms such as rhinitis, wheezing, dyspnea, etc., the indications of immunotherapy must be weighed carefully against the risk of temporarily aggravating the symptoms by the injection itself.

Also, there is some evidence, although inconclusive, that routine immunizations may exacerbate autoimmune diseases.<sup>6,7,8</sup> Hyposensitization should be given cautiously to patients with this predisposition. Patients with severe cardiorespiratory symptoms are at an additional risk during a systemic reaction. The physician must weigh risk to benefit in these cases.

**WARNINGS**

See warnings at the beginning of this package insert.

Patients should always be observed for at least 20 - 30 minutes after any injection. In the event of a marked systemic reaction (for a description of systemic reactions see Adverse Reaction Section), application of a tourniquet above the injection site and intramuscular administration of 0.2 mL to 1.0 mL (0.01 mg/kg) of Epinephrine Injection (1:1000) is recommended. This dose can be repeated after 15 minutes, as needed. Maximal recommended dose for children between 2 and 12 years of age is 0.5 mL. The tourniquet is then gradually released at 15 minute intervals. Patients under treatment with beta-blockers may be refractory to the usual dose of epinephrine. **DO NOT GIVE ALLERGENIC EXTRACTS INTRAVENOUSLY.**

Volume expanders and vasopressor agents may be required to reverse hypotension. Inhalation bronchodilators and parenteral aminophylline may be required to reverse bronchospasm. In cases of respiratory obstruction, oxygen and intubation may be necessary. Life-threatening reactions unresponsive to the above may require cardiopulmonary resuscitation.

A reduction in starting dose is recommended in the following circumstances:

1. Change to a new lot of extract from the same manufacturer;
2. Change to a different manufacturers extract;
3. Change in the extract formula;
4. Change to an extract bearing a later expiration date;
5. When a prolonged lapse in time has occurred since the last injection.

Withhold allergenic extracts temporarily or reduce the dose in patients with any one of the following conditions:

- Severe rhinitis or asthma symptoms;
- Infection or flu accompanied by fever;
- Exposure to excessive amounts of clinically relevant allergen prior to therapy

Allergenic extracts slowly become less potent with age. During the course of treatment, it may be necessary to continue therapy with a vial of extract bearing a later expiration date. The initial dose of the extract bearing the later expiration date should be lowered to a safe non-reaction-eliciting level. When switching one standardized extract with another, at least 75% reduction in dose is suggested.

Patients with unstable asthma or steroid dependent asthmatics and patients with underlying cardiovascular disease are at greater risk to a fatal outcome from a systemic allergic reaction<sup>12</sup>.

See also **PRECAUTIONS** and **ADVERSE REACTIONS**.

**PRECAUTIONS**

**Information for Patients:** Patients should be instructed to describe any active allergic symptoms such as rhinitis, wheezing, dyspnea, etc. prior to injection including any late reactions from previous administration. Patients should be instructed to remain in the office for 20 to 30 minutes after injection to monitor for adverse reactions. Also, see **ADVERSE REACTIONS** and **WARNINGS** sections.

**General:**

1. In the presence of active symptoms such as rhinitis, wheezing, dyspnea, etc., the indications of immunotherapy must be weighed carefully against the risk of temporarily aggravating the symptoms by the injection itself. Objective assessment of pulmonary function such as Peak Expiratory Flow Rate (PEFR) before allergen administration and prior to discharge may be useful in unstable asthmatics to reduce the chances of exacerbation of the patient's asthma. If the protective action of allergenic extract injections is considered essential for the patient's welfare, appropriate symptomatic therapy with antihistaminic, beta-adrenergic or other drugs might be needed either prior to or in conjunction with the allergenic extract injections.
2. Store allergenic extracts between 2° and 8°C at all times, even during use.
3. Injections are to be given subcutaneously with the usual sterile precautions using a Tuberculin syringe.
4. Care must be taken to avoid injecting into a blood vessel. Pull gently on syringe plunger to determine if a blood vessel has been entered (See boxed Warnings).
5. Use standard aseptic precautions when making dilutions.
6. Extracts in 50% glycerin can cause discomfort at the site of the injection during the injection. Glycerinated extracts diluted for intradermal testing must be diluted at least twenty-five-fold to less than 2% glycerin (by volume), as glycerin above this level can cause false positive intradermal skin tests. Use of negative control skin test containing an equal concentration of glycerin as the allergen when evaluating intradermal skin tests is recommended.
7. Standardized concentrates of allergenic extracts must be diluted prior to initiation of immunotherapy.

**Pregnancy - Category C:** Animal reproduction studies have not been conducted with allergenic extracts. It is also not known whether allergenic extracts can cause fetal harm when administered to a pregnant woman, or can affect reproduction capacity.

Controlled studies of hyposensitization with moderate to high doses of allergenic extracts during conception and all trimesters of pregnancy have failed to demonstrate any risk to the fetus or to the mother<sup>13</sup>. However, on the basis of histamine's known ability to contract the uterine muscle, the release of significant amounts of histamine from allergen exposure of hyposensitization overdose should be avoided on theoretical grounds. Therefore, allergenic extracts should be used cautiously in a pregnant woman, and only if clearly needed.

**Pediatric Use:** Children can receive the same dose as adults, however, to minimize discomfort associated with dose volume it may be advisable to reduce the volume of the dose by one-half and administer the injection at two different sites.

**Geriatric Use:** Studies in geriatric patients have not been conducted. Physicians should consider risk to benefit of immunotherapy in this patient population.

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when allergenic extracts are administered to a nursing woman.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Studies in animals have not been performed.

**Drug Interactions:** Drugs can interfere with the performance of skin tests.<sup>9</sup>

Antihistamines: Response to mediator (histamine) released by allergens is suppressed by antihistamines. The length of suppression varies and is dependent on individual patient, type of antihistamine and length of time the patient has been on antihistamines. The duration of this suppression may be as little as 24 hours to several days.

Tricyclic Antidepressants: These exert a potent and sustained decrease of skin reactivity to histamine which may last for a few weeks.

Beta2 Agonists: Oral terbutaline and parenteral ephedrine, in general, have been shown to decrease allergen induced wheal.

Dopamine: Intravenous infusion of dopamine may inhibit skin test responses.

Beta Blocking Agents: Propranolol can significantly increase skin test reactivity (see boxed Warnings).

Other Drugs: Short acting steroids, inhaled beta2 agonists, theophylline and cromolyn do not seem to affect skin test response.

#### ADVERSE REACTIONS

**Local:** Reactions at the site of injection may be immediate or delayed. Immediate wheal and erythema reactions are ordinarily of little consequence; but if very large, may be the first manifestation of a systemic reaction. If large local reactions occur, the patient should be observed for systemic symptoms for which treatment is outlined below. However, systemic reactions may occur in the absence of large local reactions.

Delayed reactions start several hours after injection with local edema, erythema, itching or pain. They are usually at their peak at 24 hours, and usually require no treatment. Antihistamine drugs may be administered orally.

The next therapeutic dose should be reduced to the dose which did not elicit a reaction, and subsequent doses increased more slowly, i.e., use of intermediate dilutions.

**Systemic:** It should be noted that anaphylaxis and deaths following the injection of mite and other extracts, including grass pollen extracts have been reported by The British Committee on Safety in Medicine.<sup>10</sup> Fatalities from immunotherapy in the United States since 1945 have been extensively reviewed by Lockey, R. F., et al.<sup>11</sup> Reid, M.J., et al.<sup>12</sup> and also more recently by Bernstein, D. I. et al.<sup>15</sup>. With careful attention to dosage and administration, such reactions occur infrequently, but it must be remembered that allergenic extracts are highly potent to sensitive individuals and OVERDOSE could result in anaphylactic symptoms. Therefore, it is imperative that physicians administering allergenic extracts understand and be prepared for the treatment of severe reactions.

Systemic reactions are characterized by one or more of the following symptoms: sneezing, mild to severe generalized urticaria, itching, other than at the injection site, extensive or generalized edema, wheezing, asthma, dyspnea, cyanosis, hypotension, syncope and upper airway obstruction. Symptoms may progress to shock and death. Patients should always be observed for at least 20 - 30 minutes after any injection. Volume expanders and vasopressor agents may be required to reverse hypotension. Inhalational bronchodilators and parenteral aminophylline may be required to reverse bronchospasm. Severe airway obstruction, unresponsive to bronchodilator, may require tracheal intubation and use of oxygen. In the event of a marked systemic reaction, application of a tourniquet above the injection site and the administration of 0.2 mL to 1.0 mL of Epinephrine Injection (1:1000) intramuscular is recommended. Maximal recommended dose for children under 2 years of age is 0.3 mL. Maximal recommended dose for children between 2 and 12 years of age is 0.5 mL. The tourniquet should not be left in place without loosening for 90 seconds every 15 minutes.

The next therapeutic injection of extract should be reduced to the dose which did not elicit a reaction, and subsequent doses increased more slowly; i.e., use of intermediate dilutions.

Adverse Events should be reported via MedWatch (1-800-FDA-1088), Adverse Experience Reporting, HFM-210 Center for Biologics Evaluation & Research, Food & Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

#### OVERDOSAGE

Signs and symptoms of overdose are typically local and systemic reactions. For a description and management of overdose reactions,

refer to "Adverse Reactions" section above.

#### DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

When diluting bulk extracts, use of Sterile Diluent for Allergenic Extracts or Sterile Diluent for Allergenic Extracts Normal Saline with HSA are recommended. Dilutions should be made with sterile disposable syringes using aseptic technique. Commonly 10 fold dilutions are used to achieve a desired concentration for intradermal testing or initiation and continuation of immunotherapy. For example transferring 0.5 mL of a 10,000 BAU/mL extract into 4.5 mL of diluent will yield 5 mL of extract at 1,000 BAU/mL. Prepare as many additional serial dilutions as necessary to reach the appropriate concentration.

**Stock mixtures of grass pollen extracts are compounded from individual grass pollen extracts. The total potency per milliliter (mL) of these mixtures is described on the container label, where space permits. The contribution each individual component is expressed in the supplemental labeling accompanying the vial.**

**Diagnosis** - In diagnosing the sensitive individual, the symptom history must be associated with exposure to the allergen. Skin testing is used in conjunction with a definitive history for diagnosing individual sensitivities.

An excellent method of recording results is to cover the skin reaction with transparent tape, outline the erythema first then the wheal with an indelible pen, then remove the tape and transfer it to the patient's permanent record. For preferred results, it is recommended that the actual measurement of the extent of both responses be recorded. This can be accomplished by measuring the longest erythema diameter, then selecting the mid-point of that line and measuring at a 90° angle to that line to determine the orthogonal diameter. The sum of these two measurements is the sum of erythema (ΣE); the sum of wheal diameters is determined in a similar manner.

Patient's response is graded on the basis of the size of erythema and/or wheal.

Percutaneous (prick/scratch/puncture) test:

Prick, scratch, or puncture skin tests should be performed initially using a glycerinated extract at 10,000 BAU/mL.

What follows are general guidelines for percutaneous testing<sup>14</sup>. Different devices and/or techniques influence the size of the reaction, therefore it is important to refer to the device manufacturer's or distributor's instructions when grading reactions. As a negative control the diluent should be tested and included in the interpretation in the skin test reactions. Use of a positive control such as histamine base at 1 mg/mL should be used to assess skin test reactivity.

0 No reaction or less than control

+ Erythema greater than control, smaller than a nickel (21 mm diameter)

++ Erythema greater than a nickel in diameter, no wheal

+++ Wheal and erythema without pseudopods

++++ Wheal and erythema with pseudopods

Intradermal test:

Intradermal testing should start with a dilute solution, usually in the range of 0.1 BAU/mL or less.

Glycerinated extracts diluted for intradermal testing may be diluted at least 25-fold to less than 2% glycerin (by volume) as glycerin above this level can cause false positive intradermal skin tests. Use a negative control skin test with glycerin content equal to the glycerin content of the allergen dose used for intradermal testing. Use of a positive control such as histamine base at 0.1 mg/mL or 0.01 mg/mL should be used to test reactivity.

On the forearm or upper outer aspect of the arm, using a 26 - 27 gauge, short bevel needle, inject intradermally 0.05 mL of the intradermal test solution. Skin whealing responses should be observed 10 - 20 minutes after administering the test.

A negative skin test is one where the sum of erythema was 0 or equal to the sum of the wheal. As a negative control, the diluent should be tested and included in the interpretation of the skin reactions. What follows are general guidelines intradermal testing<sup>14</sup>.

0 No reaction or less than negative control

+ 3-4 mm wheal with erythema, or erythema alone larger than a nickel (21 mm diameter)

++ 4-8 mm wheal and erythema without pseudopods

+++ Over 8 mm wheal and erythema without pseudopods

++++ Wheal and erythema with pseudopods

**Immunotherapy** - Starting dose for immunotherapy is related directly to a patient's sensitivity as determined by carefully executed skin testing. Degree of sensitivity can be established by determination of D50 (the intradermal dose, base three, that produces a ΣE = 50 mm).1

A general rule is to begin at 1/10 of the dose that produces sum of erythema of 50 mm (approximately a 2+ positive skin test reaction). For example, if a patient exhibits a 2+ intradermal reaction to 1 BAU/mL, the first dose should be no higher than 0.05 mL of 0.1 BAU/mL. Dosage may be increased by 0.05 mL each time until 0.5 mL is reached, at which time the next 10-fold more concentrated dilution can be used, beginning with 0.05 mL, if no untoward reaction is observed.

If a tolerated dose of allergenic extract has been established, the initial dose from the new extract should be reduced to 25% of the previously well tolerated dose (see also Precautions).

You are encouraged to report patient reactions to skin testing and/or immunotherapy to ALK. Your contact information is toll-free 1-855-216-6497 or email [AdverseEvents@alk.net](mailto:AdverseEvents@alk.net)

Interval between doses in the early stages of immunotherapy is no more than once to twice a week, and may gradually be increased to once every two weeks. Generally, maintenance injections may be given as infrequently as once every two weeks to once a month.

Injections are given subcutaneously preferably in the arm. It is advantageous to give injections in alternate arms and routinely in the same area. In some patients, a local tolerance to the allergen may develop thus preventing a possible severe local reaction.

After inserting the needle, but before injecting the dose, pull plunger of the syringe slightly. If blood returns in the syringe, discard the syringe and contents and repeat injection at another site.

Bulk concentrated extracts must be diluted for initial therapy and intradermal skin testing. For recommended diluent, refer to DOSAGE AND ADMINISTRATION section.

Use standard aseptic precautions when making dilutions. The first dose of the new extract should be reduced at least 75% of the amount of the dosage from the previous extract.

Stability studies indicate that undiluted products will retain its potency under recommended storage conditions. Stability studies for undiluted forms of this product are not complete. It is recommended that minimal amounts of the concentrate be diluted so that the diluted product is used up within a relatively short period of time; i.e., preferably not more than four weeks.

#### HOW SUPPLIED

For percutaneous testing, 5 mL vial, 10,000 BAU/mL and 100,000 BAU/mL (except Bermuda grass 10,000 BAU/mL only) in glycerin 50% (v/v)

For immunotherapy, 10 mL, 30 mL, and 50 mL vials 10,000 BAU/mL in glycerin 50% (v/v), or 10 mL, 30 mL and 50 mL vials 100,000 BAU/mL in glycerin 50% (v/v). Bermuda is available only at 10,000 BAU/mL.

**STORAGE:** To maintain stability of allergenic extracts, proper storage conditions are essential. Bulk concentrates and diluted extracts are to be stored at 2° to 8° C even during use. Bulk or diluted extracts are not to be frozen. Do not use after the expiration date shown on the vial label.

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ALK-Abello, Inc. 2009

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ALLERGENIC EXTRACT  
STANDARDIZED MITE

(Dermatophagoides farinae and Dermatophagoides pteronyssinus)

**WARNINGS**

Standardized allergenic extract is intended for use by physicians who are experienced in the administration of standardized (AU/mL) allergenic extracts for immunotherapy and the emergency care of anaphylaxis, or for use under the guidance of an allergy specialist. Standardized allergenic extracts are not directly interchangeable with allergenic extracts of the same labeled potency from different manufacturers. The patient must be re-evaluated with the newly selected extract. The initial dose must be based on skin testing as described in the dosage and administration section of this insert. Patients being switched from other types of extracts to standardized allergenic extracts should be started as though they were coming under treatment for the first time. Patients should be instructed to recognize adverse reaction symptoms and cautioned to contact the physician's office if reaction symptoms occur. As with all allergenic extracts, severe systemic reactions may occur. Patients with unstable asthma or steroid dependent asthmatics and patients with underlying cardiovascular disease are at greater risk. In certain individuals, these life-threatening reactions may result in death. Patients should be observed for 20 to 30 minutes following treatment, and emergency measures, as well as personnel trained in their use, should be immediately available in the event of a life-threatening reaction.

This product should not be injected intravenously. Deep subcutaneous routes have proven to be safe. See the warnings, precautions, adverse reactions and over-dosage sections below.

Sensitive patients may experience severe anaphylactic reactions resulting in respiratory obstruction, shock, coma and/or death.

Patients receiving beta-blockers may not be responsive to epinephrine or inhaled bronchodilators. Respiratory obstruction not responding to parenteral or inhaled bronchodilators may require theophylline, oxygen, intubation and the use of life support systems. Parenteral fluid and/or plasma expanders may be utilized for treatment of shock. Adrenocorticosteroids may be administered parenterally or intravenously. Refer to the warnings, precautions and adverse reaction sections below.

Adverse events are to be reported to MedWatch (1-800-FDA-1088), Adverse Event Reporting, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852-9787.

Port Washington, NY 11050  
U.S. Government License No. 1256

**DESCRIPTION**

Allergenic Extract Standardized Mite in the accompanying vial is a sterile solution and contains glycerin 50% v/v and phenol 0.4% (preservative). Inert ingredients include sodium chloride for isotonicity and sodium bicarbonates, as a buffer. The mites (*D. farinae* and/or *D. pteronyssinus*), used as source material for this extract, were cultured by Biopol Laboratories on a medium consisting of yeast and pork. The whole-body mites were separated from the culture medium and the harvested mites contained less than 1% culture medium material.

Several manufacturers submitted to FDA, intradermal skin test data on Biopol Laboratory's mite medium extract using patients who were puncture test positive (sum of erythema equal to or greater than 40 mm) to either *D. farinae* or *D. pteronyssinus* extracts. By intradermal testing, there was 1 positive (sum of erythema equal to or greater than 20 mm) in 44 individuals at an estimated 1% level of medium contamination of mites, and 4 positives in 40 individuals at an estimated 10% contamination. Two of the individuals who were skin test positive also skin tested by the puncture method with an extract of yeast (*Saccharomyces* sp) and were positive.

In ten mite sensitive patients, ALK-Abelló, Inc. observed no puncture or intradermal reactions to media from the same source at a carryover concentration equivalent to 1% of the mite extract.

For ease in use, and for lot to lot consistency, potency value is expressed in allergy units per milliliter.

This ELISA standardized mite extract was compared to a mite reference preparation supplied by FDA which was labeled 10,000 AU/mL based on skin testing.<sup>1</sup> The relative potency of this mite extract was determined by ELISA inhibition in comparison to the FDA Mite reference and is labeled in AU's (Allergy Units/mL).<sup>2</sup> Dilutions made from this product can be administered intradermally for testing, or subcutaneously for immunotherapy.

**CLINICAL PHARMACOLOGY**

Diagnostically (for skin testing) the allergen combines with IgE antibodies fixed to mast cells in the skin.<sup>3</sup> This complexing causes an increase in cellular permeability and degranulation of the mast cells releasing chemical mediators. These mediators (such as histamine) are responsible for a local inflammatory response of wheal and erythema typical of a positive skin test reaction and also, the symptoms commonly associated with allergic disease. The more mediator release, the larger the reaction (wheal and erythema).

Treatment consists of the subcutaneous injection of gradually increasing doses of the allergens to which the patient is allergic. It has been demonstrated that this method of treatment induces an increased tolerance to the allergens responsible for the symptoms on subsequent exposure. Although the exact relationships between allergen, skin sensitizing antibody (IgE) and the blocking antibody (IgG) have not been precisely established, clinically confirmed immunological studies have adduced evidence of the efficacy of hypsensitization therapy.

Numerous controlled studies have demonstrated the clinical efficacy of immunotherapy with cat, dust mites and some pollen extracts.<sup>4</sup> Nevertheless, responses are not uniform but variable, and in a few

studies, the majority of the patients reported no appreciable improvement.

**INDICATIONS AND USAGE**

This product is indicated for the diagnosis and treatment of hypersensitivity in patients with symptoms compatible with dust mite allergy.

Hyposensitization (injection) therapy is a treatment for patients exhibiting allergic reactions to seasonal pollens, dust mites, molds, animal danders, and various other inhalants, in situations where the offending allergen cannot be avoided. Mixtures of standardized mite (*D. farinae* and *D. pteronyssinus*) should be considered for treatment of patients who are sensitive to both species.

Prior to the initiation of therapy, clinical sensitivity should be established by careful evaluation of the patient's history confirmed by diagnostic skin testing. Hyposensitization should not be prescribed for sensitivities to allergens which can be easily avoided.

**CONTRAINDICATIONS**

There are no known absolute contraindications to immunotherapy. However, a patient should not be immunized with preparations of allergens to which the patient has not demonstrated symptoms and positive skin tests. In most cases, immunotherapy is not indicated for those allergens that can be eliminated or minimized by environmental control.

Also, there is some evidence, although inconclusive, that routine immunizations may exacerbate autoimmune diseases.<sup>5,6,7</sup> Hyposensitization should be given cautiously to patients with this predisposition. Patients with severe cardiorespiratory symptoms are at additional risk during a systemic reaction. The physician must weigh the risk to benefit in these cases.

Patients on beta-blockers are not candidates for immunotherapy, as they can be non-responsive to beta-agonists that may be required to reverse a systemic reaction. Also, see BOXED WARNING section.

In the presence of active symptoms such as rhinitis, wheezing, dyspnea, etc., the indications of immunotherapy must be weighed carefully against the risk of temporarily aggravating the symptoms by the injection itself.

**WARNINGS**

See warnings at the beginning of this package insert. Standardized allergenic extracts are not directly interchangeable with allergenic extracts of the same labeled potency from different manufacturers. The patient must be re-evaluated with the newly selected extract.

A reduction in starting dose is recommended in the following circumstances:

1. Changing to a new lot of extract from the same manufacturer
2. Using product from a different manufacturer
3. Using non-standardized extract or any other change in formula
4. Changing to a product bearing a later expiration date
5. When a prolonged lapse in time has occurred since the last injection

Withhold allergenic extracts temporarily or reduce the dose in patients with any one of the following conditions:

- Severe rhinitis or asthma symptoms;
- Infection or flu accompanied by fever;
- Exposure to excessive amounts of clinically relevant allergen prior to therapy.

Allergenic extracts slowly become less potent with age. During the course of treatment, it may be necessary to continue therapy with a vial of extract bearing a later expiration date. The initial dose of the extract bearing the later expiration date should be lowered to a safe non-reaction-eliciting level. When switching one standardized extract with another, at least 75% reduction in dose is suggested.

Patients should always be observed for at least 20 to 30 minutes after any injection. In the event of a marked systemic reaction such as urticaria, angioedema, wheezing, dyspnea, respiratory obstructions, hypotension and coma, application of a tourniquet above the injection site and administration of 0.2 mL to 1.0 mL (0.01 mg/kg) of Epinephrine Injection (1:1000) is recommended. Maximal recommended dose for children between 2 and 12 years of age is 0.5 mL. The tourniquet should not be left in place without loosening for 90 seconds every 15 minutes. Patients under treatment with beta-blockers may be refractory to the usual dose of epinephrine.

Volume expanders and vasopressor agents may be required to reverse hypotension. Inhalation bronchodilators and parenteral aminophylline may be required to reverse bronchospasm. In cases of respiratory obstruction, oxygen and intubation may be necessary. Life-threatening reactions unresponsive to the above may require cardiopulmonary resuscitation. **DO NOT GIVE INTRAVENOUSLY.**

Mite Extracts (*D. farinae* and/or *D. pteronyssinus*) contain small (<1%) amounts of residual media components (pork and yeast). The physician should proceed with caution when using mite extract in mite sensitive individuals that also demonstrate sensitivity to these media components and only if clearly warranted.

In the presence of active symptoms such as rhinitis, wheezing, dyspnea, etc., the indications of immunotherapy must be weighed carefully against the risk of temporarily aggravating the symptoms by the injection itself. If the protective action of allergenic extract injections is considered essential for the patient's welfare, appropriate symptomatic therapy with antihistaminic, adrenergic or other drugs might be needed either prior to or in conjunction with allergenic extract injections.

**PRECAUTIONS**

**INFORMATION TO PATIENTS:**

Patients should be instructed to describe any active allergic symptoms such as rhinitis, wheezing, dyspnea, etc., prior to injection including any

late reactions from previous administration. Patients should remain in doctor's office for 20-30 minutes following injections and be instructed to report any local or systemic symptoms before leaving. Also, see **ADVERSE REACTIONS and WARNINGS** Sections.

If the protective action of allergenic extract injections is considered essential for the patient's welfare, appropriate symptomatic therapy with antihistaminic, adrenergic or other drugs might be needed either prior to or in conjunction with the allergenic extract injections.

**GENERAL**

1. Store allergenic extracts between 2° - 8°C at all times, even during use.
2. Use sterile precautions. Using a sterile tuberculin syringe, injections are given subcutaneously. A separate syringe must be used for each patient to prevent transmission of hepatitis and other infectious disease.
3. Care must be taken to avoid injecting into a blood vessel. Pull gently on syringe plunger to determine if a blood vessel has been entered (See Warnings).
4. Extracts in 50% glycerin can cause discomfort at the site of the injection during the injection.
5. Standardized concentrates of allergenic extracts must be diluted prior to initiation of immunotherapy.
6. Dilute allergenic extracts may be more potent when diluted with Albumin saline than those which do not contain stabilizers such as albumin.

**PREGNANCY - CATEGORY C:** Animal reproduction studies have not been conducted with allergenic extracts. It is also not known whether allergenic extracts can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

Controlled studies of hypsensitization with moderate to high doses of allergenic extracts during conception and all trimesters of pregnancy have failed to demonstrate any risk to the fetus or to the mother. However, on the basis of histamine's known ability to contract the uterine muscle, the release of significant amounts of histamine from allergen exposure of hypsensitization overdose should be avoided on theoretical grounds. Therefore, allergenic extracts should be used cautiously in a pregnant woman, and only if the benefit outweighs the risk.

**PEDIATRIC USE:** Children can receive the same dose as adults, however, to minimize the discomfort associated with dose volume it may be advisable to reduce the volume of the dose by half and administer the injection at two different sites.

**GERIATRIC USE:** Studies in geriatric patients have not been conducted. Physicians should consider risk to benefit of immunotherapy in this patient population.

**NURSING MOTHERS:** It is not known if allergens administered subcutaneously appear in human milk. Because many drugs are excreted in human milk, caution should be exercised when allergenic extracts are administered to a nursing woman.

**CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:** Long term studies in animals have not been performed.

**DRUG INTERACTIONS:** Drugs can interfere with the performance of skin tests.<sup>8</sup>

Antihistamines: Response to mediator (histamine) released by allergens is suppressed by antihistamines. The length of suppression varies and is dependent on individual patient, type of antihistamine and length of time the patient has been on antihistamines. The duration of this suppression may be as little as 24 hours to several days.

Tricyclic Antidepressants: These exert a potent and sustained decrease of skin reactivity to histamine which may last for a few weeks.

Beta2 Agonists: Oral terbutaline and parenteral ephedrine, in general, have been shown to decrease allergen induced wheal.

Dopamine: Intravenous infusion of dopamine may inhibit skin test responses.

Beta Blocking Agents: Propranolol can significantly increase skin test reactivity (See **WARNINGS**).

Other Drugs: Short acting steroids, inhaled beta2 agonists, theophylline and cromolyn do not seem to affect skin test response.

**ADVERSE REACTIONS**

**Local:** Reactions at the site of injection may be immediate or delayed. Immediate wheal and erythema reactions are ordinarily of little consequence, but if very large, may be the first manifestation of systemic reaction. If large local reactions occur, the patient should be observed for systemic symptoms for which treatment is outlined below. However, systemic reactions may occur in the absence of large local reactions.

Delayed reactions start several hours after injection with local edema, erythema, itching or pain. They are usually at their peak at 24 hours and usually require no treatment. Antihistamine drugs may be administered orally.

The next therapeutic dose should be reduced to the dose which did not elicit a reaction, and subsequent doses increased more slowly, i.e., use of intermediate dilutions.

**Systemic:** Reports from regulatory authorities in Sweden to the FDA, indicated that several deaths have been associated with the use of mite extracts. The FDA was subsequently informed that these deaths may have been related to use by physicians untrained in the administration of potent extracts rather than a product defect. It should be noted that anaphylaxis and deaths following the injection of mite and other



extracts have also been reported by The British Committee on Safety in Medicine.<sup>9</sup> Fatalities from immunotherapy in the United States since 1945 have been extensively reviewed by Lockey, R F, et al<sup>10</sup>, Reid M J et al.<sup>11</sup> and more recently by Bernstein, D. I. et al<sup>12</sup>. With careful attention to dosage and administration, such reactions occur infrequently, but it must be remembered that allergenic extracts are highly potent to sensitive individuals and **OVERDOSE** could result in anaphylactic symptoms. Therefore, it is imperative that physicians administering allergenic extracts understand and be prepared for the treatment of severe reactions.

Systemic reactions are characterized by one or more of the following symptoms: Sneezing, mild to severe general urticaria, itching other than at the injection site, extensive or generalized edema, wheezing, asthma, dyspnea, cyanosis, hypotension, syncope and upper airway obstruction. Symptoms may progress to shock and death. Patients should always be observed for 20 to 30 minutes after any injection. Volume expanders and vasopressor agents may be required to reverse hypotension. Inhalational bronchodilators and parenteral aminophylline may be required to reverse bronchospasm. Severe airway obstruction, unresponsive to bronchodilator, may require tracheal intubation and use of oxygen. In the event of a marked systemic reaction, application of a tourniquet above the injection site and the administration 0.2 mL to 1.0 mL of Epinephrine Injection (1:1000) is recommended. Maximal recommended dose for children under 2 years of age is 0.3 mL. Maximal recommended dose for children between 2 and 12 years of age is 0.5 mL. The tourniquet should not be left in place without loosening for 90 seconds every 15 minutes.

The next therapeutic injection of extract should be reduced to the dose which did not elicit a reaction, and subsequent doses increased more slowly, i.e., use of intermediate dilutions.

**OVERDOSE**

Signs and symptoms of overdose are typically local and systemic reactions. For a description and management of overdose reactions, refer to "Adverse Reactions" section above.

**DOSAGE AND ADMINISTRATION**

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

When diluting bulk extracts, use of either Sterile Diluent for Allergenic Extracts or Sterile Diluent for Allergenic Extracts Normal Saline with HSA is recommended. Dilutions should be made with sterile disposable syringes using aseptic technique. Commonly 10 fold dilutions are used to achieve a desired concentration for intradermal testing or initiation and continuation of immunotherapy. For example, transferring 0.5 mL of a 10,000 AU/mL extract into 4.5 mL of diluent will yield 5 mL of extract @ 1,000 AU/mL. Prepare as many additional serial dilutions as necessary to reach the appropriate concentration.

Care should be exercised to avoid cross contamination of allergens if mixing with other allergenic extracts. The use of separate syringes for each allergen and diluent when compounding patient mixes is recommended.

Diagnosis - In diagnosing the sensitive individual, the symptom history must be associated with exposure to the allergen. Skin testing is used in conjunction with a definitive history for diagnosing individual sensitivities.

An excellent method of recording results is to cover the skin reaction with transparent tape, outline the erythema first then the wheal with an indelible pen, then remove the tape and transfer it to the patient's permanent record. For preferred results, it is recommended that the actual measurement of the extent of both responses be recorded. This can be accomplished by measuring the longest erythema diameter, then selecting the mid-point of that line and measuring at a 90° angle to that line to determine the orthogonal diameter. The sum of these two measurements is the sum of erythema (ΣE); the sum of wheal diameters is determined in a similar manner.

Patient's response is graded on the basis of the size of erythema and/or wheal.

Percutaneous (prick/scratch/puncture) test:

Prick, scratch, or puncture skin tests should be performed initially using an extract specially made for this purpose. The usual dose is one drop.

In a skin test study of 10 patients who were determined to be allergic to mite (D. farinae), the mean puncture test (using a bifurcated needle) to a solution containing 10,000 AU/mL had a sum of erythema of 73 mm (range 43 - 138 mm) and a sum of wheal of 17 mm (range 7 - 31 mm).

In another skin test study of 11 patients who were determined to be allergic to mite (D. pteronyssinus), the mean puncture test (using a bifurcated needle) to a solution containing 10,000 AU/mL had a sum of erythema of 84 mm (range 56 - 112 mm) and a sum of wheal of 20 mm (range 7 - 33 mm).

What follows are general guidelines for percutaneous testing. Different devices and/or techniques influence the size of the reaction, therefore it is important to refer to the device manufacturer's or distributor's instructions when grading reactions.

0 No wheal. Erythema absent or very slight (not more than 1 mm in diameter).

+ Wheal absent or very slight erythema present (not more than 3 mm diameter).

++ Wheal not more than 3 mm diameter, or erythema not more than 5 mm diameter.

+++ Wheal between 3 mm and 5 mm in diameter with erythema. Possible pseudopodia and itching.

++++ Any larger reaction with itching and possible pain.

Intradermal test:

On the forearm or upper outer aspect of the arm, using a 26 - 27 gauge, short bevel needle, inject intradermally .05 mL of the intradermal test solution. Skin whealing responses should be observed 10 - 20 minutes after administering the test.

In a skin test study of the 10 mite puncture reactive patients (D. farinae) described above, the mean intradermal dose for ΣE = 50 mm was 0.01 AU/mL ( range = <0.0003 to 0.4 AU/mL).

In the skin test study of the 11 mite puncture reactive patients (D. pteronyssinus) described above, the mean intradermal dose for ΣE = 50 mm was 0.006 AU/mL ( range = <0.0007 to 0.05 AU/mL).

Intradermal testing should start with a dilute solution, usually in the range of 1 AU or less.

Glycerinated extracts diluted for intradermal testing may be diluted at least 25 fold to less than 2% glycerin (by volume) as glycerin above this level can cause false positive intradermal skin tests.

A negative skin test is one where the sum of erythema was 0 or equal to the sum of the wheal. As a negative control, the diluent should be tested and included in the interpretation of the skin reactions.

0 No increase in size of bleb since injection. No erythema.

+ An increase in size of bleb and a wheal not more than 5 mm diameter with associated erythema.

++ Wheal between 5 mm and 8 mm in diameter with erythema.

+++ Wheal between 8 mm and 12 mm in diameter with erythema and possible pseudopodia, itching or pain.

++++ Any larger reaction with itching and pain and possible diffuse blush of the skin surrounding the reaction area.

Immunotherapy - Starting dose for immunotherapy is related directly to a patient's sensitivity as determined by carefully executed skin testing. Degree of sensitivity can be established by determination of D50 (the intradermal dose, base three, that produces a ΣE = 50 mm).<sup>1</sup>

A general rule is to begin at 1/10 of the dose that produces sum of erythema of 50 mm (approximately a 2+ positive skin test reaction). For example, if a patient exhibits a 2+ intradermal reaction to 1 AU/mL, the first dose should be no higher than 0.05 mL of 0.1 AU/mL. Dosage may be increased by 0.05 mL each time until 0.5 mL is reached, at which time the next 10-fold more concentrated dilution can be used, beginning with 0.05 mL, if no untoward reaction is observed. (See beginning of **DOSAGE AND ADMINISTRATION** section for instructions in preparing dilutions of concentrates.)

If a tolerated dose of allergenic extract has been established, the initial dose from the new extract should be reduced by 75% of the previously well tolerated dose (see also Precautions).

Interval between doses in the early stages of immunotherapy is no more than once to twice a week, and may gradually be increased to once every two weeks. Generally, maintenance injections may be given as infrequently as once every two weeks to once a month. The progress of patients on immunotherapy should be closely monitored. If improvement is realized a usual course of treatment may be from 3 to 5 years. If progress is unsatisfactory for a year or more, discontinuation of immunotherapy should be considered.

Injections are given subcutaneously preferably in the arm. It is advantageous to give injections in alternate arms and routinely in the same area. In some patients, a local tolerance to the allergen may develop thus preventing a possible severe local reaction.

After inserting the needle, but before injecting the dose, pull plunger of the syringe slightly, if blood returns in the syringe, discard the syringe and contents and repeat injection at another site.

Bulk concentrated extracts must be diluted for initial therapy and intradermal skin testing. For recommended diluent, refer to the beginning of the **DOSAGE AND ADMINISTRATION** section.

Use standard aseptic precautions when making dilutions. The first dose of the new extract should be reduced at least 50% - 75% of the amount of the dosage from the previous extract.

Stability studies for diluted and undiluted forms of this product are not complete. Indications are the undiluted product will retain its potency under recommended storage conditions at least until the expiration date on the vial label is reached. It is recommended that minimal amounts of the concentrate be diluted so that the diluted product is used up within a relatively short period of time, i.e., preferably not more than four weeks.

**HOW SUPPLIED**

For percutaneous testing, 5 mL vial, 10,000 AU/mL in glycerin 50% (V/V).

For immunotherapy, 10 mL, 30 mL and 50 mL vials of bulk concentrate, 10,000 AU/mL in glycerin 50% (V/V).

**STORAGE:** To maintain stability of allergenic extracts, proper storage conditions are essential. Bulk concentrates and diluted extracts are to be stored at 2° to 8° C even during use. Bulk or diluted extracts are not to be frozen. Do not use after the expiration date shown on the vial label.

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ALLERGENIC EXTRACT  
(STANDARDIZED CAT HAIR)  
DESCRIPTION

**WARNING**

This product should be used only by or under the direction of physicians experienced in administering allergens to the maximum tolerated dose and the emergency treatment of anaphylaxis, and only where adequate means for treating severe systemic reactions are immediately available.

This standardized cat hair extract is not interchangeable with non-standardized extracts, cat pelt extracts or with extracts labeled in allergy units per ml (AU/ml). See Description, Warnings, and Dosage and Administration sections for further information.

Allergenic extracts may potentially elicit a severe life-threatening systemic reaction, rarely resulting in death<sup>1</sup>. Because of the possibility of severe systemic reactions, the patient should be instructed in the recognition of anaphylactic symptoms, observed in the office for 20 to 30 minutes after each injection, and warned to return to the office if symptoms of an allergic reaction occur. Serious adverse events should be reported to the FDA MedWatch Program:

**Adverse Event Reporting**

5600 Fishers Lane Rockville, MD 20852-9787, (1-800-FDA-1088)

Patients receiving beta-blockers may not be responsive to epinephrine or inhaled bronchodilators, and the risk of severely complicating the treatment of systemic reactions should be carefully considered before a decision to treat is reached. Care should also be taken with patients with unstable or steroid-dependent asthma, or with underlying cardiovascular disease.

Before administering this or any allergenic extract, physicians should be thoroughly familiar with the information in this insert, especially the Warnings, Precautions, and Adverse Reactions sections.

**DESCRIPTION**

Standardized cat hair extract is manufactured from source material obtained from the wash of cat hair clippings, which is then concentrated and absorbed onto powdered cat hair. Cat albumin and other serum-related non-Fel d 1 allergens, found in cat pelt extracts, have not been included in this extract. Cat albumin is not an important allergen for 80% of cat-sensitive patients<sup>2</sup>. They are supplied as sterile solutions, for scratch, intradermal or subcutaneous administration. The inactive ingredients are as shown in Table 1.

Table 1		
Allergenic Extracts, Inactive Ingredients		
Extract Formulation	Ingredient	Concentration(%)
Glycerinated	Sodium Chloride	0.5
	Sodium Bicarbonate	0.25
	Glycerin	50(v/v)

Standardized cat hair extracts containing 10 to 19.9 Fel d 1 units per ml are assigned 10,000 Bioequivalent Allergy Units per ml (BAU/ml) based on quantitative skin testing<sup>3</sup>. Standardized cat hair extracts containing 5 to 9.9 Fel d 1 units per ml are assigned 5,000 BAU/ml.

Isoelectric focusing (IEF) patterns of these standardized cat extracts have been shown to be predictive of the presence of non-Fel d 1 allergens. IEF has been adopted by the FDA as a release criterion. Therefore, all lots of Standardized Cat Hair extract are required to be compared by IEF to Center for Biologics Evaluation and Research (CBER) Cat Hair Extract Reference<sup>4</sup>.

Allergenic extracts must be diluted before use in intradermal diagnosis or in the initial stages of treatment.

**CLINICAL PHARMACOLOGY<sup>5</sup>**

The mode of action of allergenic extracts is under investigation.

The skin test reaction occurring in previously sensitized individuals is probably related to the interaction of antigen with IgE antibody and the subsequent release of histamine from mast cells. The therapeutic action of allergenic extracts may be related to the production of IgG (blocking) antibodies that remove allergenic proteins from the blood stream. Effective immunotherapy with allergenic extracts is usually associated with a shift in T-cell populations from a TH2 predominant type to a TH1 predominant population. This shift has been associated with changes in certain cytokines and other mediators. Immunotherapy also produces an initial rise in specific IgE levels, which then decrease as therapy continues.

Immunotherapy using cat extract has been studied by several investigators. Generally, it is believed that hyposensitization with this product is helpful in reducing allergic symptoms associated with environmental exposure to cat allergens.<sup>6,7</sup>

In skin test studies of ten patients who were determined to be allergic to cat, the average puncture test (using a bifurcated needle) to a Cat Hair Extract containing 10,000 BAU/ml produced a mean  $\sum$  E of 82.4 mm with a range of 61 to 110 mm and a mean  $\sum$  W of 15.6 mm with a range of 9 to 19 mm.

In this skin test study of cat-sensitive patients, the study subjects exhibited the following intradermal test responses:

		BAU/ml to elicit 50 mm sum of diameter of erythema reaction.	
Allergen	Number of Persons	Mean	Range
Cat Hair	10	0.015	0.0007-0.21

**INDICATIONS AND USAGE**

Standardized Cat Hair allergenic extracts are indicated for the diagnostic skin testing and immunotherapy of patients whose histories indicate that they experience allergic symptoms upon natural exposure to the specific allergens.

**CONTRAINDICATIONS**

The product is contraindicated for use in subjects who are not clinically allergic to the specified allergen, or who are not reactive to ALK-Abelló extract. No other absolute contraindications to immunotherapy with allergenic extracts are known.

However, the risk of serious systemic anaphylactic reactions to any potent allergenic extract suggests a number of preexisting conditions that should be considered relative contraindications. Among those conditions are acute infections, immune disease, severe cardiac disease, pulmonary diseases such as asthma with a significant irreversible component, and treatment with  $\beta$ -adrenergic antagonist drugs ("beta-blockers"). See also Warnings, Precautions, and Adverse Reactions.

**WARNINGS**

See additional warnings given in the box at the beginning of this insert.

Do not use this extract or allow its use until you have read this insert, and have taken adequate precautions to prevent inadvertent dosage errors. See Dosage and Administration for further information.

Some patients are highly sensitive to allergenic extracts, and in such patients even a small skin test dose could result in a serious systemic reaction. Adequate means to treat such reactions must be immediately available, including the following equipment<sup>8</sup>: stethoscope and sphygmomanometer; tourniquets, syringes, hypodermic needles, and large-bore (14 gauge) needles; aqueous epinephrine HCl 1:1000; oxygen, intravenous fluids, and the equipment for administering them; oral airway; diphenhydramine or similar antihistamine; aminophylline and corticosteroids for intravenous injection; and vasopressor.

Observing the following precautions will reduce the risk of serious systemic reactions:

- Do not begin immunotherapy without establishing the appropriate initial dose by skin testing (see Dosage and Administration), and do not inject the undiluted extract concentrate at any time unless tolerance has been demonstrated.
- When changing to an extract from a different manufacturer, establish the proper dosage by skin testing.
- When changing to a different lot of extract, reduce the dose by 50-75%; this is particularly important after using an extract that is near its expiration date.
- Take care to properly prepare, label, store, and control all dilutions.
- Use caution in dosing of high-risk steroid-dependent labile asthmatics.

DO NOT GIVE INTRAVENOUSLY. After inserting the needle subcutaneously, but before injecting the dose, retract the plunger of the syringe slightly. If blood appears in the syringe, discard the syringe and its contents and repeat the injection at another site. Subcutaneous injection is recommended because intracutaneous or intramuscular injections are more likely to produce local reactions.

Observe the patient at 20 to 30 minutes after injection, and be alert for the signs of impending reaction. Make sure the patient understands that serious delayed reactions can occur later on, how to recognize them, and what to do if they occur.

Patients who are receiving beta-blocking medication are high-risk patients for immunotherapy, because systemic reactions to the extract may be more severe in such patients<sup>9</sup>, and because the beta-blocker may impair the ability to reverse the reaction<sup>10</sup> in such patients. This risk should be carefully weighed before a decision to treat is reached. Care should also be taken with patients with unstable or steroid-dependent asthma, or with underlying cardiovascular disease.

This and any allergenic extract should be temporarily withheld or its dosage reduced under any of these conditions<sup>11</sup>:

- When the patient has an unexpectedly severe local or any systemic reaction to the previous dose.
- If the patient is experiencing allergic symptoms such as rhinitis or asthma, or is ill with flu or infection accompanied by fever.
- If an unusually long time has passed since the previous injection.
- If the patient is exposed to excessive amounts of clinically relevant allergen prior to therapy.

Allergic patients differ widely in their sensitivity to this or any allergenic extract, and no single dosage regimen can be recommended for all patients. Progression to the next higher dose requires tolerance of the previous one, and the regimen must be modified if any of the conditions described above occur. Such modifications should include weaker dilutions and smaller dosage increments.

**PRECAUTIONS**

**General:**

Patient compliance is an important consideration in the decision to initiate immunotherapy with any potent allergenic extract. Therapy should not be initiated if in the judgment of the physician the patient cannot be depended upon to respond promptly and properly to an impending

adverse reaction, or to report such reactions.

Care must be taken to control the preparation, labeling, storage, and use of dilutions. The ramifications of inadvertent overdosage are severe (see Warnings and Adverse Reactions), and so procedural safeguards such as training programs, color-coded labeling, storage controls, and auditing are recommended.

As with the administration of any parental drug, observe all aspects of aseptic technique. In both testing and treatment, use a separate sterilized needle and syringe for each individual patient, to prevent transmission of hepatitis and other infectious agents from one person to another.

**Information For Patients:**

The patient should be told to remain in the office for 20 to 30 minutes after injection, and be alert for the signs of impending reaction.

The patient should be instructed that serious delayed reactions can occur later on, and that these must be reported to the physician immediately. These reactions include swelling or tenderness at the site of injection, rhinorrhea, sneezing, coughing, shortness of breath, nausea, dizziness, wheezing, rash or faintness.

**Drug Interaction:**

Patients who are receiving beta-blocking medication are high-risk patients for immunotherapy, because systemic reactions to the extract may be more severe in such patients<sup>9</sup>, and because the beta-blocker may impair the ability to reverse the reaction<sup>10</sup>.

The patient should not take antihistamines prior to skin testing, since the pharmacological actions of such drugs might interfere with the skin test response. Discontinue regular antihistamines for 3-10 days and longacting antihistamines such as Astemizole for as long as 60 days before skin testing<sup>12</sup>. Also, be aware that the concurrent use of antihistamines during immunotherapy might mask an otherwise observable local reaction to an injection.

**Carcinogenesis, Mutagenesis, Impairment Of Fertility:** No long term studies with this or any allergenic extract have been carried out to determine their effect on carcinogenesis, mutagenesis, or impairment of fertility.

**Pregnancy Category C:** Animal reproduction studies have not been conducted with allergenic extracts. It is also not known whether allergenic extracts can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Allergenic extracts should be given to a pregnant woman only if clearly needed.

On the basis of histamine's known ability to contract uterine muscle, any reaction that would release significant amounts of histamine, whether occurring from allergen exposure or immunotherapy overdose, should be avoided.

**Nursing mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when allergenic extracts are administered to a nursing woman.

**Geriatric Use:** Clinical studies of allergenic extracts have not included sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

**Pediatric Use:** Clinical studies of allergenic extracts did not include sufficient numbers of pediatric patients to determine whether they respond differently from older patients. Other reported clinical experience has not identified differences in responses between pediatric and adult patients. In general, dose selection for a pediatric patient should be cautious, usually starting at the low end of the dosing range.

**ADVERSE REACTIONS**

Severe anaphylactic reactions to this extract can occur in extremely allergic patients and at any dosage level. Do not use this extract unless you are prepared to deal with these reactions, and until you have read and understood the warnings, precautions, and dosage and administration sections of this insert.

The most serious systemic reaction that can occur is anaphylactic shock, which, while rare, is life threatening and must be treated immediately. Among other systemic reactions that have occurred are laryngeal edema, fainting, pallor, bradycardia, hypotension, bronchospasm, angioedema, cough, sneezing, conjunctivitis, rhinitis, and urticaria.

Should a serious systemic reaction occur:

- Inject 0.3-0.5 ml of 1:1000 epinephrine into the opposite arm; this may be repeated every 5 to 10 minutes, as a succession of smaller doses is more effective and less dangerous than a single larger one. Use a smaller dose for infants and children, in the range of 0.01 ml/kg of body weight.
- Apply a tourniquet proximal to the injection site; loosen it at least every 10 minutes interval/inject no more than 0.1 ml of 1:1000 epinephrine at the injection site, to delay the absorption of the remaining extract.
- Beta adrenergic agonists or aminophylline may be helpful in alleviating bronchospasm and airway obstruction. Other treatments that may be of benefit include H1 antihistamines (e.g., 1 mg/kg diphenhydramine) and glucocorticoids (e.g., 120 mg methylprednisolone).

These measures will almost always reverse the reaction, but in the rare instances when they do not, then the full armamentarium of emergency medicine may be required, among them: direct laryngoscopy, direct current cardioversion, tracheotomy, and intracardiac injection of drugs<sup>8</sup>.

The occurrence of a severe systemic reaction to an injection of this extract does not contraindicate further therapy, but the next dose given should be reduced by at least 90%, and raised very slowly thereafter. If

a pattern of systemic reactions— even very mild ones— appears, then the benefits of continued treatment must be carefully weighed against the substantial demonstrated risk.

Local reactions, even relatively severe but transient redness, swelling and discomfort, are the normal physiologic response to the allergens and to the volume of the fluid injected, and in their milder forms are not unexpected. Local reactions generally subside quickly and do not require treatment, but application of cold to the injection site or other symptomatic measures may be useful. However, severe local reactions should be considered a warning of potential systemic reaction if that dosage is continued. Always reduce the dose substantially if such a local reaction occurs.

Overdosage: See Adverse Reactions section.

DOSAGE AND ADMINISTRATION

Dilution

Allergenic extract concentrates must be diluted before use in intradermal skin testing or the initial stages of immunotherapy. As with any parenteral product, always use careful aseptic technique in preparing dilutions, assuring that the vials, diluents, and syringes are sterile, and that the dilutions are prepared under aseptic conditions. Sterile diluents that can be used include Normal Saline, Buffered Saline, 50% glycerin or Albumin Saline (HSA).

To obtain the concentrations required for intradermal testing or for the initial stages of immunotherapy, prepare serial 5 or 10-fold dilutions of the concentrate to achieve the concentrations specified in Table 2 or 3, below. The relatively small 0.5 ml volume conserves the original concentration, and is convenient because sterile diluent is readily available in prefilled 2.0 and 4.5 ml volumes.

Table 2 Examples of Ten-fold Dilution Series			
Dilution Number	Add This Volume/Dilution of Extract	To This Diluent Volume	To Obtain Extract at the Following Concentration (BAU/mL)
0	Concentrate		10,000
1	0.5 ml concentrate	4.5 ml	1,000
2	0.5 ml dilution # 1	4.5 ml	100
3	0.5 ml dilution # 2	4.5 ml	10
4	0.5 ml dilution # 3	4.5 ml	1.0
5	0.5 ml dilution # 4	4.5 ml	0.10
6	0.5 ml dilution # 5	4.5 ml	0.01

Table 3 Examples of Five-fold Dilution Series			
Dilution Number	Add This Volume/Dilution of Extract	To This Diluent Volume	To Obtain Extract at the Following Concentration (BAU/mL)
0	Concentrate		5,000
1	0.5 ml concentrate	2.0 ml	1,000
2	0.5 ml dilution # 1	2.0 ml	200
3	0.5 ml dilution # 2	2.0 ml	40
4	0.5 ml dilution # 3	2.0 ml	8
5	0.5 ml dilution # 4	2.0 ml	1.6
6	0.5 ml dilution # 5	2.0 ml	0.32

For each vial, record the date of dilution on the label.

Skin Testing

Scratch or prick-puncture testing should be performed using the 10,000 BAU/ml concentrate, a negative control (diluent) and a positive control (histamine, 1.8 mg/ml). Extract for intradermal testing can be prepared by diluting the concentrate with any appropriate aqueous sterile diluent, as described above. A 100 BAU/ml concentration is also available for intradermal testing.

The following skin testing protocol can be recommended:

1. The location for both prick and intradermal testing is usually the flexor surface of the forearm. Use aseptic technique throughout.
2. Perform a preliminary skin prick test with the extract concentrate, by placing a drop of the extract on the skin and then using a needle to prick the skin gently through the drop. Use a normal diluent as a negative control and histamine as a positive control. Read the test after 15 minutes. Patients reacting strongly to the prick test should be considered highly sensitive to the extract, and suitable precautions should be taken. A suggested grading system appears in Table 4. If the histamine control is negative, the possibility of skin non-reactivity must be considered.
3. Begin intradermal testing, generally starting at the 100 BAU/ml dilution if the prick test was negative, or at 0.1 or 0.01 BAU/ml if the test was positive or if no prick test was done. Use a separate, sterilized syringe and needle for each extract and each patient. Introduce the needle into the superficial skin layers until the bevel is completely buried, then slowly inject approximately 0.02 - 0.05 ml.

4. Measure the wheal and erythema after 15 minutes, and determine the degree of response to the injection, in comparison to the negative control. A suggested grading system appears in Table 5.
5. If the intradermal reaction is negative at the initial concentration, continue intradermal testing with 10-fold increments in the concentration until a clearly positive response has been obtained or a peak concentration of 100 BAU/ml has been tested, whichever occurs first.

Table 4 Skin Test Grading System <sup>12</sup>	
Grade	Wheal Results
0	No Wheal / same size as negative
+	<Half the Histamine Diameter
++	Half the Histamine Diameter
+++	Same Size as Histamine Control
++++	Size of Histamine Control +2mm

Table 5 Intradermal Skin Test Grading System <sup>13</sup>		
Grade	Mean Diameters (mm)	
	Wheal	Erythema
0	<5.0	<5.0
±	5.0-10.0	5.0-10.0
1+	5.0-10.0	11.0-20.0
2+	5.0-10.0	21.0-30.0
3+	5.0-10.0, or pseudopods	31.0-40
4+	>15.0, many pseudopods	>40.0

The interpretation of the skin response is based on the size of the wheal, the size of the erythema, and the appearance of irregular, spreading, pseudopodlike projections from the test area. The presence of the latter indicates marked hypersensitivity. A patient is considered sensitive to the test extract if there is a reaction of 1+ or greater at a concentration of 100 BAU/ml or less, providing that the 1+ reaction is in relation to the negative control.

Immunotherapy

Administer the extract solution subcutaneously, using a suitable sterile 1 ml syringe and a 25-27 gauge 1/4 to 5/8 inch needle. The injections are typically given in the lateral aspect of the upper arm.

Dosage of allergenic extracts is a highly individualized matter<sup>12</sup>, and varies according to the degree of sensitivity of the patient, the clinical response, and tolerance of the extract administered previously.

A safe starting dose for any allergic patient is that dose which on intradermal testing produces a 1+ reaction. For most patients a starting dose that is 0.1 ml of 0.01 BAU/ml dilution of the extract concentrate should be well tolerated, although in some very sensitive patients a more dilute concentration may be required.

If no untoward symptoms are observed following the initial injection, the dose can be increased gradually for each subsequent injection until the injection volume reaches 0.6 -0.8 ml. Then begin using the next more concentrated ten-fold dilution, and proceed with this dosage pattern until the maintenance dose-defined as that dose that either relieves the patient's symptoms or is the highest that the patient can tolerate is reached. Care must be taken, however, in administering a volume greater than 0.2 ml of any extract in 50% glycerin; such injections can be painful to the patient due to the glycerin content.

After each injection, evaluate the patient's skin reaction and overall response to determine whether the next scheduled dose can be given:

- If a single dose results in more than a moderate local reaction (>50 mm wheal) within 1/2 hour, the same dose should be repeated at the next visit – or visits – until the patient has tolerated it.
- If any systemic manifestation of sensitivity occurs during or following a visit, or if a single dose results in an excessive local reaction (>100 mm wheal) within 1/2 hour, the total dosage for the next visit should be reduced to half of the dose that caused the reaction.
- Delayed local reactions (occurring 24-48 hours after injection) are relatively common, and do not appear to predict difficulties with future doses. As a rule, therefore, dosage adjustment is not required in most instances. However, at the physician's discretion and for the comfort of the patient, if delayed large local reactions over 10 mm are reported, the subsequent dose should be held at the same level as the one causing the reaction.

The optimal interval between doses of allergenic extract has not been definitely established. However, as is customarily practiced, injections are given 1, 2, or 3 times per week until the maintenance dose of extract is reached. At this time, the injection interval may be increased to 2 weeks, then to 3 weeks and finally to 4 weeks depending on the clinical status. If the patient does not return for 6 to 8 weeks after the last injection, the dose should be reduced to 25% of the last dose. If longer than 8 weeks, a dose reduction of one, two or three dilutions may be made depending on a consideration of the components and the patient's sensitivity. The dosage and the interval between injections may need to be modified according to the clinical response of the patient. When switching patients to fresh extract, the initial dose should be reduced to one-quarter of the previous dose.

Duration of treatment: Careful selection of allergens and cautious progression to maximally tolerated doses are important elements in the success of immunotherapy. The optimal length of treatment with allergen immunotherapy is unknown. A treatment period of 3 to 5 years is common, although continuation for longer periods may be appropriate<sup>13</sup>.

Allergenic extracts, as any parenteral drug product, should be inspected visually for evidence of foreign material or discoloration prior to administration. Some variation in color is normal and a minor level of extract precipitate may occur with some extracts, but do not use the extract if there is any question of its condition exists.

HOW SUPPLIED

These allergenic extract concentrates are supplied as sterile solutions in rubber stoppered glass vials. The concentrate is available in 5, 10, 30 and 50 ml size serum vials for Immunotherapy at 5,000 BAU/ml and 10,000 BAU/ml; intradermal dilution is available in 5 ml vial size at a concentration of 100 BAU/ml; and the scratch test products are available in 5 ml dropper vials at a concentration of 10,000 BAU/ml.

To ensure maximum potency for the entire dating period, extract concentrates contain 50% glycerin (v/v) unless otherwise instructed by the physician.

Diluted extracts, special mixtures and prescription treatment sets are available at the request of the physician.

Storage: The extract concentrate and all dilutions should be kept refrigerated at

2-8°C. Do not freeze, and do not use the extract concentrate after the expiration date printed on the vial label. Extracts that contain less than 50% v/v glycerin are less stable.

LIMITED WARRANTY

We warrant that this product was prepared and tested according to the applicable standards of the FDA and was true to label when it left our hands. Because of biological differences in individuals, because this product is manufactured to be potent, and because we have no control over the conditions of use, we cannot and do not warrant either a good effect, or against an ill effect following its use. This label sets forth the complete and excluding statement of all the terms of any warranty, express or implied (including the warranty of merchantability) between ALK-Abelló, Inc., the prescriber, and the user of this product. Such representations and warranties shall not be varied, supplemented, qualified or interpreted by any prior course of dealing between the parties, or by any usage of trade unless specifically authorized in writing, signed by any officer of the corporation.

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Manufactured by:  
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731B



**HIGHLIGHTS OF PRESCRIBING INFORMATION**  
These highlights do not include all the information needed to use ODACTRA safely and effectively. See full prescribing information for ODACTRA.

**ODACTRA™** House Dust Mite (*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*) Allergen Extract  
Tablet for Sublingual Use  
Initial U.S. Approval: 2017

**WARNING: SEVERE ALLERGIC REACTIONS**

See full prescribing information for complete boxed warning.

- ODACTRA can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction. (5.1)
- Do not administer ODACTRA to patients with severe, unstable or uncontrolled asthma. (4)
- Observe patients in the office for at least 30 minutes following the initial dose. (5.1)
- Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use. (5.2)
- ODACTRA may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. (5.2)
- ODACTRA may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers. (5.2)

**INDICATIONS AND USAGE**

ODACTRA is an allergen extract indicated as immunotherapy for house dust mite (HDM)-induced allergic rhinitis, with or without conjunctivitis, confirmed by *in vitro* testing for IgE antibodies to *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* house dust mites, or skin testing to licensed house dust mite allergen extracts. ODACTRA is approved for use in adults 18 through 65 years of age. (1)

**DOSAGE AND ADMINISTRATION**

- For sublingual use only. (2)
- One tablet daily. (2.1)

- Place the tablet immediately under the tongue where it will dissolve within 10 seconds. Do not swallow for at least 1 minute. (2.2)
- Administer the first dose of ODACTRA under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. Observe patients in the office for at least 30 minutes following the initial dose. (2.2)

**DOSAGE FORMS AND STRENGTHS**

- Tablet, 12 SQ-HDM. (3)

**CONTRAINDICATIONS**

- Severe, unstable or uncontrolled asthma. (4)
- History of any severe systemic allergic reaction or any severe local reaction to sublingual allergen immunotherapy. (4)
- A history of eosinophilic esophagitis. (4)
- Hypersensitivity to any of the inactive ingredients contained in this product. (4)

**WARNINGS AND PRECAUTIONS**

- Inform patients of the signs and symptoms of serious allergic reactions and instruct them to seek immediate medical care and discontinue therapy should any of these occur. (5.1)
- In case of oral inflammation or wounds, stop treatment with ODACTRA to allow complete healing of the oral cavity. (5.7)

**ADVERSE REACTIONS**

- The most common solicited adverse reactions reported in ≥10% of subjects treated with ODACTRA were: throat irritation/itching, itching in the mouth, itching in the ear, swelling of the uvula/back of the mouth, swelling of the lips, swelling of the tongue, nausea, tongue pain, throat swelling, tongue ulcer/sore on the tongue, stomach pain, mouth ulcer/sore in the mouth, and taste alteration/food tastes different. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ALK-Abelló Inc., a subsidiary of ALK-Abelló A/S, at +1 512-252-4241 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 08/2019

**3 DOSAGE FORMS AND STRENGTHS**

ODACTRA is available as 12 SQ-HDM\* tablets that are white to off-white, circular with a debossed pentagon detail on one side.

\*SQ-HDM is the dose unit for ODACTRA. SQ is a method of standardization of biological potency, major allergen content and complexity of the allergen extract. HDM is an abbreviation for house dust mite.

**4 CONTRAINDICATIONS**

ODACTRA is contraindicated in patients with:

- Severe, unstable or uncontrolled asthma
- A history of any severe systemic allergic reaction
- A history of any severe local reaction after taking any sublingual allergen immunotherapy
- A history of eosinophilic esophagitis
- Hypersensitivity to any of the inactive ingredients contained in this product [see *Description* (11)].

**5 WARNINGS AND PRECAUTIONS**

**5.1 Severe Allergic Reactions**

ODACTRA can cause systemic allergic reactions including anaphylaxis which may be life-threatening. In addition, ODACTRA can cause severe local reactions, including laryngopharyngeal swelling, which can compromise breathing and be life-threatening. Educate patients to recognize the signs and symptoms of these allergic reactions and instruct them to seek immediate medical care and discontinue therapy should any of these occur. Allergic reactions may require treatment with epinephrine. [See *Warnings and Precautions* (5.2).]

Administer the initial dose of ODACTRA in a healthcare setting under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases and prepared to manage a life-threatening systemic or local allergic reaction. Observe patients in the office for at least 30 minutes following the initial dose of ODACTRA.

**5.2 Epinephrine**

Prescribe auto-injectable epinephrine to patients receiving ODACTRA. Instruct patients to recognize the signs and symptoms of a severe allergic reaction and in the proper use of emergency auto-injectable epinephrine. Instruct patients to seek immediate medical care upon use of auto-injectable epinephrine and to stop treatment with ODACTRA. [See *Patient Counseling Information* (17).]

See the auto-injectable epinephrine package insert for complete information.

ODACTRA may not be suitable for patients with certain medical conditions that may reduce the ability to survive a serious allergic reaction or increase the risk of adverse reactions after epinephrine administration. Examples of these medical conditions include but are not limited to: markedly compromised lung function (either chronic or acute), unstable angina, recent myocardial infarction, significant arrhythmia, and uncontrolled hypertension.

ODACTRA may not be suitable for patients who are taking medications that can potentiate or inhibit the effect of epinephrine. These medications include:

**Beta-adrenergic blockers:** Patients taking beta-adrenergic blockers may be unresponsive to the usual doses of epinephrine used to treat serious systemic reactions, including anaphylaxis. Specifically, beta-adrenergic blockers antagonize the cardiostimulating and bronchodilating effects of epinephrine.

**Alpha-adrenergic blockers, ergot alkaloids:** Patients taking alpha-adrenergic blockers may be unresponsive to the usual doses of epinephrine used to treat serious systemic reactions, including anaphylaxis. Specifically, alpha-adrenergic blockers antagonize the vasoconstricting and hypertensive effects of epinephrine. Similarly, ergot alkaloids may reverse the pressor effects of epinephrine.

**Tricyclic antidepressants, levothyroxine sodium, monoamine oxidase inhibitors, and certain antihistamines:** The adverse effects of epinephrine may be potentiated in patients taking tricyclic antidepressants, levothyroxine sodium, monoamine oxidase inhibitors, and the antihistamines chlorpheniramine, and diphenhydramine.

**Cardiac glycosides, diuretics:** Patients who receive epinephrine while taking cardiac glycosides or diuretics should be observed carefully for the development of cardiac arrhythmias.

**5.3 Upper Airway Compromise**

ODACTRA can cause local reactions in the mouth or throat that could compromise the upper airway [see *Adverse Reactions* (6.1)]. Consider discontinuation of ODACTRA in patients who experience persistent and escalating adverse reactions in the mouth or throat.

**5.4 Eosinophilic Esophagitis**

Eosinophilic esophagitis has been reported in association with sublingual tablet immunotherapy [see *Contraindications* (4)]. Discontinue ODACTRA and consider a diagnosis of eosinophilic esophagitis in patients who experience severe or persistent gastroesophageal symptoms including dysphagia or chest pain.

**5.5 Asthma**

Withhold immunotherapy with ODACTRA if the patient is experiencing an acute asthma exacerbation. Re-evaluate patients who have recurrent asthma exacerbations and consider discontinuation of ODACTRA.

**5.6 Concomitant Allergen Immunotherapy**

ODACTRA has not been studied in subjects who are receiving concomitant allergen immunotherapy. Concomitant dosing with other allergen immunotherapy may increase the likelihood of local or systemic adverse reactions to either subcutaneous or sublingual allergen immunotherapy.

**5.7 Oral Conditions**

Stop treatment with ODACTRA to allow complete healing of the oral cavity in patients with oral inflammation (e.g., oral lichen planus, mouth ulcers, or thrush) or oral wounds, such as those following oral surgery or dental extraction.

**6 ADVERSE REACTIONS**

**6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In four double-blind, placebo-controlled, randomized clinical studies, a total of 1279 subjects with house dust mite-induced allergic rhinitis, with or without conjunctivitis, 18 through 65 years of age was treated with at least one dose of ODACTRA 12 SQ-HDM. Of subjects treated with ODACTRA in the four studies, 50% had mild to moderate asthma and 71% were polysensitized to other allergens in addition to HDM, including trees, grasses, weeds, molds, and animal danders. The study population was 88% White, 6% African American, 4% Asian and 55% female.

Study 1 (NCT01700192) was a randomized, double-blind, placebo-controlled study conducted in the US and Canada evaluating ODACTRA in 1482 subjects 12 years of age and older with house dust mite-induced allergic rhinitis with or without conjunctivitis. Of the 1482 subjects, 640 subjects 18 through 65 years of age received at least one dose of ODACTRA, with a median treatment duration of 267 days (range 1 to 368 days). 631 subjects received placebo. Placebo tablets contained the same inactive ingredients as ODACTRA without allergen extract and were packaged identically so that treatment

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**FULL PRESCRIBING INFORMATION**

**WARNING: SEVERE ALLERGIC REACTIONS**

- ODACTRA can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction. (5.1)
- Do not administer ODACTRA to patients with severe, unstable or uncontrolled asthma. (4)
- Observe patients in the office for at least 30 minutes following the initial dose. (5.1)
- Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use. (5.2)
- ODACTRA may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. (5.2)
- ODACTRA may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers. (5.2)

**1 INDICATIONS AND USAGE**

ODACTRA™ is an allergen extract indicated as immunotherapy for house dust mite (HDM)-induced allergic rhinitis, with or without conjunctivitis, confirmed by *in vitro* testing for IgE antibodies to *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* house dust mites, or skin testing to licensed house dust mite allergen extracts. ODACTRA is approved for use in adults 18 through 65 years of age.

ODACTRA is not indicated for the immediate relief of allergic symptoms.

**2 DOSAGE AND ADMINISTRATION**

For sublingual use only.

**2.1 Dose**

One ODACTRA tablet daily.

**2.2 Administration**

Administer the first dose of ODACTRA in a healthcare setting under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. After receiving the first dose of ODACTRA, observe the patient for at least 30 minutes to monitor for signs or symptoms of a severe systemic or a severe local allergic reaction. If the patient tolerates the first dose, the patient may take subsequent doses at home. The patient should administer ODACTRA as follows:

Take the tablet from the blister unit after carefully removing the foil with dry hands.

Place the tablet immediately under the tongue where it will dissolve within 10 seconds. Do not swallow for at least 1 minute.

Wash hands after handling the tablet.

Do not take the tablet with food or beverage.

Food or beverage should not be taken for 5 minutes after taking the tablet.

Data regarding the safety of restarting treatment after missing a dose of ODACTRA are limited. In the clinical studies, treatment interruptions for up to seven days were allowed.

Prescribe auto-injectable epinephrine to patients prescribed ODACTRA and instruct patients in the proper use of emergency self-injection of epinephrine [see *Warnings and Precautions* (5.2)].

blind/masking was maintained. Participants were monitored for unsolicited adverse events and serious adverse events (SAEs) for the duration of therapy (up to 52 weeks). Participants were monitored for solicited adverse reactions for the first 28 days following treatment initiation.

Study participants were provided side effect report cards in which they recorded the occurrence of specific solicited adverse reactions daily for the first 28 days following treatment initiation with ODACTRA or placebo. In Study 1, the most common solicited adverse reactions reported in ≥10% of subjects treated with ODACTRA were: throat irritation/tickle (67.0% vs. 20.8% placebo), itching in the mouth (61.3% vs. 14.1%), itching in the ear (51.7% vs. 11.7%), swelling of the uvula/back of the mouth (19.8% vs. 2.4%), swelling of the lips (18.0% vs. 2.7%), swelling of the tongue (15.8% vs. 2.1%), nausea (14.2% vs. 7.1%), tongue pain (14.2% vs. 3.0%), throat swelling (13.6% vs. 2.4%), tongue ulcer/sore on the tongue (11.6% vs. 2.1%), stomach pain (11.3% vs. 5.2%), mouth ulcer/sore in the mouth (10.3% vs. 2.9%), and taste alteration/food tastes different (10.0% vs. 3.6%). Table 1 summarizes all solicited adverse reactions reported within the first 28 days of treatment initiation in subjects 18 through 65 years of age using the patient-friendly term.

**Table 1: Percentages of Solicited\* Adverse Reactions Within 28 Days After Initiation of Treatment with ODACTRA (Study 1, Safety Analysis Set) in Patients 18 through 65 Years of Age (NCT01700192)**

Adverse Reaction (Patient-Friendly Term)	Study Population: Study 1 Adverse Reactions of Any Intensity		Study Population: Study 1 Adverse Reactions That Were Severe <sup>†</sup>	
	ODACTRA (N=640)	Placebo (N=631)	ODACTRA (N=640)	Placebo (N=631)
<b>Ear and labyrinth disorders</b>				
Itching in the ear	51.7%	11.7%	0.3%	-
<b>Gastrointestinal disorders</b>				
Itching in the mouth	61.3%	14.1%	0.2%	-
Swelling of the uvula/back of the mouth <sup>‡</sup>	19.8%	2.4%	-	-
Swelling of the lips	18.0%	2.7%	-	-
Swelling of the tongue	15.8%	2.1%	-	-
Nausea	14.2%	7.1%	-	-
Tongue pain	14.2%	3.0%	-	-
Tongue ulcer/sore on the tongue	11.6%	2.1%	-	-
Stomach pain	11.3%	5.2%	0.2%	-
Mouth ulcer/sore in the mouth	10.3%	2.9%	-	-
Diarrhea	6.9%	3.6%	-	-
Vomiting	2.5%	1.4%	-	-
<b>Nervous system disorders</b>				
Taste alteration/food tastes different	10.0%	3.6%	-	-
<b>Respiratory, thoracic and mediastinal disorders</b>				
Throat irritation/tickle	67.0%	20.8%	0.3%	-
Throat swelling	13.6%	2.4%	0.2%	-

In Table 1, the dashes represent no subjects.

\*Solicited adverse reactions (modified from World Allergy Organization [WAO] list of local side effects of sublingual immunotherapy [SLIT]) were those reported by subjects within the first 28 days after treatment initiation.

<sup>†</sup>Severe adverse reactions were those assessed by the investigator as severe in intensity, which is defined as incapacitating with inability to work or do usual activity.

<sup>‡</sup>The percentage of subjects reported for the patient-friendly term of "swelling of the uvula/back of the mouth" includes subjects with an enlarged uvula, palatal swelling/edema, and/or mouth swelling/edema (which can be anywhere in the mouth, not specifically back of the mouth).

In Study 1, the timing of the adverse reaction relative to exposure to ODACTRA was evaluated for 7 solicited adverse reactions (itching in the ear, itching in the mouth, swelling of the uvula/back of the mouth, swelling of the lips, swelling of the tongue, throat irritation/tickle, and throat swelling). The median time to onset of these adverse reactions following initiation of treatment with ODACTRA varied from 1 to 7 days. The median duration of these adverse reactions that occurred on the first day of treatment initiation varied from 30 to 60 minutes. These adverse reactions occurred for a median of 2 to 12 days.

In Study 1, the following unsolicited adverse events were reported in numerically more subjects treated with ODACTRA than with placebo and occurred in ≥1% of subjects 18 through 65 years of age within 28 days after initiation of treatment with ODACTRA: paresthesia oral (9.2% vs. 3.2%), tongue pruritus (4.7% vs. 1.1%), oral pain (2.7% vs. 0.6%), stomatitis (2.5% vs. 1.1%), dyspepsia (2.2% vs. 0.0%), pharyngeal erythema (2.0% vs. 0.3%), eye pruritus (1.7% vs. 1.4%), oral mucosal erythema (1.7% vs. 0.2%), upper respiratory tract infection (1.6% vs. 1.1%), sneezing (1.6% vs. 0.3%), lip pruritus (1.4% vs. 0.3%), dysphagia (1.4% vs. 0.0%), fatigue (1.3% vs. 1.0%), hypoesthesia oral (1.3% vs. 1.0%), oropharyngeal pain (1.3% vs. 0.6%), chest discomfort (1.3% vs. 0.3%), dry throat (1.3% vs. 0.3%), pruritus (1.1% vs. 1.0%), and urticaria (1.1% vs. 0.3%).

Studies 2 (NCT01454544) and 3 (NCT01644617) were randomized, double-blind, placebo-controlled studies of subjects 18 years of age and older with house dust mite-induced allergic rhinitis with or without conjunctivitis, and with or without asthma. Study 4 (NCT01433523) was a randomized, double-blind placebo-controlled study that included subjects 18 years of age and older with house dust mite-induced asthma and allergic rhinitis, with or without conjunctivitis.

Across the four clinical studies, 1279 subjects received at least one dose of ODACTRA, of whom 1104 (86%) completed at least 4 months of therapy.

The percentages of subjects in these studies who discontinued treatment because of an adverse reaction while exposed to ODACTRA or placebo were 8.1% and 3.0%, respectively. The most common adverse reactions (≥1.0%) that led to study discontinuation in subjects who received ODACTRA were throat irritation (1.5%), oral pruritus (1.3%), ear pruritus (1.1%), and mouth swelling (1.0%).

Serious adverse events were reported, 16/1279 (1.3%) among ODACTRA recipients and 23/1277 (1.8%) among placebo recipients. No deaths were reported.

Epinephrine use was reported in 5/1279 (0.4%) subjects who received ODACTRA compared to 3/1277 (0.2%) of subjects who received placebo. Of these subjects, 1 ODACTRA recipient reported a systemic allergic reaction and used epinephrine on the day of treatment initiation compared to 2 placebo recipients who reported anaphylaxis and used epinephrine 6 and 25 days after treatment initiation, respectively.

Of 1279 subjects who received ODACTRA, 34 (2.7%) reported dyspepsia compared to 0/1277 (0%) of subjects who received placebo. Twenty subjects who received ODACTRA (1.6%) reported symptoms of gastroesophageal reflux disease (GERD) compared to 3/1277 (0.2%) of subjects who received placebo.

Across 8 clinical studies conducted with different doses of ODACTRA, eosinophilic esophagitis was reported in 2/2737 (0.07%) subjects who received ODACTRA compared to 0/1636 (0%) subjects who received placebo.

## 6.2 Postmarketing Experience

The following adverse reaction has been identified during post-approval use of ODACTRA. Because this reaction is reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

*Skin and Subcutaneous Tissue Disorders:* erythema.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. Available data on ODACTRA administered to pregnant women are insufficient to inform associated risks in pregnancy.

In a fetal/embryo developmental toxicity study performed in mice, administration of ODACTRA during gestation did not reveal adverse developmental outcomes in fetuses (*see 8.1 Data*).

#### Data

##### Animal Data

In a developmental toxicity study, the effect of ODACTRA on embryo/fetal development was evaluated in mice. Animals were administered ODACTRA subcutaneously daily from day 6 to day 17 of the gestation period at up to 5 times the human sublingual dose. There were no ODACTRA-related post-implantation loss, fetal malformations or variations.

### 8.2 Lactation

#### Risk Summary

Data are not available to assess the effects of ODACTRA on the breastfed child or on milk production and excretion in the nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ODACTRA and any potential adverse effects on the breastfed child from ODACTRA or from the underlying maternal condition.

### 8.4 Pediatric Use

Safety and effectiveness have not been established in persons younger than 18 years of age.

### 8.5 Geriatric Use

Safety and effectiveness have not been established in persons older than 65 years of age.

## 10 OVERDOSAGE

Symptoms of overdose may include hypersensitivity reactions such as systemic allergic reactions or severe local allergic reactions (*see Warnings and Precautions 5.1*). In case of severe adverse reactions such as angioedema, difficulty in swallowing, difficulty in breathing, changes in voice, or feeling of fullness in the throat, immediate medical evaluation is needed. These reactions should be treated as medically indicated, including the use of epinephrine as appropriate (*see Warnings and Precautions 5.2*).

## 11 DESCRIPTION

ODACTRA tablets contain house dust mite allergen extract from *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*. ODACTRA is a sublingual tablet that dissolves within 10 seconds.

ODACTRA is available as a tablet of 12 SQ-HDM [6 SQ-HDM *D. farinae* and 6 SQ-HDM *D. pteronyssinus*]. Each tablet contains a 1:1:1:1 potency ratio of *D. farinae* group 1 allergen, *D. farinae* group 2 allergen, *D. pteronyssinus* group 1 allergen, and *D. pteronyssinus* group 2 allergen.

Inactive ingredients: gelatin NF (fish source), mannitol USP, and sodium hydroxide NF.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The precise mechanisms of action of allergen immunotherapy have not been fully established.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

ODACTRA has not been evaluated for carcinogenic potential or impairment of fertility in animals. Two *in vitro* chromosome aberration assays, an *in vitro* bacterial mutagenesis assay and a combined *in vivo* Comet and micronucleus assay for mutagenicity in rats were performed using HDM (*D. farinae* and *D. pteronyssinus*) allergen extracts. One *in vitro* chromosome aberration assay was positive. Based on the aggregated results, the weight of evidence indicates that this finding is unlikely to be of clinical relevance.

## 14 CLINICAL STUDIES

The efficacy of ODACTRA for the treatment of HDM-induced allergic rhinitis was investigated in two double-blind, placebo-controlled, randomized clinical field efficacy studies (Studies 1 and 2) and one environmental exposure chamber (EEC) study.

### Study 1 (North American Field Efficacy Study)

Study 1 was a double-blind, placebo-controlled, randomized field efficacy study conducted in the United States and Canada for a duration of up to 12 months, that compared the efficacy of ODACTRA (N=741) compared to placebo (N=741) in the treatment of HDM-induced allergic rhinitis. Subjects 12 through 85 years of age were enrolled if they had a history of symptomatic allergic rhinitis and were sensitized to *D. farinae* and/or *D. pteronyssinus* as determined by house dust mite specific IgE. Subjects were required to be symptomatic and were not taking symptom-relieving allergy medications at enrollment.

Subjects with mild to moderate asthma, defined as asthma of a severity that required, at most, a daily medium dose of an inhaled corticosteroid, were enrolled in the study.

In this study, 31% of subjects had asthma, 48% had conjunctivitis, and 76% were polysensitized to other allergens in addition to HDM, including trees, grasses, weed, animal danders and molds. The subject population was 76% White, 11% African American, 7% Asian, and 59% female. The mean age of subjects was 35 years.

The efficacy of ODACTRA in the treatment of HDM-induced allergic rhinitis was assessed through self-reporting of symptoms and medication use. Based on these self-assessments, the Total Combined Rhinitis Score (TCRS), daily symptom scores (DSS) and daily medication scores (DMS) for rhinoconjunctivitis were calculated. Daily symptoms included four nasal symptoms (runny nose, stuffy nose, sneezing, and itchy nose) and two ocular symptoms (gritty/itchy eyes and watery eyes). Each of these rhinoconjunctivitis symptoms was individually graded by subjects daily on a scale of 0 (none) to 3 (severe) and then summed. Subjects in active and placebo arms of this study were allowed to take symptom-relieving allergy medications (including oral and ocular antihistamines and nasal corticosteroids) during the study as needed. The DMS measured the use of these standard symptom-relieving allergy medications. Predefined daily maximum scores were assigned to each class of rhinitis and conjunctivitis medication as 0=none, 6=oral antihistamine, 6=ocular antihistamine, and 8=nasal corticosteroid.

The primary endpoint was the difference between the treatment and placebo groups in the average TCRS during approximately the last 8 weeks of treatment. The TCRS represents the sum of the daily rhinitis DSS and the rhinitis DMS. Other secondary endpoints in this study included the average rhinitis DSS, the average rhinitis DMS, and the Total Combined Score (TCS). The TCS represents the sum of the rhinoconjunctivitis DSS and the rhinoconjunctivitis DMS, which was then averaged during approximately the last 8 weeks of treatment.

Subjects in this study were required to stop taking symptom-relieving allergy medication during the baseline period. The mean rhinitis DSS at baseline was 7.94 out of 12 total points in both the treatment arm and in the placebo arm. The results of this study are shown in Table 2.

**Table 2: Total Combined Rhinitis Score (TCRS), Rhinitis Daily Symptom Score (DSS), Rhinitis Daily Medication Score (DMS), and Total Combined Score (TCS) During the Last 8 Weeks of Treatment with ODACTRA in Subjects 12 Years of Age and Older (Study 1, Field Efficacy Study) (NCT: NCT01700192)**

Endpoint*	ODACTRA (n=566) <sup>†</sup> Score <sup>‡</sup>	Placebo (n=620) <sup>†</sup> Score <sup>‡</sup>	Treatment Difference (ODACTRA- Placebo)	Difference Relative to Placebo <sup>§</sup>	
				Estimate	(95% CI)
Primary Endpoint					
TCRS <sup>‡</sup>	4.10	4.95	-0.80	-17.2%	(-25.0%, -9.7%)
Secondary Endpoints					
Rhinitis DSS	3.55	4.20	-0.60	-15.5%	(-24.4%, -7.3%)
Rhinitis DMS	0.65	0.79	-0.15	-18.4%	(-41.0%, 4.3%)
TCS	5.50	6.60	-1.10	-16.7%	(-24.6%, -4.0%)

TCRS=Total Combined Rhinitis Score (Rhinitis DSS + Rhinitis DMS); TCS=Total Combined Score (Rhinoconjunctivitis DSS + Rhinoconjunctivitis DMS); CI=Confidence Interval  
Analyses were based on the full analysis set (FAS), which included all randomized and treated subjects. Subjects were analyzed according to the treatment group to which they were randomized.  
\*Non-parametric analysis for TCRS, Rhinitis DSS, and TCS endpoints; Parametric analysis using zero-inflated log-normal model for Rhinitis DMS endpoint.  
<sup>†</sup>Number of subjects in analyses.  
<sup>‡</sup>For TCRS, Rhinitis DSS, and TCS endpoints, the estimated group medians are reported. Treatment difference and that relative to placebo is based on estimated group medians. For Rhinitis DMS, the estimated group means are reported. Treatment difference and that relative to placebo is based on estimated group means.  
<sup>§</sup>Difference relative to placebo computed as: (ODACTRA – placebo)/placebo x 100.  
<sup>¶</sup>The pre-specified criteria for demonstration of efficacy was defined as a TCRS difference relative to placebo less than or equal to -15 percent, and the upper bound of the 95 percent confidence interval (CI) of TCRS difference relative to placebo less than or equal to -10 percent.

#### Study 2 (European Field Efficacy Study)

This double-blind, placebo-controlled, randomized field efficacy study evaluated adult subjects 18 through 66 years of age comparing ODACTRA (N=318) and placebo (N=338) administered as a sublingual tablet daily for a duration of approximately 12 months. Subjects in this study had a history of symptomatic allergic rhinitis when exposed to house dust and were sensitized to *D. farinæ* and/or *D. pteronyssinus* as determined by house dust mite specific IgE testing. At study entry, subjects were required to be symptomatic despite taking symptom-relieving allergy medications during the baseline period.

In this study, 46% of subjects had asthma, 97% had conjunctivitis and 67% were polysensitized to other allergens in addition to HDM, including trees, grass, weeds, animal danders and molds. The study population was 98% White, <1% African American, and <1% Asian; 50% of subjects were female. The mean age of subjects in this study was 32 years. The primary efficacy endpoint was the difference relative to placebo in the average TCRS during the last 8 weeks of treatment. The mean Rhinitis DSS at baseline was 7.95 out of 12 for the treatment arm and 8.00 out of 12 total points for the placebo arm. The results of this study are shown in Table 3.

**Table 3: Total Combined Rhinitis Score (TCRS), Rhinitis Daily Symptom Score (DSS), Rhinitis Daily Medication Score (DMS), and Total Combined Score (TCS) During the Last 8 Weeks of Treatment with ODACTRA in Subjects 18 Years of Age and Older (Study 2, European Field Efficacy Study) (NCT01454544)**

Endpoint*	ODACTRA		Placebo		Treatment Difference (ODACTRA - Placebo)	Difference Relative to Placebo <sup>§</sup>	
	n <sup>†</sup>	Score <sup>‡</sup>	n <sup>†</sup>	Score <sup>‡</sup>		Estimate	(95% CI)
Primary Endpoint							
TCRS <sup>¶</sup>	318	5.71	338	6.81	-1.09	-16.1%	(-25.8%, -5.7%)
Secondary Endpoints							
Rhinitis DSS <sup>¶</sup>	318	2.84	338	3.31	-0.47	-14.1%	(-23.8%, -3.9%)
Rhinitis DMS <sup>¶</sup>	318	2.32	338	2.86	-0.54	-18.9%	(-34.7%, -1.3%)
TCS <sup>¶</sup>	241	7.91	257	9.12	-1.21	-13.2%	(-23.7%, -1.5%)

TCRS=Total Combined Rhinitis Score (Rhinitis DSS + Rhinitis DMS); TCS=Total Combined Score (Rhinoconjunctivitis DSS + Rhinoconjunctivitis DMS); CI=Confidence Interval  
\*Parametric analysis using analysis of covariance model for all endpoints.  
<sup>†</sup>Number of subjects in analyses.  
<sup>‡</sup>The estimated group least squares means are reported. Treatment difference and that relative to placebo is based on estimated group least squares means.  
<sup>§</sup>Difference relative to placebo computed as: (ODACTRA – placebo)/placebo x 100.  
<sup>¶</sup>Analysis based on FAS-MI: full analysis set with multiple imputations. The analysis treats subjects who discontinued the study before the efficacy assessment period as placebo subjects. For the primary analysis (FAS-MI) only the absolute difference was pre-specified. Additional analyses describing the corresponding pre-specified relative differences to placebo for the full analysis set (FAS): TCRS: -18.1% (-27.6%, -7.7%); rhinitis DSS: -16.2% (-25.7%, -5.8%); and rhinitis DMS: -21.4% (-36.6%, -3.2%).  
<sup>¶¶</sup>Subjects from Serbia and Croatia were excluded from the analysis of TCS because the preferred formulations of antihistamine eyedrops were not available in these countries at the time the study was conducted. The TCS analysis is based on the full analysis set (FAS). All available data used to its full extent, i.e. subjects who provided data during the efficacy assessment period.

#### Study 3 (Environmental Exposure Chamber Study)

This double-blind, placebo-controlled, randomized EEC study evaluated adult subjects 18 through 58 years of age comparing ODACTRA (N=42) and placebo (N=41) administered as a sublingual tablet daily for approximately 24 weeks. Subjects had a history of symptomatic allergic rhinitis and were sensitized to *D. farinæ* and/or *D. pteronyssinus* as determined by HDM specific IgE. In this study, 23% of subjects had asthma, 87% had conjunctivitis, and 84% were polysensitized to other allergens in addition to HDM, including tree, grass, weed, animal danders and molds. The subject population was 90% White, <1% African American, 8% Asian, and 43% female. The mean age of subjects was 27 years.

The primary endpoint was the difference relative to placebo in the average TNSS at Week 24. The Total Nasal Symptom Score (TNSS) represents the sum of 4 nasal symptoms (runny nose, stuffy nose, sneezing, and itchy nose). Secondary endpoints were the differences relative to placebo in the average TNSS at Weeks 8 and 16 and average Total Symptom Score (TSS) at Week 24, which represents the sum of TNSS plus 2 ocular symptoms (gritty/itchy eyes and watery eyes). Baseline TNSS following house dust mite EEC challenge prior to treatment was 7.74 out of 12 total points for ODACTRA and 7.32 out of 12 total points for placebo. The results of this study are shown in Table 4.

**Table 4: Total Nasal Symptom Score (TNSS) and Total Symptom Score (TSS) During HDM-Allergen Challenge (Study 3, Environmental Exposure Chamber Study) (NCT01644617)**

Endpoint*	ODACTRA (n) <sup>†</sup> Score <sup>‡</sup>	Placebo (n) <sup>†</sup> Score <sup>‡</sup>	Treatment Difference (ODACTRA - Placebo)	Difference Relative to Placebo <sup>§</sup>	
				Estimate	(95% CI)
Primary Endpoint					
TNSS – Week 24	(36) 3.83	(34) 7.45	-3.62	-48.6%	(-60.2%, -35.3%)
Secondary Endpoints					
TNSS – Week 8	(40) 5.34	(39) 6.71	-1.37	-20.4%	(-33.3%, -6.8%)
TNSS – Week 16	(39) 4.82	(38) 6.90	-2.08	-30.1%	(-42.3%, -16.8%)
TSS – Week 24	(36) 4.43	(34) 9.27	-4.84	-52.2%	(-65.0%, -37.0%)

TNSS=Total Nasal Symptom Score; TSS=Total Symptom Score (TNSS + total ocular symptom score); CI=Confidence Interval  
\*Parametric analysis using analysis of covariance for all endpoints.  
<sup>†</sup>Number of subjects in analyses.  
<sup>‡</sup>The estimated group least squares means are reported. Treatment difference and that relative to placebo is based on estimated group least squares means.  
<sup>§</sup>Difference relative to placebo computed as: (ODACTRA – placebo)/placebo x 100.

### 16 HOW SUPPLIED/STORAGE AND HANDLING

ODACTRA 12 SQ-HDM tablets are white to off-white, circular freeze-dried sublingual tablets with a debossed pentagon detail on one side.  
ODACTRA is supplied as follows:  
3 blister packages of 10 tablets (30 tablets total), NDC 52709-1701-3  
Store at controlled room temperature, 20°C-25°C (68°F-77°F). Store in the original package until use to protect from moisture.

### 17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide) and to keep ODACTRA and all medicines out of the reach of children.

#### Severe Allergic Reactions

- Advise patients that ODACTRA may cause life-threatening systemic or local allergic reactions, including anaphylaxis. Educate patients about the signs and symptoms of these allergic reactions *[see Warnings and Precautions (5.1)]*. The signs and symptoms of a severe allergic reaction may include: syncope, dizziness, hypotension, tachycardia, dyspnea, wheezing, bronchospasm, chest discomfort, cough, abdominal pain, vomiting, diarrhea, rash, pruritus, flushing, and urticaria.
- Ensure that patients have auto-injectable epinephrine and instruct patients in its proper use. Instruct patients who experience a severe allergic reaction to seek immediate medical care, discontinue ODACTRA, and resume treatment only when advised by a physician to do so. *[See Warnings and Precautions (5.2).]*
- Advise patients to read the patient information for epinephrine.
- Inform patients that the first dose of ODACTRA must be administered in a healthcare setting under the supervision of a physician and that they will be monitored for at least 30 minutes to watch for signs and symptoms of life-threatening systemic or local allergic reaction *[see Warnings and Precautions (5.1)]*.
- Because of the risk of upper airway compromise, instruct patients with persistent and escalating adverse reactions in the mouth or throat to discontinue ODACTRA and to contact their healthcare professional. *[See Warnings and Precautions (5.3).]*
- Because of the risk of eosinophilic esophagitis, instruct patients with severe or persistent symptoms of esophagitis to discontinue ODACTRA and to contact their healthcare professional. *[See Warnings and Precautions (5.4).]*

#### Asthma

- Instruct patients with asthma that if they have difficulty breathing or if their asthma becomes difficult to control, they should stop taking ODACTRA and contact their healthcare professional immediately *[see Warnings and Precautions (5.5)]*.

#### Administration Instructions

- Instruct patients to carefully remove the foil from the blister unit with dry hands and then take the sublingual tablet immediately by placing it under the tongue where it will dissolve within 10 seconds. Instruct patients to avoid swallowing for at least 1 minute. Also instruct patients to wash their hands after handling the tablet, and to avoid food or beverages for 5 minutes after taking the tablet. *[See Dosage and Administration (2.2).]*

Manufactured for: ALK-Abelló A/S

 ALK-Abelló A/S, Bøge Allé 6-8, DK-2970 Hørsholm, Denmark

U.S. License No. 1292

Manufactured by:  
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**HIGHLIGHTS OF PRESCRIBING INFORMATION**  
These highlights do not include all the information needed to use GRASTEK safely and effectively. See full prescribing information for GRASTEK.

GRASTEK® (Timothy Grass Pollen Allergen Extract)  
Tablet for Sublingual Use  
Initial U.S. Approval: 2014

**WARNING: SEVERE ALLERGIC REACTIONS**  
See full prescribing information for complete boxed warning.

- GRASTEK can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction. (5.1)
- Do not administer GRASTEK to patients with severe, unstable or uncontrolled asthma. (4)
- Observe patients in the office for at least 30 minutes following the initial dose. (5.1)
- Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use. (5.2)
- GRASTEK may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. (5.2)
- GRASTEK may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers. (5.2)

**INDICATIONS AND USAGE**  
GRASTEK is an allergen extract indicated as immunotherapy for the treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test or *in vitro* testing for pollen-specific IgE antibodies for Timothy grass or cross-reactive grass pollens. GRASTEK is approved for use in persons 5 through 65 years of age. (1)

**DOSAGE AND ADMINISTRATION**  
For sublingual use only. (2)

- One tablet daily. (2.1)
- Initiate treatment at least 12 weeks before the expected onset of each grass pollen season and continue treatment throughout the season. For sustained effectiveness for one grass pollen season

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### WARNING: SEVERE ALLERGIC REACTIONS

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

#### 3 DOSAGE FORMS AND STRENGTHS

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after cessation of treatment, GRASTEK may be taken daily for three consecutive years. (2.2)

- Place the tablet immediately under the tongue. Allow it to remain there until completely dissolved. Do not swallow for at least 1 minute. (2.2)
- Administer the first dose of GRASTEK under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. Observe patients in the office for at least 30 minutes following the initial dose. (2.2)

**DOSAGE FORMS AND STRENGTHS**  
Tablet, 2800 Bioequivalent Allergy Units (BAUs) (3)

**CONTRAINDICATIONS**  
Severe, unstable or uncontrolled asthma. (4)  
History of any severe systemic allergic reaction or any severe local reaction to sublingual allergen immunotherapy. (4)  
A history of eosinophilic esophagitis. (4)  
Hypersensitivity to any of the inactive ingredients contained in this product. (4)

**WARNINGS AND PRECAUTIONS**  
Inform patients of the signs and symptoms of serious allergic reactions and instruct them to seek immediate medical care and discontinue therapy should any of these occur. (5.1)  
In case of oral inflammation or wounds, stop treatment with GRASTEK to allow complete healing of the oral cavity. (5.7)

**ADVERSE REACTIONS**  
Adverse reactions reported in ≥5% of patients were: ear pruritus, oral pruritus, tongue pruritus, mouth edema, throat irritation. (6)

To report SUSPECTED ADVERSE REACTIONS, contact ALK-Abelló Inc, a subsidiary of ALK-Abelló A/S, at +1 512-252-4241 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 12/2019

## 3 DOSAGE FORMS AND STRENGTHS

GRASTEK is available as 2800 Bioequivalent Allergy Unit (BAU) tablets that are white to off-white, circular with a debossed round detail on one side.

## 4 CONTRAINDICATIONS

GRASTEK is contraindicated in patients with:

- Severe, unstable or uncontrolled asthma
- A history of any severe systemic allergic reaction
- A history of any severe local reaction after taking any sublingual allergen immunotherapy
- A history of eosinophilic esophagitis
- Hypersensitivity to any of the inactive ingredients [gelatin, mannitol and sodium hydroxide] contained in this product [see Description (11)].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Severe Allergic Reactions

GRASTEK can cause systemic allergic reactions including anaphylaxis which may be life-threatening. In addition, GRASTEK can cause severe local reactions, including laryngopharyngeal swelling, which can compromise breathing and be life-threatening. Educate patients to recognize the signs and symptoms of these allergic reactions and instruct them to seek immediate medical care and discontinue therapy should any of these occur. Allergic reactions may require treatment with epinephrine. [See Warnings and Precautions (5.2).]

Administer the initial dose of GRASTEK in a healthcare setting under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases and prepared to manage a life-threatening systemic or local allergic reaction. Observe patients in the office for at least 30 minutes following the initial dose of GRASTEK.

### 5.2 Epinephrine

Prescribe auto-injectable epinephrine to patients receiving GRASTEK. Instruct patients to recognize the signs and symptoms of a severe allergic reaction and in the proper use of emergency auto-injectable epinephrine. Instruct patients to seek immediate medical care upon use of auto-injectable epinephrine and to stop treatment with GRASTEK. [See Patient Counseling Information (17).]

See the epinephrine package insert for complete information.  
GRASTEK may not be suitable for patients with certain medical conditions that may reduce the ability to survive a serious allergic reaction or increase the risk of adverse reactions after epinephrine administration. Examples of these medical conditions include but are not limited to: markedly compromised lung function (either chronic or acute), unstable angina, recent myocardial infarction, significant arrhythmia, and uncontrolled hypertension.

GRASTEK may not be suitable for patients who are taking medications that can potentiate or inhibit the effect of epinephrine. These medications include:

**Beta-adrenergic blockers:** Patients taking beta-adrenergic blockers may be unresponsive to the usual doses of epinephrine used to treat serious systemic reactions, including anaphylaxis. Specifically, beta-adrenergic blockers antagonize the cardiostimulating and bronchodilating effects of epinephrine.

**Alpha-adrenergic blockers, ergot alkaloids:** Patients taking alpha-adrenergic blockers may be unresponsive to the usual doses of epinephrine used to treat serious systemic reactions, including anaphylaxis. Specifically, alpha-adrenergic blockers antagonize the vasoconstricting and hypertensive effects of epinephrine. Similarly, ergot alkaloids may reverse the pressor effects of epinephrine.

**Tricyclic antidepressants, levothyroxine sodium, monoamine oxidase inhibitors and certain antihistamines:** The adverse effects of epinephrine may be potentiated in patients taking tricyclic antidepressants, levothyroxine sodium, monoamine oxidase inhibitors, and the antihistamines chlorpheniramine, and diphenhydramine.

**Cardiac glycosides, diuretics:** Patients who receive epinephrine while taking cardiac glycosides or diuretics should be observed carefully for the development of cardiac arrhythmias.

### 5.3 Upper Airway Compromise

GRASTEK can cause local reactions in the mouth or throat that could compromise the upper airway [see Adverse Reactions (6.1 and 6.2)]. Consider discontinuation of GRASTEK in patients who experience persistent and escalating adverse reactions in the mouth or throat.

### 5.4 Eosinophilic Esophagitis

Eosinophilic esophagitis has been reported in association with sublingual tablet immunotherapy [see Contraindications (4) and Adverse Reactions (6.2)]. Discontinue GRASTEK and consider a diagnosis of eosinophilic esophagitis in patients who experience severe or persistent gastro-esophageal symptoms including dysphagia or chest pain.

### 5.5 Asthma

GRASTEK has not been studied in subjects with moderate or severe asthma or any subjects who required daily medication to treat asthma.

Withhold immunotherapy with GRASTEK if the patient is experiencing an acute asthma exacerbation. Reevaluate patients who have recurrent asthma exacerbations and consider discontinuation of GRASTEK.

### 5.6 Concomitant Allergen Immunotherapy

GRASTEK has not been studied in subjects who are receiving concomitant allergen immunotherapy. Concomitant dosing with other allergen immunotherapy may increase the likelihood of local or systemic adverse reactions to either subcutaneous or sublingual allergen immunotherapy.

### 5.7 Oral Inflammation

Stop treatment with GRASTEK to allow complete healing of the oral cavity in patients with oral inflammation (e.g., oral lichen planus, mouth ulcers or thrush) or oral wounds, such as those following oral surgery or dental extraction.

## 6 ADVERSE REACTIONS

Adverse reactions reported in ≥5% of patients were: ear pruritus, oral pruritus, tongue pruritus, mouth edema, and throat irritation.

### 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

#### Adults

The safety data described below are based on 6 clinical trials which randomized 3589 subjects 18 through 65 years of age with Timothy grass pollen induced rhinitis with or without conjunctivitis, including 1669 subjects who were exposed to at least one dose of GRASTEK. Of the subjects treated with GRASTEK, 25% had mild asthma and 80% were sensitized to other allergens in addition to grass. The subject population was 88% White, 7% African American, and 3% Asian. Subjects were 52% male, and 88% of subjects were between 18 and 50 years of age. Subject demographics in placebo-treated subjects were similar to the active group.

The most common adverse reactions reported in subjects treated with GRASTEK were oral pruritus (26.7% vs 3.5% placebo), throat irritation (22.6% vs 2.8%), ear pruritus (12.5% vs 1.1%) and mouth edema (11.1% vs 0.8%). The percentage of subjects who discontinued from the clinical trials because of an adverse reaction while exposed to GRASTEK or placebo was 4.9% and 0.9%, respectively. The most

common adverse reactions that led to study discontinuation in subjects who were exposed to GRASTEK were pharyngeal edema and oral pruritus.

Seven adult subjects (7/1669; 0.4%) who received GRASTEK experienced treatment-related systemic allergic reactions that led to discontinuation of GRASTEK in four out of the seven subjects.

- Five of the seven subjects had reactions on Day 1 of treatment with GRASTEK. Symptoms included swelling of lips/mouth; oral/pharyngeal itching; ear itching, sneezing, rhinorrhea, throat irritation, dysphonia, dysphagia, chest discomfort, and rash. Three of the five subjects received treatment with epinephrine and antihistamines, and one of the three also received oral corticosteroids. One of the five subjects who had a reaction on Day 1 of treatment with GRASTEK also had a reaction on Day 2 of treatment with GRASTEK. Symptoms on Day 2 included oral burning sensation; rhinorrhea; and throat irritation.
- One of the seven subjects had a reaction on Day 2 after tolerating treatment with GRASTEK on Day 1. Symptoms included edema of the lower lip, epigastric discomfort and dizziness.
- One of the seven subjects developed chest tightness and shortness of breath on Day 42 of treatment with GRASTEK.

Adverse reactions reported in  $\geq 1\%$  of subjects treated with GRASTEK are shown in Table 1.

**Table 1: Adverse Reactions Reported in  $\geq 1\%$  of Adults Treated with GRASTEK**

Adverse Reaction	GRASTEK (N=1669)	PLACEBO (N=1645)
<b>Nervous System Disorders</b>		
Headache	2.1%	1.3%
<b>Ear and Labyrinth Disorders</b>		
Ear pruritus	12.5%	1.1%
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		
Throat irritation	22.6%	2.8%
Pharyngeal edema	3.4%	0.1%
Dry throat	1.7%	0.4%
Oropharyngeal pain	1.6%	1.0%
Nasal discomfort	1.6%	1.0%
Throat tightness	1.4%	0.2%
Dyspnea	1.1%	0.4%
<b>Gastrointestinal Disorders</b>		
Oral pruritus	26.7%	3.5%
Mouth edema	11.1%	0.8%
Paraesthesia oral	9.8%	2.0%
Tongue pruritus	5.7%	0.5%
Lip swelling	4.0%	0.2%
Swollen tongue	2.8%	0.1%
Dyspepsia	2.3%	0.1%
Hypoesthesia oral	2.3%	1.0%
Nausea	1.8%	0.6%
Oral discomfort	1.6%	0.3%
Oral mucosal erythema	1.5%	0.6%
Lip edema	1.3%	0.1%
Glossitis	1.3%	0.1%
Stomatitis	1.1%	0.3%
Tongue disorder	1.1%	0.2%
Tongue edema	1.1%	0.4%
Glossodynia	1.0%	0.3%
Dysphagia	1.0%	0.2%
Palatal edema	1.0%	0.1%
<b>Skin and Subcutaneous Tissue Disorders</b>		
Pruritus	2.4%	1.0%
Urticaria	1.7%	0.9%
<b>General Disorders and Administration Site Conditions</b>		
Chest discomfort	1.6%	0.5%
Fatigue	1.4%	0.4%

Adverse reactions of interest that occurred in  $\leq 1\%$  of GRASTEK recipients include abdominal pain and gastroesophageal reflux.

#### Pediatrics

Safety data are based on 3 clinical trials which randomized 881 subjects between 5 and 17 years of age with grass pollen induced rhinitis with or without conjunctivitis. Overall, 445 subjects received at least one dose of GRASTEK. Of the subjects treated with GRASTEK, 31% had mild asthma and 86% were sensitized to other allergens in addition to grass. The subject population was 86% White, 7% African American and 3% multi-racial. The majority (66%) of subjects were male. The mean age of subjects was 11.7 years. Subject demographics in placebo-treated subjects were similar to the active group.

The most common adverse reactions in pediatric subjects treated with GRASTEK were oral pruritus (24.4% vs 2.1% placebo), throat irritation (21.3% vs 2.5%) and mouth edema (9.8% vs 0.2%). The percentage of subjects who discontinued from the clinical trials because of an adverse reaction while exposed to GRASTEK or placebo was 6.3% and 0.7%, respectively.

One pediatric subject (1/447; 0.2%) who received GRASTEK experienced a treatment-related systemic allergic reaction consisting of lip angioedema, slight dysphagia due to the sensation of a lump in the throat, and intermittent cough which was of moderate intensity on Day 1. The subject was treated with epinephrine, recovered, and was discontinued from the trial.

Adverse reactions reported in  $\geq 1\%$  of subjects treated with GRASTEK are shown in Table 2.

**Table 2: Adverse Reactions Reported in  $\geq 1\%$  of Pediatric Subjects Treated with GRASTEK**

Adverse Reaction	GRASTEK (N=447)	PLACEBO (N=434)
<b>Nervous System Disorders</b>		
Headache	3.4%	1.8%
<b>Ear and Labyrinth Disorders</b>		
Ear pruritus	7.2%	0.5%
<b>Eye Disorders</b>		

Eye pruritus	3.4%	2.1%
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		
Throat irritation	21.3%	2.5%
Oropharyngeal pain	4.0%	1.4%
Pharyngeal erythema	3.6%	0.7%
Pharyngeal edema	2.9%	0%
Cough	2.7%	1.2%
Dyspnea	2.0%	0.5%
Nasal discomfort	1.6%	0.9%
Nasal congestion	1.6%	0.5%
Sneezing	1.6%	0.7%
<b>Gastrointestinal Disorders</b>		
Oral pruritus	24.4%	2.1%
Mouth edema	9.8%	0.2%
Tongue pruritus	9.2%	0.9%
Lip swelling	7.2%	0.5%
Paraesthesia oral	5.4%	1.2%
Oral mucosal erythema	4.9%	0.9%
Lip pruritus	2.9%	0.2%
Swollen tongue	2.5%	0%
Dysphagia	2.0%	0%
Nausea	1.6%	0.5%
Oral discomfort	1.6%	0.2%
Stomatitis	1.3%	0%
Hypoesthesia oral	1.1%	0.2%
Glossodynia	1.1%	0.2%
<b>Skin and Subcutaneous Tissue Disorders</b>		
Urticaria	1.8%	0.2%
<b>General Disorders and Administration Site Conditions</b>		
Chest discomfort	2.0%	0.5%

## 6.2 Postmarketing Experience

### Postmarketing Safety Studies

In European post-approval studies which included 1,666 patients treated with GRASTEK (marketed under the name GRAZAX), reported serious adverse reactions assessed as related to GRASTEK use included anaphylactic reaction, asthma exacerbation, hoarseness, laryngitis, oral ulceration, and ulcerative colitis exacerbation.

### Spontaneous Postmarketing Reports

The following adverse reactions have been identified during post-approval use of GRASTEK (marketed under the name GRAZAX in Europe). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These include: altered state of consciousness, anaphylactic shock, angioedema, asthma exercise induced, chest pressure, diarrhea, difficulty speaking, dizziness, drowsiness, enlarged uvula, eosinophilic esophagitis, erythema facial, face edema, forced expiratory volume decreased, heart rate increased, heart rate irregular, hyperventilation, hypotension, laryngeal discomfort, oral pain, oxygen saturation decreased, peak expiratory flow rate decreased, pneumonia, rash, respiratory distress, sensation of foreign body, status asthmaticus, stridor, swelling of neck, throat pruritus, tremor, vital capacity decreased, vomiting, and wheezing. Included in these reports was an adult male with asthma who experienced anaphylactic shock within two minutes of administration of GRASTEK. The patient experienced depressed level of consciousness, hypotension, increased heart rate, wheezing, urticaria, and face edema.

Eosinophilic esophagitis has been reported following treatment with GRASTEK (marketed under the name GRAZAX). The clinical details of some postmarketing reports are consistent with a drug-induced effect, including at least one case with resolution of symptoms upon discontinuation of GRASTEK, relapse after resuming GRASTEK and resolution again after discontinuation of GRASTEK.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively. Available human data do not establish the presence or absence of GRASTEK-associated risks during pregnancy.

In two reproductive and developmental toxicity studies mice were administered Timothy grass pollen extract daily by buccal cavity at doses approximately 6.7 times the human sublingual dose. In one study doses were administered during gestation and lactation. In the other study doses were administered prior to mating and during gestation. These studies revealed no evidence of harm to the mother or the fetus due to GRASTEK (see 8.1 Data).

#### Data

##### Animal Data

A pre- and postnatal developmental study and a combined fertility/developmental toxicity study were conducted in mice. In these studies, the effect of Timothy grass (*Phleum pratense*) pollen allergen extract, the active component of GRASTEK, on embryo-fetal development was evaluated. In the pre- and postnatal developmental toxicity study female mice were administered Timothy grass pollen allergen extract by buccal cavity daily from day 6 of gestation to day 17 of lactation at doses approximately 6.7 times the human sublingual dose. In the combined fertility/developmental toxicity study, female mice were administered Timothy grass pollen allergen extract daily by buccal cavity administration from 14 days prior to mating and until day 15 of the gestation period (male animals were administered the same dose daily for 4 weeks before pairing and during pairing) at doses approximately 6.7 times the human sublingual dose. Fertility was normal and there were no treatment-related post-implementation losses, fetal malformations or variations.

### 8.2 Lactation

#### Risk Summary

It is not known if GRASTEK is excreted in human milk. Data are not available to assess the effect of GRASTEK on milk production or on the breast-fed child. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for GRASTEK and any potential adverse effects on the breast-fed child from GRASTEK or from the underlying maternal condition.

### 8.4 Pediatric Use

Efficacy and safety of GRASTEK have been established in children and adolescents 5 through 17 years of age. The safety and efficacy in pediatric patients below 5 years of age have not been established.

### 8.5 Geriatric Use

There is no clinical trial experience with GRASTEK in patients over 65 years of age.

## 11 DESCRIPTION

GRASTEK tablets contain pollen allergen extract from Timothy grass (*Phleum pratense*). GRASTEK is a sublingual tablet. GRASTEK is available as a tablet of 2800 BAU of Timothy grass pollen allergen extract. Inactive ingredients: gelatin NF (fish source), mannitol USP and sodium hydroxide NF.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The precise mechanisms of action of allergen immunotherapy are not known.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed in animals to evaluate the carcinogenic potential of GRASTEK. There were no positive findings in the *in vitro* mouse lymphoma and the bacterial reverse mutation assays for mutagenicity using Timothy grass (*Phleum pratense*) pollen allergen extract. A combined fertility/developmental toxicity study in male and female mice revealed no evidence of impaired fertility due to Timothy grass pollen allergen extract administered daily prior to mating and during gestation at approximately 6.7 times the human sublingual dose (see 8.1 Data).

## 14 CLINICAL STUDIES

The efficacy of GRASTEK in the treatment of allergic rhinitis with or without conjunctivitis in Timothy grass pollen allergic subjects 5 years of age and older, with or without mild asthma, was evaluated during the first grass pollen season in two trials of approximately 24 weeks treatment duration. The sustained effect of GRASTEK was evaluated in one trial conducted over 5 grass pollen seasons. All three trials were randomized, double-blind, parallel group, multicenter clinical trials. Subjects had a history of grass pollen induced rhinitis with or without conjunctivitis and sensitivity to Timothy grass pollen as determined by specific testing (IgE). In these three studies, subjects initiated GRASTEK or placebo daily for 12 weeks prior to the pollen season. In the long-term study, subjects received GRASTEK or placebo daily for 3 consecutive years and were followed for 2 years without treatment.

Efficacy was established by self-reporting of rhinoconjunctivitis daily symptom scores (DSS) and daily medication scores (DMS). Daily rhinoconjunctivitis symptoms included four nasal symptoms (runny nose, stuffy nose, sneezing, and itchy nose), and two ocular symptoms (gritty/itchy eyes and watery eyes). The rhinoconjunctivitis symptoms were measured on a scale of 0 (none) to 3 (severe). Subjects in clinical trials were allowed to take symptom-relieving medications (including systemic and topical antihistamines and topical and oral corticosteroids) as needed. The daily medication score measured the use of standard open-label allergy medications. Predefined values were assigned to each class of medication. Generally, systemic and topical antihistamines were given the lowest score, topical steroids an intermediate score, and oral corticosteroids the highest score. The sums of the DSS and DMS were combined into the Total Combined Score (TCS) which was averaged over the entire grass pollen season.

### 14.1 First Season Efficacy

#### Adults and Children

This placebo-controlled trial evaluated 1501 subjects 5 through 65 years of age (approximately 80% were 18 years and older) comparing GRASTEK (N=752) and placebo (N=749) administered as a sublingual tablet daily for approximately 24 weeks. The subject population was 84% White, 9% African American and 4% Asian. The majority of subjects were male (52%). In this study, approximately 25% of subjects had mild, intermittent asthma and 85% of all subjects were sensitized to other allergens in addition to grass pollen. Subjects with a clinical history of symptomatic allergies to non-grass pollen allergens that required treatment during the grass pollen season were excluded from the studies. All treatment groups were balanced with regard to baseline characteristics.

Subjects treated with GRASTEK had a decrease in the TCS throughout the grass pollen season compared to placebo-treated subjects. Similarly, the DSS and DMS were decreased in subjects treated

with GRASTEK compared to placebo throughout the grass pollen season, and the TCS was decreased compared to placebo during the peak grass pollen season (see Table 3).

Table 3: Total Combined Scores (TCS), Rhinoconjunctivitis Daily Symptom Scores (DSS), and Daily Medication Scores (DMS) During the Grass Pollen Season

Endpoint*	GRASTEK (N) <sup>†</sup> Score <sup>‡</sup>	Placebo (N) <sup>†</sup> Score <sup>‡</sup>	Treatment Difference (GRASTEK – Placebo)	Difference Relative to Placebo <sup>§</sup> Estimate (95% CI)
TCS Entire Season	(629) 3.24	(672) 4.22	-0.98	-23% (-36.0, -13.0)
TCS Peak Season	(620) 3.33	(663) 4.67	-1.33	-29% (-39.0, -15.0)
DSS Entire Season	(629) 2.49	(672) 3.13	-0.64	-20% (-32.0, -10.0)
DMS Entire Season	(629) 0.88	(672) 1.36	-0.48	-35% (-49.3, -20.8)

TCS=Total Combined Score (DSS + DMS); DSS=Daily Symptom Score; DMS=Daily Medication Score.

\* Non-parametric analysis for TCS and DSS endpoints: Parametric analysis using zero-inflated log-normal model for DMS.

† Number of subjects in analyses.

‡ For TCS and DSS endpoints the group medians are reported, treatment difference and that relative to placebo is based on group medians. For DMS, the group means are reported and difference relative to placebo is based on estimated group means.

§ Difference relative to placebo computed as: (GRASTEK - placebo)/placebo x 100.

#### Children

This double-blind clinical trial of approximately 24 weeks duration evaluated 344 pediatric subjects 5 to 17 years of age who were treated with either GRASTEK or placebo once daily. The subject population was 88% White, 7% African American, and 2% Asian. The majority (65%) of subjects were male. The mean age of subjects was 12.3 years. In this study, 26% of subjects had mild intermittent asthma and most subjects (89%) were sensitized to other allergens in addition to grass pollen. Subjects with a clinical history of symptomatic allergies to non-grass pollen allergens that required treatment during the grass pollen season were excluded from the studies. All treatment groups were balanced with regard to baseline characteristics.

Pediatric subjects treated with GRASTEK had a decrease in TCS throughout the grass pollen season compared to placebo treated subjects (see Table 4). Similarly, the DSS and DMS were decreased in GRASTEK compared to placebo throughout the grass pollen season.

Table 4: Total Combined Scores (TCS), Rhinoconjunctivitis Daily Symptom Scores (DSS), and Daily Medication Scores (DMS) During the Entire Grass Pollen Season

Endpoint*	GRASTEK (N=149) <sup>†</sup> Score <sup>‡</sup>	Placebo (N=158) <sup>†</sup> Score <sup>‡</sup>	Treatment Difference (GRASTEK – Placebo)	Difference Relative to Placebo <sup>§</sup> Estimate

				(95% CI)
TCS	4.62	6.25	-1.63	-26% (-38.2, -10.1)
DSS	3.71	4.91	-1.20	-24% (-36.4, -9.1)
DMS	0.91	1.33	-0.42	-32% (-57.7, 4.0)

TCS=Total combined score (DSS + DMS); DSS=Daily Symptom Score; DMS=Daily Medication Score.

\* Parametric analysis using analysis of variance model for all endpoints.

† Number of subjects in analyses.

‡ The estimated group means are reported and difference relative to placebo is based on estimated group means.

§ Difference relative to placebo computed as: (GRASTEK - placebo)/placebo x 100.

## 14.2 Sustained Effect

### Adult Subjects 18 Years and Older

The sustained effect of GRASTEK was measured in a 5-year double-blind study. The study included 634 randomized subjects between 18 and 65 years of age. The subject population was 96% White, 2% Asian and 1% African American. The majority (59%) of subjects were male. The mean age of subjects was 34 years. Subjects received either GRASTEK or placebo daily for 3 consecutive years and were then observed for 2 subsequent years during which they did not receive study drug. Subjects treated with GRASTEK had a decrease in TCS throughout the grass pollen season during the three years of active treatment. This effect was sustained during the grass pollen season in the first year after discontinuation of GRASTEK (see Table 5), but not in the second year.

Table 5: Rhinoconjunctivitis Total Combined Score (TCS), Daily Symptom Score (DSS), and Daily Medication Score (DMS) During the Entire Grass Pollen Season from the 5-Year Study

Endpoint	Difference Relative to Placebo* (95% CI)			
	Treatment Year 1 N=568 <sup>†</sup>	Treatment Year 2 <sup>†</sup> N=316 <sup>†</sup>	Treatment Year 3 N=287 <sup>†</sup>	Post Treatment Year 1 N=257 <sup>†</sup>
TCS	-34.2% (-42.0%, -26.3%)	-40.9% (-51.8%, -29.5%)	-34.0% (-45.5%, -21.4%)	-27.2% (-39.9%, -12.4%)
DSS	-31.2% (-38.8%, -23.4%)	-36.2% (-46.5%, -26.2%)	-29.0% (-40.3%, -16.3%)	-26.2% (-37.6%, -12.2%)
DMS	-38.4% (-49.8%, -26.5%)	-45.5% (-60.4%, -28.2%)	-40.1% (-55.4%, -21.2%)	-28.6% (-46.3%, -6.0%)

TCS=Total Combined Score (DSS + DMS); DSS=Daily Symptom Score; DMS=Daily Medication Score.

\* Difference relative to placebo computed as: (GRASTEK - placebo)/placebo x 100.

† Number of subjects in analyses.

‡ Study extended from 1 to 5 years (site closures, subject unwillingness to participate beyond 1 year).

## 16 HOW SUPPLIED/STORAGE AND HANDLING

GRASTEK 2800 BAU tablets are white to off-white, circular sublingual tablets with a debossed round ~~GRASTEK~~ logo. GRASTEK is supplied as follows:  
3 blister packages of 10 tablets (30 tablets total). NDC 52709-1501-3

Store at controlled room temperature 20°C-25°C (68°F-77°F); excursions permitted between 15°C-30°C (59°F-86°F). Store in the original package until use to protect from moisture.

## 17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide) and to keep GRASTEK and all medicines out of the reach of children.

### Severe Allergic Reactions

Advise patients that GRASTEK may cause life-threatening systemic or local allergic reactions, including anaphylaxis. Educate patients about the signs and symptoms of these allergic reactions [see Warnings and Precautions (5.1)]. The signs and symptoms of a severe allergic reaction may include: syncope, dizziness, hypotension, tachycardia, dyspnea, wheezing, bronchospasm, chest discomfort, cough, abdominal pain, vomiting, diarrhea, rash, pruritus, flushing, and urticaria.

Ensure that patients have auto-injectable epinephrine and instruct patients in its proper use. Instruct patients who experience a severe allergic reaction to seek immediate medical care, discontinue GRASTEK, and resume treatment only when advised by a physician to do so. [See Warnings and Precautions (5.2).]

### Advise patients to read the patient information for epinephrine.

Inform patients that the first dose of GRASTEK must be administered in a healthcare setting under the supervision of a physician and that they will be monitored for at least 30 minutes to watch for signs and symptoms of a life-threatening systemic or local allergic reaction [see Warnings and Precautions (5.1)].

Because of the risk of upper airway compromise, instruct patients with persistent and escalating adverse reactions in the mouth or throat to discontinue GRASTEK and to contact their healthcare professional. [See Warnings and Precautions (5.3).]

Because of the risk of eosinophilic esophagitis, instruct patients with severe or persistent symptoms of esophagitis to discontinue GRASTEK and to contact their healthcare professional. [See Warnings and Precautions (5.4).]

Inform parents/guardians that GRASTEK should only be administered to children under adult supervision [see Dosage and Administration (2.2)].

### Asthma

Instruct patients with asthma that if they have difficulty breathing or if their asthma becomes difficult to control, they should stop taking GRASTEK and contact their healthcare professional immediately [see Warnings and Precautions (5.5)].

### Administration Instructions

Instruct patients to carefully remove the foil from the blister unit with dry hands and then take the sublingual tablet immediately by placing it under the tongue where it will dissolve. Also instruct patients to wash their hands after handling the tablet, and to avoid food or beverages for 5 minutes after taking the tablet. [See Dosage and Administration (2.2).]

Manufactured for: ALK-Abelló A/S



ALK-Abelló A/S, Bøge Allé 6-8, DK-2970 Hørsholm, Denmark

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**HIGHLIGHTS OF PRESCRIBING INFORMATION**  
These highlights do not include all the information needed to use RAGWITEK safely and effectively. See full prescribing information for RAGWITEK.

**RAGWITEK®** (Short Ragweed Pollen Allergen Extract)  
Tablet for Sublingual Use  
Initial U.S. Approval: 2014

**WARNING: SEVERE ALLERGIC REACTIONS**  
See full prescribing information for complete boxed warning.

- RAGWITEK can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction. (5.1)
- Do not administer RAGWITEK to patients with severe, unstable or uncontrolled asthma. (4)
- Observe patients in the office for at least 30 minutes following the initial dose. (5.1)
- Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use. (5.2)
- RAGWITEK may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. (5.2)
- RAGWITEK may not be suitable for patients who are unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers. (5.2)

**INDICATIONS AND USAGE**  
RAGWITEK is an allergen extract indicated as immunotherapy for the treatment of short ragweed pollen-induced allergic rhinitis, with or without conjunctivitis, confirmed by positive skin test or *in vitro* testing for pollen-specific IgE antibodies for short ragweed pollen. RAGWITEK is approved for use in adults 18 through 65 years of age. (1)

**DOSAGE AND ADMINISTRATION**  
For sublingual use only.  
• One tablet daily. (2.1)

- Initiate treatment at least 12 weeks before the expected onset of ragweed pollen season and continue treatment throughout the season. (2.2)
- Place the tablet immediately under the tongue. Allow it to remain there until completely dissolved. Do not swallow for at least 1 minute. (2.2)
- Administer the first dose of RAGWITEK under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. Observe patients in the office for at least 30 minutes following the initial dose. (2.2)

**DOSAGE FORMS AND STRENGTHS**

- Tablet, 12 Amb a 1-Unit (Amb a 1-U) (3)

**CONTRAINDICATIONS**

- Severe, unstable or uncontrolled asthma. (4)
- History of any severe systemic allergic reaction or any severe local reaction to sublingual allergen immunotherapy. (4)
- A history of eosinophilic esophagitis. (4)
- Hypersensitivity to any of the inactive ingredients contained in this product. (4)

**WARNINGS AND PRECAUTIONS**

- Inform patients of the signs and symptoms of serious allergic reactions and instruct them to seek immediate medical care and discontinue therapy should any of these occur. (5.1)
- In case of oral inflammation or wounds, stop treatment with RAGWITEK to allow complete healing of the oral cavity. (5.7)

**ADVERSE REACTIONS**

- Adverse reactions reported in ≥5% of patients were: throat irritation, oral pruritus, ear pruritus, oral paraesthesia, mouth edema, and tongue pruritus. (6)

To report SUSPECTED ADVERSE REACTIONS, contact ALK-Abelló Inc., a subsidiary of ALK-Abelló A/S, at +1 512-252-4241 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 04/2017

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\*Sections or subsections omitted from the full prescribing information are not listed.

**FULL PRESCRIBING INFORMATION**

**WARNING: SEVERE ALLERGIC REACTIONS**

- RAGWITEK can cause life-threatening allergic reactions such as anaphylaxis and severe laryngopharyngeal restriction. (5.1)
- Do not administer RAGWITEK to patients with severe, unstable or uncontrolled asthma. (4)
- Observe patients in the office for at least 30 minutes following the initial dose. (5.1)
- Prescribe auto-injectable epinephrine, instruct and train patients on its appropriate use, and instruct patients to seek immediate medical care upon its use. (5.2)
- RAGWITEK may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. (5.2)
- RAGWITEK may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers. (5.2)

**1 INDICATIONS AND USAGE**

RAGWITEK® is an allergen extract indicated as immunotherapy for the treatment of short ragweed pollen-induced allergic rhinitis, with or without conjunctivitis, confirmed by positive skin test or *in vitro* testing for pollen-specific IgE antibodies for short ragweed pollen. RAGWITEK is approved for use in adults 18 through 65 years of age.

RAGWITEK is not indicated for the immediate relief of allergic symptoms.

**2 DOSAGE AND ADMINISTRATION**

For sublingual use only.

**2.1 Dose**

One RAGWITEK tablet daily.

**2.2 Administration**

Administer the first dose of RAGWITEK in a healthcare setting under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases. After receiving the first dose of RAGWITEK, observe the patient for at least 30 minutes to monitor for signs or symptoms of a severe systemic or a severe local allergic reaction. If the patient tolerates the first dose, the patient may take subsequent doses at home.

Take the tablet from the blister unit after carefully removing the foil with dry hands.

Place the tablet immediately under the tongue. Allow it to remain there until completely dissolved. Do not swallow for at least 1 minute.

Wash hands after handling the tablet.

Do not take the tablet with food or beverage. Food or beverage should not be taken for the following 5 minutes after taking the tablet.

Initiate treatment at least 12 weeks before the expected onset of ragweed pollen season and continue treatment throughout the season. The safety and efficacy of initiating treatment in season have not been established.

Data regarding the safety of restarting treatment after missing a dose of RAGWITEK are limited. In the clinical trials, treatment interruptions for up to seven days were allowed.

Prescribe auto-injectable epinephrine to patients prescribed RAGWITEK and instruct them in the proper use of emergency self-injection of epinephrine [see *Warnings and Precautions* (5.2)].

**3 DOSAGE FORMS AND STRENGTHS**

RAGWITEK is available as 12 Amb a 1-Unit (Amb a 1-U) tablets that are white to off-white, circular with a debossed double hexagon on one side.

**4 CONTRAINDICATIONS**

RAGWITEK is contraindicated in patients with:

- Severe, unstable or uncontrolled asthma
- A history of any severe systemic allergic reaction
- A history of any severe local reaction after taking any sublingual allergen immunotherapy
- A history of eosinophilic esophagitis
- Hypersensitivity to any of the inactive ingredients [gelatin, mannitol, and sodium hydroxide] contained in this product [see *Description* (11)].

**5 WARNINGS AND PRECAUTIONS**

**5.1 Severe Allergic Reactions**

RAGWITEK can cause systemic allergic reactions including anaphylaxis which may be life-threatening. In addition, RAGWITEK can cause severe local reactions, including laryngopharyngeal swelling, which can compromise breathing and be life-threatening. Educate patients to recognize the signs and symptoms of these allergic reactions and instruct them to seek immediate medical care and discontinue therapy should any of these occur. Allergic reactions may require treatment with epinephrine. [See *Warnings and Precautions* (5.2).]

Administer the initial dose of RAGWITEK in a healthcare setting under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases and prepared to manage a life-threatening systemic or local allergic reaction. Observe patients in the office for at least 30 minutes following the initial dose of RAGWITEK.

**5.2 Epinephrine**

Prescribe auto-injectable epinephrine to patients receiving RAGWITEK. Instruct patients to recognize the signs and symptoms of a severe allergic reaction and in the proper use of emergency auto-injectable epinephrine. Instruct patients to seek immediate medical care upon use of auto-injectable epinephrine and to stop treatment with RAGWITEK. [See *Patient Counseling Information* (17).]

See the epinephrine package insert for complete information.

RAGWITEK may not be suitable for patients with certain medical conditions that may reduce the ability to survive a serious allergic reaction or increase the risk of adverse reactions after epinephrine administration. Examples of these medical conditions include but are not limited to: markedly compromised lung function (either chronic or acute), unstable angina, recent myocardial infarction, significant arrhythmia, and uncontrolled hypertension.

RAGWITEK may not be suitable for patients who are taking medications that can potentiate or inhibit the effect of epinephrine. These medications include:

**Beta-adrenergic blockers:** Patients taking beta-adrenergic blockers may be unresponsive to the usual doses of epinephrine used to treat serious systemic reactions, including anaphylaxis. Specifically, beta-adrenergic blockers antagonize the cardiostimulating and bronchodilating effects of epinephrine.

**Alpha-adrenergic blockers, ergot alkaloids:** Patients taking alpha-adrenergic blockers may be unresponsive to the usual doses of epinephrine used to treat serious systemic reactions, including anaphylaxis. Specifically, alpha-adrenergic blockers antagonize the vasoconstricting and hypertensive effects of epinephrine. Similarly, ergot alkaloids may reverse the pressor effects of epinephrine.

**Tricyclic antidepressants, levothyroxine sodium, monoamine oxidase inhibitors, and certain antihistamines:** The adverse effects of epinephrine may be potentiated in patients taking tricyclic antidepressants, levothyroxine sodium, monoamine oxidase inhibitors, and the antihistamines chlorpheniramine, and diphenhydramine.

**Cardiac glycosides, diuretics:** Patients who receive epinephrine while taking cardiac glycosides or diuretics should be observed carefully for the development of cardiac arrhythmias.

**5.3 Upper Airway Compromise**

RAGWITEK can cause local reactions in the mouth or throat that could compromise the upper airway [see *Adverse Reactions* (6.1)]. Consider discontinuation of RAGWITEK in patients who experience persistent and escalating adverse reactions in the mouth or throat.

**5.4 Eosinophilic Esophagitis**

Eosinophilic esophagitis has been reported in association with sublingual tablet immunotherapy [see *Contraindications* (4)]. Discontinue RAGWITEK and consider a diagnosis of eosinophilic esophagitis in patients who experience severe or persistent gastro-esophageal symptoms including dysphagia or chest pain.

**5.5 Asthma**

Subjects with asthma who participated in clinical trials had asthma of a severity that required, at most, a daily low dose of an inhaled corticosteroid. RAGWITEK has not been studied in subjects with moderate or severe asthma.

Withhold immunotherapy with RAGWITEK if the patient is experiencing an acute asthma exacerbation. Reevaluate patients who have recurrent asthma exacerbations and consider discontinuation of RAGWITEK.

**5.6 Concomitant Allergen Immunotherapy**

RAGWITEK has not been studied in subjects who are receiving concomitant allergen immunotherapy. Concomitant dosing with other allergen immunotherapy may increase the likelihood of local or systemic adverse reactions to either subcutaneous or sublingual allergen immunotherapy.

**5.7 Oral Inflammation**

Stop treatment with RAGWITEK to allow complete healing of the oral cavity in patients with oral inflammation (e.g., oral lichen planus, mouth ulcers, or thrush) or oral wounds, such as those following oral surgery or dental extraction.

**6 ADVERSE REACTIONS**

Adverse reactions reported in ≥5% of patients were: throat irritation, oral pruritus, ear pruritus, oral paraesthesia, mouth edema, and tongue pruritus.

**6.1 Clinical Trials Experience**

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

In 4 placebo-controlled clinical trials, 1057 subjects 18 years of age and older with short ragweed pollen-induced rhinitis, with or without conjunctivitis, received at least one dose of RAGWITEK, of whom 327 (31%) completed at least 12 weeks of therapy. Of the subjects treated with RAGWITEK, 52% were male, 25% had mild asthma, and 82% were sensitized to other allergens in addition to ragweed pollen. The subject population was 83% White, 12% African American, and 2% Asian. Subject demographics in placebo-treated subjects were similar to the active group. The pooled analysis includes safety data from two 28-day safety studies and safety data from the first 28 days of two 52-week safety and efficacy studies. Adverse reactions reported in ≥1% of subjects in the 28-day pooled analysis treated with RAGWITEK are shown in Table 1.

The most common adverse reactions reported in subjects treated with RAGWITEK were throat irritation (16.6% vs 3.3% placebo), oral pruritus (10.9% vs 2.0%), ear pruritus (10.4% vs 1.1%), and oral paraesthesia (10.0% vs 4.0%). The percentage of subjects who discontinued from the clinical trials because of an adverse reaction while exposed to RAGWITEK or placebo was 4.4% and 0.8%,



respectively. The most common adverse reactions that led to study discontinuation in subjects who were exposed to RAGWITEK were mouth edema, swollen tongue, and dysphagia.

One subject (1/1057; 0.1%) who received RAGWITEK experienced a treatment-related severe systemic allergic reaction that led to discontinuation of RAGWITEK. The subject had local reactions starting on Day 1 of treatment with RAGWITEK. On Day 6 symptoms progressed and included swelling of the throat, dyspnea, nausea, and lightheadedness. The subject fully recovered after treatment with epinephrine (self-administered), antihistamines, and oral corticosteroids.

**Table 1: Adverse Reactions Reported in ≥1% of Subjects Treated with RAGWITEK (28-day pooled analysis)**

Adverse Reaction	RAGWITEK (N=1057)	Placebo (N=757)
<b>Ear and Labyrinth Disorders</b>		
Ear pruritus	10.4%	1.1%
<b>Respiratory, Thoracic and Mediastinal Disorders</b>		
Throat irritation	16.6%	3.3%
Oropharyngeal pain	1.5%	0.7%
Throat tightness	1.3%	0.5%
<b>Gastrointestinal Disorders</b>		
Oral pruritus	10.9%	2.0%
Paraesthesia oral	10.0%	4.0%
Mouth edema	6.1%	0.5%
Tongue pruritus	5.1%	0.5%
Lip swelling	3.0%	0.4%
Swollen tongue	2.9%	0.5%
Lip pruritus	1.5%	0.1%
Dry mouth	1.4%	0.7%
Tongue edema	1.3%	0.5%
Nausea	1.1%	0.3%
Palatal edema	1.1%	0%
Dysphagia	1.0%	0%
<b>Skin and Subcutaneous Tissue Disorders</b>		
Pruritus	1.8%	1.3%
<b>General Disorders and Administration Site Conditions</b>		
Chest discomfort	1.0%	0%

The overall safety profile beyond Day 28 in the two 52-week trials was similar to that observed in the pooled 28-day analysis.

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of RAGWITEK. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders: glossodynia.

Skin and Subcutaneous Tissue Disorders: angioedema.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. Available human data do not establish the presence or absence of RAGWITEK-associated risks during pregnancy.

In an embryo/fetal developmental toxicity study, RAGWITEK subcutaneously administered to mice during gestation at doses up to approximately 3 times the human sublingual dose did not reveal adverse developmental outcomes in fetuses (*see 8.1 Data*).

#### Data

##### Animal Data

In a developmental toxicity study, the effect of RAGWITEK on embryo/fetal development was evaluated in mice. Animals were administered RAGWITEK subcutaneously daily from day 6 to day 15 of the gestation period at doses approximately 1 to 3 times the human sublingual dose of 12 Amb a 1-U. There were no RAGWITEK-related post-implantation losses, fetal malformations or variations.

### 8.2 Lactation

#### Risk Summary

It is not known whether RAGWITEK is present in human milk. Data are not available to assess the effects of RAGWITEK on the breastfed child or on milk production/excretion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RAGWITEK and any potential adverse effects on the breastfed child from RAGWITEK or from the underlying maternal condition.

### 8.4 Pediatric Use

RAGWITEK is not approved for use in pediatric patients because safety and efficacy have not been established.

### 8.5 Geriatric Use

RAGWITEK is not approved for use in patients over 65 years of age because safety and efficacy have not been established.

## 11 DESCRIPTION

RAGWITEK tablets contain pollen allergen extract from Short Ragweed (*Ambrosia artemisiifolia*). RAGWITEK is a sublingual orally disintegrating tablet that dissolves rapidly. RAGWITEK is available as a tablet of 12 Amb a 1-U of short ragweed pollen allergen extract. Inactive ingredients: gelatin NF (fish source), mannitol USP, and sodium hydroxide NF.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The precise mechanisms of action of allergen immunotherapy are not known.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed in animals to evaluate the carcinogenic potential of RAGWITEK. There were no positive findings in a combined *in vivo* Comet and micronucleus assay in rats using Short Ragweed (*Ambrosia artemisiifolia*) pollen allergen extract.

Fertility studies have not been performed with Short Ragweed pollen allergen extract.

## 14 CLINICAL STUDIES

The efficacy of RAGWITEK in the treatment of ragweed pollen-induced allergic rhinitis, with or without conjunctivitis, was investigated in two double-blind, placebo-controlled clinical trials in adults 18 through 50 years of age. Subjects received RAGWITEK or placebo for approximately 12 weeks prior to the start of the ragweed pollen season and throughout the ragweed pollen season.

The subject population was 86% White, 9% African American, and 3% Asian. The subject population was almost equally divided between males and females. Overall, the mean age of subjects was 36 years. Subjects with asthma who participated in clinical trials had asthma of a severity that required, at most, a daily low dose of an inhaled corticosteroid. Approximately 16% of subjects had mild asthma at baseline.

Efficacy was established by self-reporting of rhinoconjunctivitis daily symptom scores (DSS) and daily medication scores (DMS). Daily rhinoconjunctivitis symptoms included four nasal symptoms (runny nose, stuffy nose, sneezing, and itchy nose), and two ocular symptoms (gritty/itchy eyes and watery eyes). The rhinoconjunctivitis symptoms were measured on a scale of 0 (none) to 3 (severe). Subjects in clinical trials were allowed to take symptom-relieving medications (including systemic and topical antihistamines, and topical and oral corticosteroids) as needed. The daily medication score measured the use of standard open-label allergy medications. Predetermined values were assigned to each class of medication. Generally, systemic and topical antihistamines were given the lowest score, topical steroids an intermediate score, and oral corticosteroids the highest score.

The sums of the DSS and DMS were combined into the Total Combined Score (TCS) which was averaged over the peak ragweed pollen season. Also, in each study, the average TCS over the entire ragweed season was assessed. Other endpoints in both studies included the average DSS during the peak and entire ragweed season, and the average DMS during the peak ragweed season.

#### Trial 1

The first study was a placebo-controlled trial which evaluated subjects 18 through 50 years of age comparing RAGWITEK (n=187) and placebo (n=188) administered as a sublingual tablet daily. In this trial, approximately 22% of subjects had mild asthma and 85% were sensitized to other allergens in addition to short ragweed. Subjects with asthma who participated in this trial had asthma of a severity that required, at most, a daily low dose of an inhaled corticosteroid. Subjects with a clinical history of symptomatic allergies to non-short ragweed pollen allergens that required treatment during the ragweed pollen season were excluded from the trial. The subject population was 78% White, 12% African American, and 8% Asian, and almost equally divided between males and females. The mean age of subjects in this study was 35.4 years. The two treatment groups were balanced with regard to baseline characteristics. The results of this study are shown in Table 2.

#### Trial 2

The second study was a placebo-controlled trial which evaluated subjects 18 through 50 years of age comparing RAGWITEK (n=194) and placebo (n=198) administered as a sublingual tablet daily. Approximately 17% of subjects had mild asthma and 78% were sensitized to other allergens in addition to short ragweed. Subjects with asthma who participated in this trial had asthma of a severity that required, at most, a daily low dose of an inhaled corticosteroid. Subjects with a clinical history of symptomatic allergies to non-short ragweed pollen allergens that required treatment during the ragweed pollen season were excluded from the trial. The subject population was 88% White, 8.9% African American, 2% Asian, and almost equally divided between males and females. The mean age of subjects in this study was 36.4 years. The two treatment groups were balanced with regard to baseline characteristics. The results of this study are shown in Table 3.

A decrease in TCS during the peak ragweed season for subjects treated with RAGWITEK compared to placebo-treated subjects was demonstrated in both trials. Subjects treated with RAGWITEK also showed a decrease in the average TCS from the start of and throughout the entire ragweed pollen season. Similar decreases were observed in subjects treated with RAGWITEK for other endpoints (*see Tables 2 and 3*).

**Table 2: Trial 1: Total Combined Scores (TCS), Rhinoconjunctivitis Daily Symptom Scores (DSS), and Daily Medication Scores (DMS) During the Ragweed Pollen Season**

Endpoint*	RAGWITEK (N) <sup>†</sup> Score <sup>‡</sup>	Placebo (N) <sup>†</sup> Score <sup>‡</sup>	Treatment Difference (RAGWITEK – Placebo)	Difference Relative to Placebo <sup>§</sup> Estimate (95% CI)
<b>TCS Peak Season<sup>¶</sup></b>	(159) 6.22	(164) 8.46	-2.24	-26% (-38.7, -14.6)
<b>TCS Entire Season</b>	(160) 5.21	(166) 7.01	-1.80	-26% (-37.6, -13.5)
<b>DSS Peak Season</b>	(159) 4.65	(164) 5.59	-0.94	-17% (-28.6, -4.6)
<b>DSS Entire Season</b>	(160) 4.05	(166) 4.87	-0.82	-17% (-28.5, -4.5)
<b>DMS Peak Season</b>	(159) 1.57	(164) 2.87	-1.30	-45% (-65.4, -27.0)

TCS=Total Combined Score (DSS + DMS); DSS=Daily Symptom Score; DMS=Daily Medication Score.

<sup>†</sup> Parametric analysis using analysis of variance model for all endpoints.

<sup>‡</sup> Number of subjects in analyses.

<sup>§</sup> The estimated group means are reported and difference relative to placebo is based on estimated group means.

<sup>¶</sup> Difference relative to placebo computed as: (RAGWITEK - placebo)/placebo x 100.

<sup>¶</sup> Peak ragweed season was defined as maximum 15 days with the highest moving average pollen counts during the ragweed season.

**Table 3: Trial 2: Total Combined Scores (TCS), Rhinoconjunctivitis Daily Symptom Scores (DSS), and Daily Medication Scores (DMS) During the Ragweed Pollen Season**

Endpoint*	RAGWITEK (N) <sup>†</sup> Score <sup>‡</sup>	Placebo (N) <sup>†</sup> Score <sup>‡</sup>	Treatment Difference (RAGWITEK – Placebo)	Difference Relative to Placebo <sup>§</sup> Estimate (95% CI)
<b>TCS Peak Season<sup>¶</sup></b>	(152) 6.41	(169) 8.46	-2.04	-24% (-36.5, -11.3)
<b>TCS Entire Season</b>	(158) 5.18	(174) 7.09	-1.92	-27% (-38.8, -14.1)
<b>DSS Peak Season</b>	(152) 4.43	(169) 5.37	-0.94	-18% (-29.2, -4.5)
<b>DSS Entire Season</b>	(158) 3.62	(174) 4.58	-0.96	-21% (-31.6, -8.8)
<b>DMS Peak Season</b>	(152) 1.99	(169) 3.09	-1.10	-36% (-55.8, -14.6)
<b>Season</b>				

TCS=Total Combined Score (DSS + DMS); DSS=Daily Symptom Score; DMS=Daily Medication Score.

<sup>†</sup> Parametric analysis using analysis of variance model for all endpoints.

<sup>‡</sup> Number of subjects in analyses.

<sup>§</sup> The estimated group means are reported and difference relative to placebo is based on estimated group means.

<sup>¶</sup> Difference relative to placebo computed as: (RAGWITEK - placebo)/placebo x 100.

<sup>¶</sup> Peak ragweed season was defined as maximum 15 days with the highest moving average pollen counts during the ragweed season.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

RAGWITEK 12 Amb a 1-U tablets are white to off-white, circular sublingual tablets with a debossed double hexagon on one side.

RAGWITEK is supplied as follows:

3 blister packages of 10 tablets (30 tablets total), NDC 52709-1601-3

9 blister packages of 10 tablets (90 tablets total), NDC 52709-1601-9

Store at controlled room temperature, 20°C-25°C (68°F-77°F); excursions permitted between 15°C-30°C (59°F-86°F). Store in the original package until use to protect from moisture.

## 17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Medication Guide) and to keep RAGWITEK and all medicines out of the reach of children.

### Severe Allergic Reactions

Advise patients that RAGWITEK may cause life-threatening systemic or local allergic reactions, including anaphylaxis. Educate patients about the signs and symptoms of these allergic reactions [see *Warnings and Precautions* (5.1)]. The signs and symptoms of a severe allergic reaction may include: syncope, dizziness, hypotension, tachycardia, dyspnea, wheezing, bronchospasm, chest discomfort, cough, abdominal pain, vomiting, diarrhea, rash, pruritus, flushing, and urticaria.

Ensure that patients have auto-injectable epinephrine and instruct patients in its proper use. Instruct patients who experience a severe allergic reaction to seek immediate medical care, discontinue RAGWITEK, and resume treatment only when advised by a physician to do so. [See *Warnings and Precautions* (5.2).]

Advise patients to read the patient information for epinephrine.

Inform patients that the first dose of RAGWITEK must be administered in a healthcare setting under the supervision of a physician and that they will be monitored for at least 30 minutes to watch for signs and symptoms of life-threatening systemic or local allergic reaction [see *Warnings and Precautions* (5.1)].

Because of the risk of upper airway compromise, instruct patients with persistent and escalating adverse reactions in the mouth or throat to discontinue RAGWITEK and to contact their healthcare professional. [See *Warnings and Precautions* (5.3).]

Because of the risk of eosinophilic esophagitis, instruct patients with severe or persistent symptoms of esophagitis to discontinue RAGWITEK and to contact their healthcare professional. [See *Warnings and Precautions* (5.4).]

### Asthma

Instruct patients with asthma that if they have difficulty breathing or if their asthma becomes difficult to control, they should stop taking RAGWITEK and contact their healthcare professional immediately [see *Warnings and Precautions* (5.5)].

### Administration Instructions

Instruct patients to carefully remove the foil from the blister unit with dry hands and then take the sublingual tablet immediately by placing it under the tongue where it will dissolve. Also instruct patients to wash their hands after handling the tablet, and to avoid food or beverages for 5 minutes after taking the tablet. [See *Dosage and Administration* (2.2).]

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Manufactured for: ALK-Abelló A/S



ALK-Abelló A/S, Bøge Allé 6-8, DK-2970 Hørsholm, Denmark

U.S. License No. 1292

Manufactured by:

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## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OTIPRIO safely and effectively. See full prescribing information for OTIPRIO.

OTIPRIO® (ciprofloxacin otic suspension), for intratympanic or otic use

Initial U.S. Approval: 1987

### RECENT MAJOR CHANGES

Indications and Usage (1)	3/2018
Dosage and Administration (2)	3/2018

### INDICATIONS AND USAGE

OTIPRIO is a fluoroquinolone antibacterial indicated for the following conditions:

- The treatment of pediatric patients (age 6 months and older) with bilateral otitis media with effusion undergoing tympanostomy tube placement. (1)
- The treatment of acute otitis externa in patients 6 months of age and older due to *Pseudomonas aeruginosa* and *Staphylococcus aureus*. (1)

### DOSAGE AND ADMINISTRATION

- OTIPRIO is for intratympanic or otic administration by a healthcare professional only. (2.1)
- OTIPRIO is intended for single-patient use with up to two doses available in each vial. (2.1)
- For bilateral otitis media with effusion, administer OTIPRIO as a single intratympanic administration of one 0.1 mL (6 mg) dose into each affected ear, following suctioning of the middle ear effusion. (2.1)
- For acute otitis externa, administer OTIPRIO as a single 0.2 mL (12 mg) administration to the affected ear(s). (2.1)
- See Full Prescribing Information for directions for OTIPRIO dose preparation. (2.2)

### DOSAGE FORMS AND STRENGTHS

Otic Suspension: Each OTIPRIO vial contains 1 mL of 6% (60 mg/mL) ciprofloxacin otic suspension. (3)

### CONTRAINDICATIONS

OTIPRIO is contraindicated in patients with a history of hypersensitivity to ciprofloxacin, to quinolones, or to any component of OTIPRIO. (4)

### WARNINGS AND PRECAUTIONS

Potential for Microbial Overgrowth: OTIPRIO may result in overgrowth of non-susceptible bacteria and fungi. (5.1)

### ADVERSE REACTIONS

Otitis Media with Effusion: The most frequently occurring adverse reactions (with an incidence rate greater than 3%) were nasopharyngitis and irritability. (6.1)

Acute Otitis Externa: The most frequently occurring adverse reactions (with an incidence rate of at least 2%) were: ear pruritus, headache, otitis media and ear discomfort. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Otonomy at 1-800-826-6411 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 3/2018

## FULL PRESCRIBING INFORMATION: CONTENTS\*

1	INDICATIONS AND USAGE	12	CLINICAL PHARMACOLOGY
2	DOSAGE AND ADMINISTRATION	12.1	Mechanism of Action
2.1	Dosage and Important Administration Instructions	12.3	Pharmacokinetics
2.2	Preparation of OTIPRIO	12.4	Microbiology
3	DOSAGE FORMS AND STRENGTHS	13	NONCLINICAL TOXICOLOGY
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5	WARNINGS AND PRECAUTIONS	13.2	Animal Toxicology and/or Pharmacology
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\*Sections or subsections omitted from the full prescribing information are not listed.

## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

OTIPRIO is indicated for

- The treatment of pediatric patients (6 months of age and older) with bilateral otitis media with effusion undergoing tympanostomy tube placement.
- The treatment of acute otitis externa in patients 6 months of age and older due to *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

### 2 DOSAGE AND ADMINISTRATION

#### 2.1 Dosage and Important Administration Instructions

- OTIPRIO is for intratympanic or otic administration by a healthcare professional only.

- OTIPRIO is intended for single-patient use, discard unused portion.
- For bilateral otitis media with effusion, administer OTIPRIO as a single intratympanic administration of one 0.1 mL (6 mg) dose into each affected ear of pediatric patients (6 months of age and older), following suctioning of middle ear effusion.
- For acute otitis externa, administer OTIPRIO as a single 0.2 mL (12 mg) administration to the external ear canal of each affected ear of patients aged 6 months and older.

#### 2.2 Preparation of OTIPRIO

Directions for OTIPRIO dose preparation and handling are presented in Figure 1. The directions differ for each indication. Follow the correct directions.

**Figure 1: Preparation and dosing directions for Acute Otitis Externa and for Otitis Media with Effusion.**

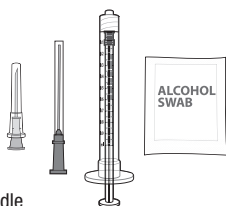
**Dosing directions differ for each indication.  
Follow the correct directions.**

#### Acute Otitis Externa

##### STEP 1 Preparation for ACUTE OTITIS EXTERNA

Materials needed:

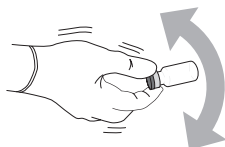
- 1 vial of OTIPRIO (for single patient with unilateral or bilateral AOE)
- For each affected ear:
  - One 1 mL luer lock syringe
  - One 18G-21G preparation needle
  - One 20-24G, 1.5 inch **blunt, flexible** catheter or comparable administration needle
- Alcohol pad
- Optional: ice pack and drape to keep OTIPRIO vial cold.



**Keep product cold during preparation. If OTIPRIO thickens during preparation, place the vial back in refrigeration.**

##### STEP 2 OTIPRIO Mixing

To keep the vial cold during shaking, hold the OTIPRIO vial by the aluminum seal to prevent gelation. **Shake the vial for 5 to 8 seconds** to mix well until a visually homogenous suspension is obtained.



**Always hold the vial by the aluminum seal to prevent gelation.**

##### STEP 3 OTIPRIO Removal

Using an 18-21G needle, withdraw 0.3 mL of the suspension into the 1 mL syringe.



##### STEP 4 Replace with the Administration Needle

Replace the needle with a 20-24G, 1.5 inch **blunt, flexible catheter** to be used for administration.

**Do not prime the syringe until after the administration needle has been attached.**



##### STEP 5 Priming the Administration Needle for ACUTE OTITIS EXTERNA

Prime the needle leaving a dose of **0.2 mL** (0.2 cc).



##### STEP 6 Preparing Second Dose for Bilateral Administration Only

Repeat Steps 3, 4 and 5 to prepare a second syringe for the other ear and dispose of the vial.



**Use a different syringe for each ear.**



##### AFTER PREPARATION

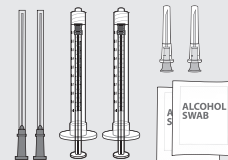
Syringes can be kept at room temperature or in the refrigerator prior to administration. Keep syringes on their side. Discard syringes if not administered in 3 hours.

#### Otitis Media with Effusion

##### STEP 1 Preparation for OTITIS MEDIA with EFFUSION

Materials needed:

- 1 vial of OTIPRIO (for single patient, enough for bilateral use)
- Two 1 mL luer lock syringes
- Two 18G-21G preparation needles
- Two 20-24G, 2-3 inch **blunt, flexible** catheters or comparable administration needles
- Alcohol pads
- Optional: ice pack and drape to keep OTIPRIO vial cold.



**Keep product cold during preparation. If OTIPRIO thickens during preparation, place the vial back in refrigeration.**

##### STEP 2 OTIPRIO Mixing

To keep the vial cold during shaking, hold the OTIPRIO vial by the aluminum seal to prevent gelation. **Shake the vial for 5 to 8 seconds** to mix well until a visually homogenous suspension is obtained.



**Always hold the vial by the aluminum seal to prevent gelation.**

##### STEP 3 OTIPRIO Removal

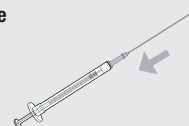
Using an 18-21G needle, withdraw 0.3 mL of the suspension into the 1 mL syringe.



##### STEP 4 Replace with the Administration Needle

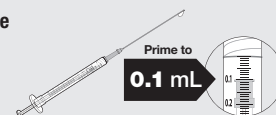
Replace the needle with a 20-24G, 2-3 inch **blunt, flexible catheter** to be used for administration.

**Do not prime the syringe until after the administration needle has been attached.**



##### STEP 5 Priming the Administration Needle for OTITIS MEDIA with EFFUSION

Prime the needle leaving a dose of **0.1 mL** (0.1 cc).



##### STEP 6 Preparing Second Dose for Bilateral Administration Only

Repeat Steps 3, 4 and 5 to prepare a second syringe for the other ear and dispose of the vial.



**Use a different syringe for each ear.**



##### AFTER PREPARATION

Syringes can be kept at room temperature or in the refrigerator prior to administration. Keep syringes on their side. Discard syringes if not administered in 3 hours.

**OR**

### 3 DOSAGE FORMS AND STRENGTHS

Otic Suspension: Each 1 mL of OTIPRIO contains a white, preservative-free, sterile otic suspension consisting of 6% (60 mg/mL) ciprofloxacin in a single-patient use glass vial.

### 4 CONTRAINDICATIONS

OTIPRIO is contraindicated in patients with a history of hypersensitivity to ciprofloxacin, to other quinolones, or to any of the components of OTIPRIO.

### 5 WARNINGS AND PRECAUTIONS

#### 5.1 Potential for Microbial Overgrowth

OTIPRIO may result in overgrowth of non-susceptible bacteria and fungi. If such infections occur, institute alternative therapy.

### 6 ADVERSE REACTIONS

#### 6.1 Clinical Trials Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

##### Otitis Media with Effusion

In two randomized, sham-controlled Phase 3 clinical trials, 530 pediatric patients with bilateral otitis media with effusion undergoing tympanostomy tube placement were treated with OTIPRIO or sham administered intratympanically as a single dose (0.1 mL to each ear). The median age of the pediatric patients enrolled in the clinical trials was 1.5 years; 62% of patients were 6 months through 2 years of age and 38% of patients were greater than 2 years of age.

Adverse reactions that occurred in at least 3% of OTIPRIO patients and at an incidence greater than sham are presented in Table 1.

Table 1: Adverse Reactions in Phase 3 Otitis Media with Effusion Trials

Adverse Reactions	OTIPRIO (N=357)	Sham (N=173)
Nasopharyngitis	5%	4%
Irritability	5%	3%
Rhinorrhea	3%	2%

##### Acute Otitis Externa

In a single randomized, sham controlled Phase 3 clinical trial, 259 pediatric and adult patients with acute otitis externa were treated with OTIPRIO or sham administered by a healthcare professional to the external ear canal as a single dose (0.2 mL to each affected ear). The median age of the patients enrolled in the clinical trial was 34 years; 26% were pediatric patients (age 3 to 17 years), 65% were adults (age 18 to 64 years), and 8% were elderly patients (age 65 years and older).

Adverse reactions that occurred in at least 2% of OTIPRIO patients and at an incidence greater than sham are presented in Table 2.

Table 2: Adverse Reactions in Phase 3 Acute Otitis Externa Trial

Adverse Reactions	OTIPRIO (N=127)	Sham (N=132)
Ear Pruritus	2%	2%
Headache	2%	1%
Otitis Media	2%	1%
Ear Discomfort	2%	0%

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

##### Risk Summary

Animal reproduction studies have not been conducted with OTIPRIO. No adequate and well-controlled studies have been performed in pregnant women. Because of the negligible systemic exposure associated with clinical administration of OTIPRIO, this product is expected to be of minimal risk for maternal and fetal toxicity when administered to pregnant women.

#### 8.2 Lactation

##### Risk Summary

Ciprofloxacin is excreted in human milk with systemic administration. However, because of the negligible systemic exposure after otic application, nursing infants of mothers receiving OTIPRIO should not be affected.

#### 8.4 Pediatric Use

The safety and effectiveness of OTIPRIO for the treatment of pediatric patients (6 months of age and older) with bilateral otitis media with effusion undergoing tympanostomy tube placement was established in 530 patients who participated in the Phase 3 trials. The median age of patients enrolled in the clinical trials was 1.5 years; 62% of patients were 6 months through 2 years of age and 38% of patients were greater than 2 years of age [see Adverse Reactions (6.1) and Clinical Studies (14)].

The safety and effectiveness of OTIPRIO for the treatment of acute otitis externa was established in 67 pediatric patients (3 through 17 years of age) who participated in the Phase 3 trial; 57% of patients were 3 through 11 years of age and 43% of patients were 12 through 17 years of age. The safety and efficacy observed in the pediatric patients was no different from the older population. OTIPRIO is indicated for the treatment of acute otitis externa in pediatric patients 6 months of age and older. [see Indications and Usage (1), Dosage and Administration (2), Adverse Reactions (6.1) and Clinical Studies (14)].

The safety and effectiveness of OTIPRIO in infants below 6 months of age have not been established for the treatment of pediatric patients with bilateral otitis media with effusion undergoing tympanostomy tube placement and acute otitis externa.

#### 8.5 Geriatric Use

Clinical studies of OTIPRIO did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients [see Adverse Reactions (6.1) and Clinical Studies (14)].

### 11 DESCRIPTION

OTIPRIO (ciprofloxacin otic suspension) 6% contains the synthetic fluoroquinolone antibacterial, ciprofloxacin. OTIPRIO is for intratympanic administration for otitis media with effusion and otic administration to the external ear canal for acute otitis externa. OTIPRIO is supplied as a white, preservative-free, sterile otic suspension of 6% (w/v) ciprofloxacin in a neutral pH, buffered, isotonic solution in a single-patient use glass vial containing 1 mL. The glass vial is fitted with a stopper not made with natural rubber latex. The inactive ingredients are poloxamer 407, sodium chloride, tromethamine, hydrochloric acid and water for injection (WFI).

The thermosensitive suspension exists as a liquid at room temperature or below and gels when warmed [see How Supplied/Storage and Handling (16)].

Ciprofloxacin has the following nomenclature:

1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid. Its empirical formula is  $C_{17}H_{18}FN_3O_3$  and its molecular weight is 331.3.

Its chemical structure is as follows:

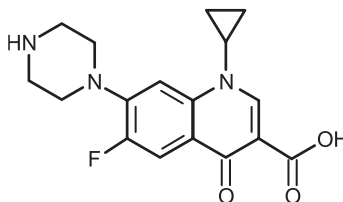


Figure 2: Structure of Ciprofloxacin

### 12 CLINICAL PHARMACOLOGY

#### 12.1 Mechanism of Action

Ciprofloxacin is a fluoroquinolone antibacterial [see Microbiology (12.4)].

#### 12.3 Pharmacokinetics

The plasma concentration of ciprofloxacin following otic administration of OTIPRIO was not measured.

#### 12.4 Microbiology

##### Mechanism of Action

The bactericidal action of ciprofloxacin results from interference with the enzyme DNA gyrase, which is needed for the synthesis of bacterial DNA.

##### Resistance

Bacterial resistance to fluoroquinolones can develop through chromosomally- or plasmid-mediated mechanisms. *In vitro* studies demonstrated cross-resistance between ciprofloxacin and some fluoroquinolones. There is generally no cross-resistance between ciprofloxacin and other classes of antibacterial agents, such as beta-lactams or aminoglycosides.

##### Antimicrobial Activity

Ciprofloxacin has been shown to be active against most isolates of the following bacteria:

- Gram-positive Bacteria
  - Staphylococcus aureus*
  - Streptococcus pneumoniae*
- Gram-negative Bacteria
  - Haemophilus influenzae*
  - Moraxella catarrhalis*
  - Pseudomonas aeruginosa*

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin, and the test results are listed below:

Salmonella/Microsome Test (Negative)  
Escherichia coli DNA Repair Assay (Negative)  
Mouse Lymphoma Cell Forward Mutation Assay (Positive)  
Chinese Hamster V79 Cell HGPRT Test (Negative)  
Syrian Hamster Embryo Cell Transformation Assay (Negative)  
Saccharomyces cerevisiae Point Mutation Assay (Negative)  
Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative)  
Rat Hepatocyte DNA Repair Assay (Positive)

Thus, 2 of the 8 *in vitro* tests were positive, but results of the following 3 *in vivo* test systems gave negative results:

Rat Hepatocyte DNA Repair Assay  
Micronucleus Test (Mice)  
Dominant Lethal Test (Mice)

Long-term carcinogenicity studies in mice and rats have been completed for ciprofloxacin. After daily oral doses of 750 mg/kg in mice and 250 mg/kg in rats (for mice and rats respectively, approximately 300 and 200 times the maximum recommended clinical dose of otological ciprofloxacin based upon body surface area, assuming total absorption of ciprofloxacin from the ear of a patient treated with OTIPRIO) were administered for up to 2 years, there was no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species.

Fertility studies performed in rats at oral doses of ciprofloxacin up to 100 mg/kg/day revealed no evidence of impairment. This would be approximately 80 times the maximum recommended clinical dose of otological ciprofloxacin based upon body surface area, assuming total absorption of ciprofloxacin from the ear of a patient treated with OTIPRIO.

### 13.2 Animal Toxicology and/or Pharmacology

Guinea pigs dosed in the middle ear with OTIPRIO exhibited no drug-related structural or functional changes of the cochlear hair cells.

## 14 CLINICAL STUDIES

### 14.1 Bilateral Otitis Media with Effusion

Two randomized, multicenter, sham-controlled clinical trials in 532 pediatric patients with bilateral otitis media with effusion undergoing myringotomy with tympanostomy tube placement evaluated the safety and efficacy of OTIPRIO when administered intratympanically as a single dose (NCT 01949155 and NCT 01949142). The median age of patients enrolled in the clinical trials was 1.5 years; 62% of patients were 6 months through 2 years of age and 38% of patients were greater than 2 years of age. The efficacy endpoint for both trials was the cumulative proportion of study treatment failures through Day 15, defined as the occurrence of any of the following events: otorrhea as determined by a blinded assessor on or after 3 days post-surgery, otic or systemic antibacterial drug use for any reason any time post-surgery, as well as patients who missed visits or were lost-to-follow-up. Table 3 presents the results from each Phase 3 trial.

**Table 3: Cumulative Proportion of Treatment Failures Through Day 15 in Phase 3 Trials (Otitis Media with Effusion)**

	Trial 1 (N=266)			Trial 2 (N=266)		
	OTIPRIO	Sham	Difference (Sham – OTIPRIO) (95% CI)	OTIPRIO	Sham	Difference (Sham – OTIPRIO) (95% CI)
Treatment Failure	25% (44/179)	45% (39/87)	20% (8%, 32%) <sup>2</sup>	21% (38/178)	45% (40/88)	24% (12%, 36%) <sup>2</sup>
Reason for Failure <sup>1</sup>						
Otorrhea	7%	11%		7%	27%	
Otic antibacterial drugs	6%	17%		5%	8%	
Systemic antibacterial drugs	2%	5%		3%	3%	
Lost-to-follow-up and missed visit	10%	11%		6%	7%	

<sup>1</sup> the earliest occurring treatment failure event, and patients were classified as a treatment failure due only to that component for the remainder of the study

<sup>2</sup> P-value <0.001 for Cochran-Mantel-Haenszel test (adjusted for age-group)

Administration of OTIPRIO did not lead to impairment in hearing function, middle ear function or tube patency by Day 29.

### 14.2 Acute Otitis Externa

One randomized multicenter, sham-controlled clinical trial in 262 pediatric and adult patients with unilateral or bilateral acute otitis externa was designed to evaluate the safety and efficacy of OTIPRIO when administered by a healthcare professional as a single dose to the external ear canal to patients aged 6 months and older (NCT 02801370). The median age of patients enrolled in the clinical trials was 34 years; 26% of patients were 3 to 17 years of age, 65% of patients were 18 to 64 years of age, and 8% of patients were greater than 65 years of age. No patients less than 3 years of age were enrolled.

The primary efficacy endpoint was the proportion of patients with clinical response at Day 8. Clinical response was defined as the complete absence of signs and symptoms of acute otitis externa (i.e., tenderness, erythema, edema, and otorrhea as determined by the blinded assessor), and no concomitant systemic or topical antibacterial drug (given in the study ear) was taken for any reason at or prior to the study visit. Table 4 contains the proportions of patients with clinical response at Day 8 in both the intent to treat (ITT) population which contains all subjects who were randomized and did not have group A streptococci cultured on Day 1 and the microbiological ITT population which contains all ITT subjects who had a positive culture for *S. aureus* or *P. aeruginosa* on Day 1.

**Table 4: Proportion of Patients with Clinical Response at Study Day 8 (Acute Otitis Externa)**

Study Population	OTIPRIO	Sham	% Difference (OTIPRIO - Sham) (95% CI)
Intention to Treat (ITT) N=260	69% 90/130	46% 60/130	23.1 <sup>1</sup> (10.66, 34.62)
Microbiological ITT (Mic-ITT) N=108	60% 31/52	34% 19/56	25.7 <sup>2</sup> (6.57, 43.32)

<sup>1</sup> p<0.001 from a Fisher's exact test.

<sup>2</sup> p=0.012 from a Fisher's exact test.

ITT population = all patients who were randomized and did not have group A streptococci cultured on Day 1.

Mic-ITT population = all ITT patients who had a positive culture for *S. aureus* or *P. aeruginosa* on Day 1.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

OTIPRIO is a sterile, preservative-free, otic suspension of 6% (60 mg/mL, w/v) ciprofloxacin in a neutral pH buffered, isotonic solution containing poloxamer 407.

Each OTIPRIO carton contains 1 mL of 6% (60 mg/mL, w/v) ciprofloxacin in a 2 mL single-patient use glass vial fitted with a stopper not made with natural rubber latex. (NDC 69251-201-01)

OTIPRIO should be stored at 2 to 8°C (36 to 46°F) until prior to use to prevent thickening during preparation. Protect from light. Store in the original carton until dose preparation.

## 17 PATIENT COUNSELING INFORMATION

Advise patients and their caregiver(s) that there may be drainage from the ear the first few days following ear tube surgery, but if the ear becomes painful, or continuous ear discharge is noted, or the patient develops a fever, advise patients and their caregiver(s) to consult their physician.

For acute otitis externa, advise patients and/or their caregivers that if the ear continues to be painful, swollen or itchy after a week, they should consult their physician.

### Distributed by:

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OTIPRIO® is a registered trademark of Otonomy.

U.S. Patent Nos: 8,318,817, 9,205,048, 9,220,796, 9,233,068, 9,486,405, and 9,603,796

OTI0122.0318

# ORDERING INFORMATION



US Fax: 888-329-2551

## FAX ORDER FORM\*

## REQUESTED DELIVERY DATE: \_\_\_\_\_

To better meet or exceed your expectations, please include a date in which you would like to receive products in your office. Please note, when faxing, requested delivery date must be a minimum of 48 hours out from the time order is received by ALK. If products are needed urgently (within 48 hours) it is best to call our Customer Service department for personalized order placement. Extracts are normally shipped overnight and Ancillary items (vials, diluents, syringes) are sent via ground delivery (generally 3 – 5 business days from shipping date).

SPECIAL INSTRUCTIONS:

Date: \_\_\_\_\_ Customer No.: \_\_\_\_\_ Contact Person: \_\_\_\_\_

Phone: \_\_\_\_\_ Fax: \_\_\_\_\_ P.O. Number: \_\_\_\_\_

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QTY	ITEM DESCRIPTION	VIAL SIZE	CONCENTRATION	AQ	GLY	C-AL	SCR	ID

AQ = Aqueous GLY = Glycerin C-AL = Center-AI SCR = Scratch ID = Intradermal

Please Check All That Applies:☐ Invoice Account ☐ Visa ☐ MasterCard ☐ American Express ☐ Discover

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# Ordering Information

## ALK STANDARD TERMS AND CONDITIONS

**1. DEFINITIONS:** "Agreement" is the purchase agreement entered into by and between ALK and Buyer for the purchase of OGS, and the ST&C incorporated by reference in writing into it. "Buyer" is the entity purchasing OGS from ALK. "Goods" is defined in the New York Uniform Commercial Code. Goods or Services that are the subject of the Agreement are referred to as "OGS". "Services" are anything of value ALK provides that is not Goods. "ST&C" are the standard terms and conditions related to the purchase of OGS from ALK.

**2. ACCEPTANCE:** ALK accepts Buyer's order for OGS and agrees to fulfil it upon execution of an Agreement, and the earliest of: (a) Buyer's receipt of ALK's invoice for the OGS order; or (b) delivery of OGS. Subject to these ST&C, the Agreement may not be modified or cancelled except in a document signed by both parties.

**3. SHIPMENT:** ALK will arrange shipment consistent with Buyer's designated delivery date, and at Buyer's expense for all customs, duties and fees. A minimum of 48 hours' notice is required. If OGS are required within 48 hours, Buyer should contact ALK's Customer Service department. All shipments must include packing slips. Allergenic extracts are shipped to arrive the next day, and are normally shipped Monday, Tuesday, Wednesday and Thursday only to avoid weekend delays. Ancillary items are shipped daily via ground delivery service. Freight charges are calculated by weight of package rounded to the nearest full pound.

**4. DELIVERY; RISK OF LOSS:** Delivery will be made to Buyer's "Ship To" address, F.O.B. Shipping Point, pursuant to Incoterms 2000. Risk of loss passes to Buyer upon shipment. All OGS shall be packed for shipment by ALK in accordance with good commercial practice and applicable laws, with respect to protection of OGS during shipping and handling.

**5. LOT TRACEABILITY:** Each unit of issue, part, component, or material of OGS must be identified by lot, batch or control number traceable to its manufacturing facility. The lot or batch number must provide the capability for a lot or batch purge, if applicable, in the event of any field action or the determination of an adverse condition or discrepancy. The terms "lot, batch or control number" are defined in 21 CFR Part 210.3.

**6. PAYMENT TERMS; MINIMUM ORDER:** All payment terms, including any discounts, are calculated on the invoice date. Invoices are payable within 30 days of receipt. All prices are subject to change without notice. A minimum order of \$50 is required. Please combine orders to achieve these minimums. A service charge of not more than \$10 will be applied to orders of less than \$50.

**7. TERMINATION:** Subject to Section 8, if Buyer refuses to accept delivery of OGS or any installments, at ALK's election, the Agreement, including any OGS order(s), may be deemed breached and terminated by ALK in its entirety.

**8. INSPECTION:** Buyer shall promptly inspect OGS upon delivery, and report any damage, defect, loss in transit, or other shipping errors ascertainable upon a visual inspection or otherwise reasonably apparent within 5 days of delivery. If such damage could not reasonably have been discovered within such period, then Buyer must report to ALK within 5 days after Buyer discovers or reasonably should have discovered such concealed damage (but in no event later than 30 days of receipt). Buyer shall hold damaged OGS for inspection by the insurer, the carrier, or ALK's designated representative for 15 business days after notifying ALK of the damage. If ALK is unable to remedy or replace the defective or damaged OGS (at ALK's sole discretion), it shall notify Buyer, and in ALK's sole discretion, ALK shall promptly reverse the invoice for the defective or damaged OGS or, if payment for the defective or damaged OGS has been made by Buyer, credit the amount paid by Buyer for such defective or damaged OGS. ALK shall not be responsible for OGS that is damaged, altered, lost or otherwise tampered with, after receipt by Buyer.

**9. RETURNS:** Buyer shall contact ALK Sales Support at 800-325-7354 for all OGS return and/or credit issues. Allergenic extracts and sterile products may not be returned unless shipped by a ALK error. Subject to Section 8, all items shipped in error or damaged in shipment (accompanied by a signed bill of lading noting damage) must be reported to ALK Sales Support. Returns are permitted ONLY with prior authorization from the Sales Support Department. OGS return requests initiated in response to customer order errors will be subject to a 15% processing charge, provided that the item is eligible for restocking per ALK's Restocking Policy. Per the Restocking Policy, ALK is not able to restock allergy extracts. Buyer will be notified promptly as to the results of all return investigations. Upon investigation and approval of Buyer's return claim, a credit will be issued to Buyer's account and/or replacement OGS will be shipped to Buyer. A revised invoice will not be sent; however, a copy of the credit memo will be sent and/or faxed to the number or address on record. OGS return claims will remain open for 60 days from the date of return notification to ALK. If 60 days has elapsed, and OGS have not

been returned and/or other required actions from Buyer have not been completed to process the return or credit, the OGS return claim will be permanently closed.

**10. INSURANCE:** If requested, Buyer will provide ALK with a certificate of insurance, including Product and Completed Operations Liability, with a minimum combined single limit of not less than \$2 million per occurrence.

**11. WARRANTIES:** ALK warrants that each OGS shall not on the date of shipment by ALK, be adulterated or misbranded within the meaning of the FD&C Act. This warranty is in lieu of all other warranties, express or implied, and ALK expressly disclaims any and all other warranties including, without limitation, any warranty of merchantability, fitness for any particular purpose or non-infringement. ALK makes no warranty whatsoever, express or implied, and assumes no liability to Buyer or anyone else with respect to the OGS including, without limitation, any warranty in respect of: (i) the purity, standards or other characteristics of an OGS if the immediate container has been opened by Buyer or anyone else after shipment by ALK (other than immediately prior to its use by the end user); (ii) the continued availability of any OGS; or (iii) the use of OGS other than as specified on the labels, and in the prescribing information for OGS. EXCEPT AS PROVIDED IN THIS SECTION 11, ALK MAKES NO WARRANTY THAT THE OGS ARE FIT FOR ANY PARTICULAR PURPOSE, AND UNDER NO CIRCUMSTANCES SHALL ALK BE LIABLE TO BUYER FOR INDIRECT OR CONSEQUENTIAL DAMAGES, AND THE WARRANTY CLAIM OF BUYER AGAINST ALK SHALL BE LIMITED TO REPLACEMENT OR REPLACEMENT VALUE OF THE OGS, AT ALK'S OPTION.

**12. INDEMNIFICATION:** Buyer shall indemnify and defend ALK, its officers, directors, employees, agents, affiliates, customers and other buyers from all claims, losses, expenses (including attorney's and expert witness fees), causes of action, damage to persons or to property, and liabilities of every kind (collectively, "Damages"), arising directly or indirectly from fulfillment of the Agreement, the OGS order, or Buyer's breach of representations hereunder, except to the extent Damages were caused by ALK's gross negligence or wilful misconduct.

**13. CONFIDENTIALITY:** Buyer shall keep confidential ALK's trade secrets and any other proprietary or commercial information, including the existence of a relationship with ALK, and shall not disclose any such information to any third party without ALK's prior written permission.

**14. REPUTABLE SELLER:** Buyer represents to ALK that: (a) neither Buyer nor its employees, affiliates, representatives or agents have been debarred, suspended or proposed for debarment by any federal, state or local agency ("Ineligible Person"); and (b) it shall notify ALK immediately if any such person or entity becomes listed as an Ineligible Person. If any such person or entity becomes an Ineligible Person or ALK learns that Buyer's representations were false, ALK shall have the right to terminate any contract or business relationship with Buyer, whether covered by the Agreement or otherwise, immediately, in addition to any other remedy available to ALK.

**15. ASSIGNMENT:** Buyer may not assign or transfer the Agreement, including any OGS order(s), or any interest therein or monies payable thereunder without the prior written consent of ALK.

**16. CHOICE OF LAW:** The Agreement, including any OGS order, is governed by the laws of the State of New York, without giving effect to its choice of law provisions. Buyer consents to the personal jurisdiction of such court over it in such a matter.

**17. ENTIRE AGREEMENT:** Unless mutually agreed upon in writing elsewhere, the Agreement, including these ST&C, constitute the sole and exclusive agreement between the parties pertaining to OGS, all other language, wherever contained that contradicts any term or condition hereof is of no force or effect including, but not limited to, a separate purchase order or invoice.

Buyer shall abide by the requirements of 41 CFR §§ 60.14(a), 60-300.5(a) and 60-741.5(a). These regulations prohibit discrimination against qualified individuals based on their status as protected veterans or individuals with disabilities, and prohibit discrimination against all individuals based on their race, color, religion, sex, sexual orientation, gender identity, or national origin. Moreover, these regulations require that covered prime contractors and subcontractors take affirmative action to employ and advance in employment individuals without regard to race, color, religion, sex, sexual orientation, gender identity, national origin, protected veteran status or disability. Buyer agrees to comply with all the provisions set forth in 29 CFR Part 471, Appendix A to Subpart A (Executive Order 13496).

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