PRODUCT CATALOG

2025

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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.

With 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.

Histatrol® (histamine phosphate)
FDA approved Positive Skin Test Control.

ODACTRA® (House Dust Mite [*Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*] Allergen Extract Tablet for Sublingual Use 12 SQ-HDM)
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)
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)
FDA approved sublingual tablet to treat ragweed pollen allergies, with or without conjunctivitis.

Please see full Prescribing Information, including Boxed Warning for ODACTRA®, GRASTEK®, and RAGWITEK®, starting on page 47 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 a clear, colorless, sterile solution (0.25 ml) supplied in 1 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	Ampule Size	Concentration
PRPE	49471-001-05	PRE-PEN® (benzylpenicilloyl polylysine injection USP)	5 x 0.25 mL	6.0 x 10^{-5} M
		PRE-PEN® is sold in boxes of 5 ampules; each ampule is intended for single patient use only.		

Diagnostic Supplies

Item#	Description	Qty	Diagnostic
DILU15	Aqueous Negative Control	5 mL Multi-Dose	Intradermal Testing
NSP100	Normal Saline with Phenol (NSP) for use as a Negative Testing Control 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
ALK-8004	AllerTest-1™ devices	Box of 432	Skin Prick Testing
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 Syringes section on page 28 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), cephalosporinderived 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 or call 1-800-FDA-1088.

Please see full Prescribing Information on page 30 for additional Important Safety Information.

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

SUBLINGUAL IMMUNOTHERAPY TABLETS

ODACTRA®
GRASTEK®
RAGWITEK®

Updates are being made to the ODACTRA® Indication in 2025.
Look for the latest indication at odactrahcp.com or ask your representative for more details.

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

ODACTRA® is approved for persons as young as 12 years old.
Updates are being made to the ODACTRA® Indication in 2025.
Look for the latest indication at odactrahcp.com or ask your representative for more details.

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

Go to 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

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 12 through 65 years of age.

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

Selected 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 47.

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

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

GRASTEK® is approved for persons as young as 5 years old.

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

Patients can go to 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.

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

RAGWITEK® is the first and only FDA-approved sublingual tablet to treat ragweed pollen allergies, with or without conjunctivitis.

RAGWITEK® is approved for use in persons as young as 5 years old.

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

Patients can go to 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 pollen. RAGWITEK is approved for use in persons 5 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 (or their parents/guardians) on its appropriate use, and instruct patients (or their parents/guardians) 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

ALLERGEN EXTRACTS

POLLENS
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EPIDERMALS
FOODS

POLLENS

Name *Latin Name*	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
Acacia *Acacia dealbata*	ACAC	Tree	●	●			●	
Alder, White *Alnus rhombifolia*	ALDE	Tree		●	●	●	●	
Alfalfa *Medicago sativa*	ALFA	Cul. Crop	★	●			●	
Ash, Arizona (Velvet) *Fraxinus velutina*	ARAS	Tree	●			●		
Ash, White *Fraxinus americana*	ASH-	Tree		●	●	●	●	●
Bahia Grass *Paspalum notatum*	BAHI	Grass	●	●		●	●	
Bayberry (Wax Myrtle) *Morella cerifera*	BAYB	Tree	●	●		●	●	
Beech, American *Fagus grandifolia*	BEEC	Tree	●	●		●	●	
Birch, Black *Betula lenta*	BLBI	Tree		●	●	●		
Birch, Red *Betula nigra*	REBI	Tree		●	●	●	●	
Birch, White *Betula verrucosa*	WHBI	Tree		●	●	●	●	
Box Elder *Acer negundo*	BOEL	Tree		●	●	●	●	
Brome *Bromus inermis*	BROM	Grass	●	●	●		●	
Carelessweed *Amaranthus palmeri*	CARE	Weed		●		Available in Aqueous 1: 20 w/v and Glycerin 1:40 w/v		
Cedar, Mountain *Juniperus ashei*	MOCE	Tree		●		●	●	
Cedar, Red *Juniperus virginiana*	RECE	Tree		●		●	●	
Cocklebur *Xanthium strumarium*	COCK	Weed	●	●	●	●	●	●
Corn Pollen *Zea mays*	CORN	Cul. Crop		●			●	
Cottonwood, Eastern *Populus deltoides*	COWO	Tree		●	●	●	●	
Cottonwood, Western *Populus deltoides ssp. monilfera*	WECO	Tree	●	●		●	●	
Cypress, Arizona *Cupressus arizonica*	ARCY	Tree		●			●	
Cypress, Bald *Taxodium distichum*	BACY	Tree	●	●			●	
Dandelion *Taraxacum officinale*	DAND	Weed		●			●	
Dock, Yellow *Rumex crispus*	YEDO	Weed	●	●	●	●	●	
Dog Fennel *Eupatorium capillifolium*	DOFE	Weed	●	●			●	

Product availability is subject to change without notice.

^Please see the full list of stock mixes & full list of Standardized products on page 20.

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

POLLENS

Name *Latin Name*	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
Elm, American *Ulmus americana*	ELM-	Tree	★	•	•	•	•	•
Elm, Cedar *Ulmus crassifolia*	CEEL	Tree		•		•	•	
Elm, Chinese *Ulmus pumila*	CHEL	Tree	•	•			•	
Eucalyptus *Eucalyptus globulus*	EUCA	Tree	•	•		•	•	
Goldenrod *Solidago canadensis*	GOLD	Weed	•	•			•	
Hackberry *Celtis occidentalis*	HACK	Tree	•	•		•	•	
Hickory, Shagbark *Carya ovata*	HICK	Tree	•	•	•	•	•	
Johnson Grass *Sorghum halepense*	JOHN	Grass		•	•	•	•	•
Juniper, Western *Juniperus occidentalis*	WEJU	Tree		•		•	•	
Kochia *Kochia scoparia*	KOCH	Weed		•	•	•	•	
Lamb's Quarters *Chenopodium album*	LAQU	Weed		•	•	•	•	•
Lenscale *Atriplex lentiformis*	LENS	Weed					•	
Maple, Red *Acer rubrum*	REMA	Tree		•	•		•	
Maple, Sugar *Acer saccharum*	MAPL	Tree	•	•	•	•	•	•
Marsh Elder, Burweed *Iva xanthifolia*	BUMA	Weed	•	•		•	•	
Marsh Elder, Rough *Iva annua*	ROMA	Weed		•		•	•	
Melaleuca *Melaleuca quinquenervia*	MELA	Tree	•	•			•	
Mesquite *Prosopis juliflora*	MESQ	Tree	•	•		•	•	
Mugwort *Artemisia vulgaris*	MUGW	Weed	•	•	•	•	•	
Mulberry, Red *Morus rubra*	REMU	Tree		•		•	•	
Mulberry, White *Morus alba*	WHMU	Tree		•		•	•	
Nettle *Urtica dioica*	NETT	Weed		•			•	
Oak, Red *Quercus rubra*	REOA	Tree		•	•		•	
Oak, Virginia Live *Quercus virginiana*	VILI	Tree		•	•	•	•	
Oak, White *Quercus alba*	OAK-	Tree		•	•	•	•	•
Olive Tree *Olea europaea*	OLIV	Tree		•			•	

POLLENS

Name *Latin Name*	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
Palm, Queen *Arecastrum romanzoffiana*	QUPA	Tree		●		●	●	
Pecan Pollen *Carya illinoinensis*	PEPO	Tree		●	●	●	●	
Pepper Tree, California *Schinus molle*	CAPE	Tree	●	●			●	
Pigweed, Rough *Amaranthus retroflexus*	ROPI	Weed		●	●	●	●	
Pigweed, Spiny *Amaranthus spinosus*	SPPI	Weed	●	●		●	●	
Pine, Yellow *Pinus echinata*	YEPI	Tree		●			●	
Pine, White *Pinus strobus*	WHPI	Tree		●		●	●	
Plantain, English *Plantago lanceolata*	ENPL	Weed		●	●	●	●	●
Poplar, White *Populus alba*	POPL	Tree		●	●	●	●	
Privet *Ligustrum vulgare*	PRIV	Tree	●	●		●	●	
Quack Grass *Elymus repens*	QUGR	Grass	●			●		
Ragweed, False *Ambrosia acanthicarpa*	FARA	Weed	●	●	●		●	
Ragweed, Short *Ambrosia artemisiifolia*	SHRA	Weed		●	●	●	●	
Ragweed, Tall *Ambrosia trifida*	TARA	Weed		●	●	●	●	
Ragweed, Western *Ambrosia psilostachya*	WERA	Weed		●	●	●	●	
Russian Thistle *Salsola kali*	RUTH	Weed	●	●	●	●	●	
Sagebrush *Artemisia tridentata*	SAGE	Weed		●	●	●	●	
Sheep Sorrel *Rumex acetosella*	SHSO	Weed		●	●	●	●	
Sweet Gum *Liquidambar styraciflua*	SWGU	Tree		●		●	●	
Sycamore, American *Platanus occidentalis*	SYCA	Tree		●	●	●	●	
Walnut, Black *Juglans nigra*	BLWA	Tree		●	●	●	●	
Water Hemp, Western *Amaranthus tuberculatus*	WEWA	Weed	●	●		Available in Glycerin 1:40 w/v		
Willow, Black *Salix nigra*	BLWI	Tree	●	●	●	●	●	

Product availability is subject to change without notice.

^Please see the full list of stock mixes & full list of Standardized products on page 20.

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 40,000
4 Weed Mix *(Cocklebur, Rough Pigweed, English Plantain, Lamb's Quarters)*	4WEE	Weed	●		●	●
Mixed Ragweed *(Tall, Short)*	MIRA	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	●		●	
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	●		●	

***Standardized Products on page 20.*
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 *	FORMULATION Glycerin 1:20 w/v *
Alternaria alternata *(Alternaria alternata/Alternaria tenuis)*	ALTE	•	•	•
Aspergillus fumigatus	ASFU	•	•	•
Aureobasidium pullulans *(Pullularia pullulans)*	AURE	•	•	•
Bipolaris sorokiniana *(Bipolaris sorokiniana or Helminthosporium sativum/Drechslera sorokiniana)*	BIPO	•	•	•
Botrytis cinerea	BOTR	•	•	•
Candida albicans	CAAL	•	•	•
Cladosporium cladosporioides *(Hormodendrum cladosporioides)*	CLCL	•	•	•
Epicoccum nigrum *(Epicoccum purpurascens)*	EPIC	•	•	•
Gibberella pulicaris *(Fusarium roseum)*	GIBB	•	•	•
Mucor plumbeus	MUCO	•	•	•
Penicillium notatum	PENO	•	•	•
Rhodotorula mucilaginosa *(Rhodotorula rubra)*	RHOD	•	•	•
Saccharomyces cerevisiae *(Yeast)*	SACC	•		•
Sarocladium strictum *(Sarocladium strictum/Acremonium strictum)*	SARO	•	•	•
Trichophyton mentagrophytes	TRME	•	•	•

MOLD MIXES

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

SMUT

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

INSECTS

Name *Latin Name/(Mix Components)*	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 *Solenopsis invicta*	FIAN	Insect	●	●	●	●	
Cockroach, American *Periplaneta americana*	AMCO	Insect	●	●		●	
Cockroach, German *Blattella germanica*	GECO	Insect	●	●		●	
Cockroach, Mixed *(American, German)*	MICO	Insect	●	●		●	
Mosquito *Culex pipiens*	MOSQ	Insect	●	●			●

EPIDERMALS

Name *Latin Name/(Mix Components)*	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
Cattle Epithelium *Bos taurus*	COEP	Epidermal	●	●		●	
Dog Epithelium *Canis lupus familiaris*	DOEP	Epidermal		●	●	●	●
Feather, Mixed *(Chicken, Duck, Goose)*	MIFE	Epidermal		●	●	●	
Guinea Pig Epithelium *Cavia porcellus*	GUIN	Epidermal	★	●		●	
Horse Epithelium *Equus caballus*	HOEP	Epidermal	●	●	●	●	
Mouse Epithelium *Mus musculus*	MOEP	Epidermal	★	●		●	
Rabbit Epithelium *Oryctolagus cuniculus*	RABB	Epidermal	●	●	●	●	

FOODS

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

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

All food products come in 5 mL dropper vials.

FOODS

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

All food products come in 5 mL dropper vials.

STANDARDIZED EXTRACTS

POLLENS
POLLEN MIXES
EPIDERMALS
MITES

POLLENS

Name *Latin Name*	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 *Cynodon dactylon*	STBE	Grass		●		●			
June (Kentucky Blue) *Poa pratensis*	STJU	Grass		●	●		●		
Meadow Fescue *Festuca pratensis*	STMF	Grass		●	●		●		
Orchard *Dactylis glomerata*	STOR	Grass		●	●		●		
Ragweed, Short *Ambrosia artemisiifolia*	SHRA	Weed		●	●			●	●
Redtop *Agrostis alba*	STRT	Grass		●	●		●		
Rye, Perennial *Lolium perenne*	STPR	Grass		●	●		●		
Sweet Vernal *Anthoxanthum odoratum*	STSV	Grass	●	●	●		●		
Timothy *Phleum pratense*	STTI	Grass		●	●		●		

POLLEN MIXES

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

EPIDERMALS

Name *Latin Name*	Item #	Allergen Type	Skin Prick Diagnostic	STANDARDIZED Glycerin 10,000 BAU
Cat Hair *Felis catus*	STCH	Epidermal	●	●

MITES

Name *Latin Name/(Mix Comp.)*	Item #	Skin Prick Diagnostic	Skin Prick Diagnostic	STANDARDIZED Glycerin 10,000 AU
Dust Mite *D. farinae*	STDF	Mite	●	●
Dust Mite *D. pteronyssinus*	STDP	Mite	●	●
Mite, Mixed *(D. farinae & D. pteronyssinus)*	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 *Various Colors Available*	25
NSP4520S	4.5 mL	20 mm x 22 mm *Various Colors Available*	25
NSP8020S	8.0 mL	20 mm x 22 mm	25
NSP9020S	9.0 mL	20 mm x 22 mm *Various Colors Available*	25
NSP30	30 mL	20 mm x 29 mm (Tall)	1
NSP100	100 mL	20 mm x 52 mm	1

50 % Glycerinated

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

Saline Albumin with Phenol (HSA)

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

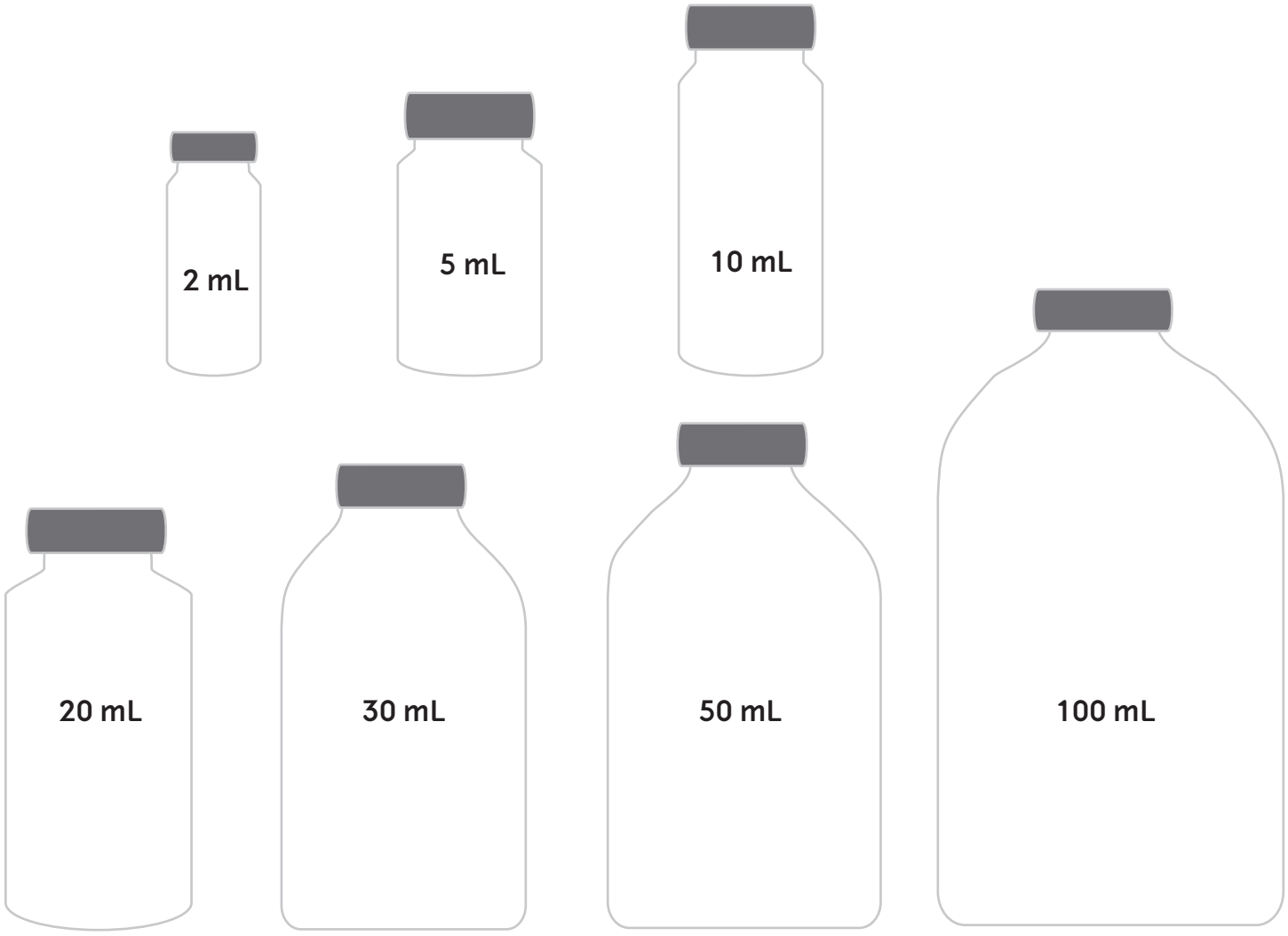
STERILE EMPTY VIALS (SEV)

Item#	Volume	Vial Size	Quantity
SEV213-25	2.0 mL	14 mm x 13 mm	25
SEV520S	5.0 mL	20 mm x 22 mm **Various Colors Available*	25
SEV1020S	10 mL	20 mm x 22 mm **Various Colors Available*	25
SEV20-16	20 mL	20 mm x 30 mm	16
SEV30	30 mL	20 mm x 36.5 mm	25
SEV50	50 mL	20 mm x 40 mm	25
SEV100	100 mL	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 25.

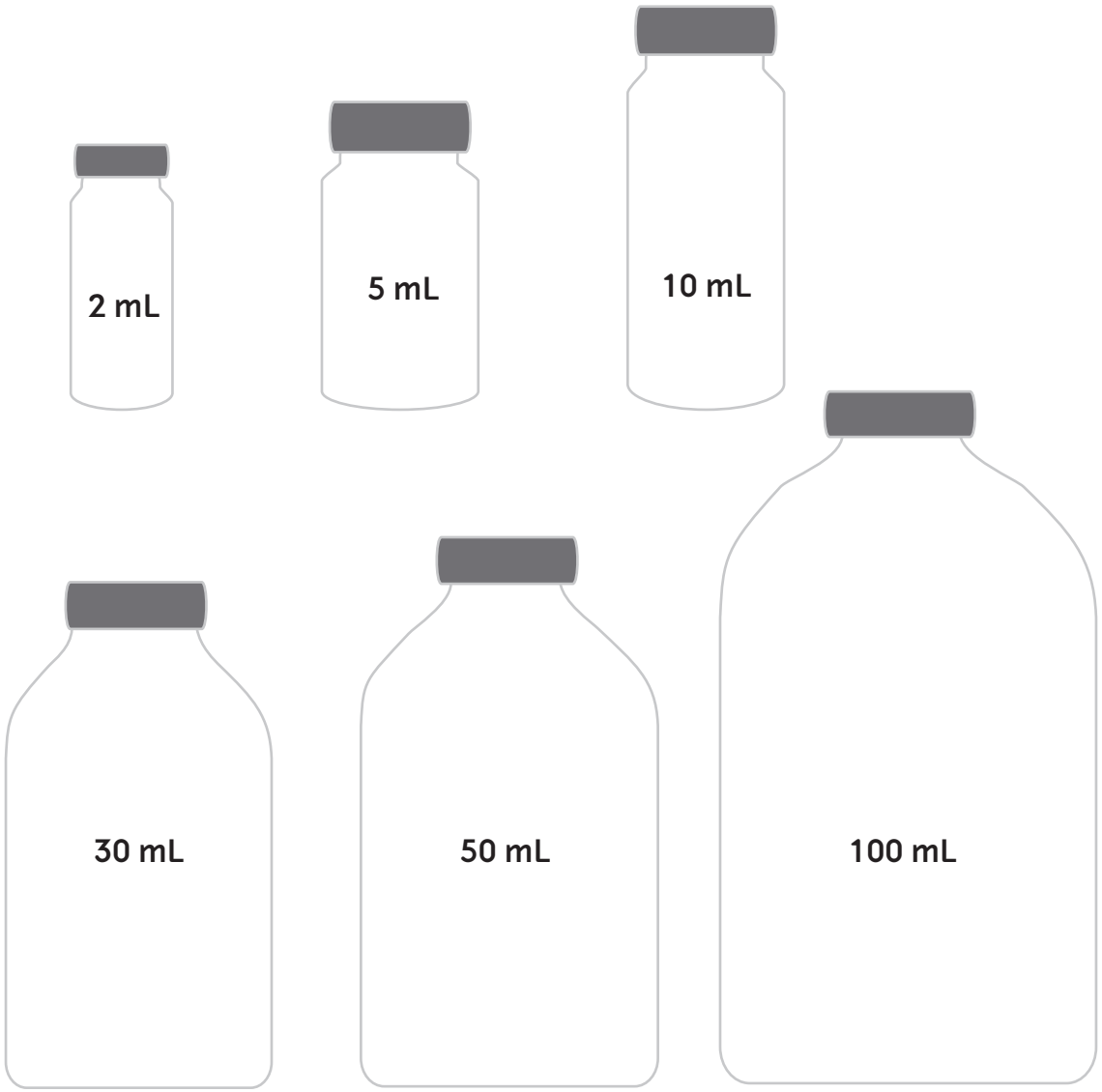
AMBER STERILE EMPTY VIALS (SEV)

Item#	Volume	Vial Size	Quantity
SEV213-25-AMB	2.0 mL	14 mm x 12 mm	25
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 #SEV213-25-AMB
2 ML 14 MM X 12 MM

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

AMBER SEV SIZE CHART



NON-STERILE VIALS AND MISC.

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

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

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

ITEM #80143
7/10 mL PLASTIC CAP

ITEM #80154
15 mL GLASS DROPPER VIAL

ITEM #80149
10 mL GLASS DROPPER VIAL

ITEM #80138
4 mL GLASS DROPPER TIP

ITEM #80151
5 mL GLASS DROPPER TIP

ITEM #80152
5 mL GLASS DROPPER VIAL

ITEM #80139
4 mL GLASS DROPPER VIAL

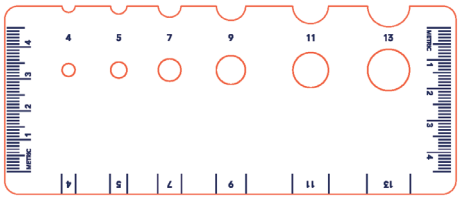
ITEM #80153
15 mL GLASS DROPPER TIP

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 (NSP)	5 mL Multi-Dose	Intradermal Testing
DILU14	Glycerinated Control 50% (GPS)	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)

Duotip-Test® II
Device, Tray and Wells

UniTest® PC Device

Multi-Test® II
Tray & Device

DEVICES, WELLS & TRAYS

The AllerTest-1™ Single Prick Testing Device features hardened plastic tines for precise, single-prick testing, with smaller tine lengths for accuracy and reduced discomfort. It's compatible with 48-well and 60-well allergen trays.

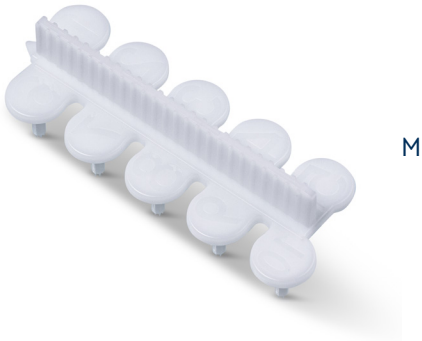
The AllerTest-8™ and AllerTest-10™ devices, with 8 and 10 heads respectively, are ergonomically designed for easy use, offering a secure grip and uniform pressure for consistent results. AllerTest™ well trays are stackable, have a separate positve and negative control, a non-slip rubber bottom for stability, and an air-tight locking mechanism to prevent contamination, compatible with both single prick and multi-head devices. *You must observe all the cautions and procedures contained in package insert for contraindications, intervals relating to drug administration and application of the test. This device is restricted by Federal Law to be used by or under order of a licensed physician or nurse practitioner.*

Skin Testing Systems

Item#	Description
ALK-8004	ALLERTEST-1 DEVICES, (BOX OF 432)
ALK-8H-006	ALLERTEST-8 DEVICES, (BOX OF 6)
ALK-10H-006	ALLERTEST-10 DEVICES, (BOX OF 6)
ALK-8H-300	ALLERTEST-8 DEVICES, (CASE OF 300)
ALK-10H-300	ALLERTEST-10 DEVICES, (CASE OF 300)
ALK-48T-001	ALLERTEST TRAY, 48 WELL TRAY & LABEL FOR ALLERTEST-8
ALK-60T-001	ALLERTEST TRAY, 60 WELL TRAY & LABEL FOR ALLERTEST-10
ALK-LABEL-48	LABEL FOR ALLERTEST 48 WELL TRAY, ALLERTEST-8
ALK-LABEL-60	LABEL FOR ALLERTEST 60 WELL TRAY, ALLERTEST-10

AllerTest-1™
Single Prick Skin Testing Device

AllerTest-8™
Multi-headed Skin Testing Device



AllerTest-10™
Multi-headed Skin Testing Device

AllerTest™
48 Well Testing Tray

AllerTest™
60 Well Testing Tray

You are encouraged to report patient reactions to skin testing and/or immunotherapy to ALK. Our contact information is toll-free 1-855-216-6497 or email AdverseEvents@alk.net. Reports can be made directly to FDA as well at www.fda.gov/medwatch or 1-800-FDA-1088.

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)
SYR80397	1.0 mL	27 G x 3/8"	Saftey Glide ID Bevel	1,000	BD	303330	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
SYR80396	0.5 mL	29 G x 1/2"	Safety Glide	400	BD	305932	4 boxes of 100 (individually wrapped)

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
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
SYR80421	3.0 mL	23 G x 1"	Reg. Bevel	800	BD	309571	8 boxes of 100

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

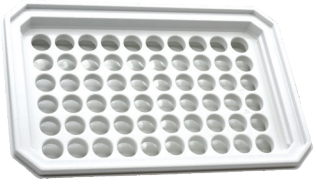
Note - Syringes available may vary and are not exclusive to the types listed above. Please call Sales Support for more information.

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 7¼″ x 1″
80301	Vial Trays for 18 mm and 22 mm base vials, 60 holes (6x10)	12″ x 7¼″ 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 ¾″
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

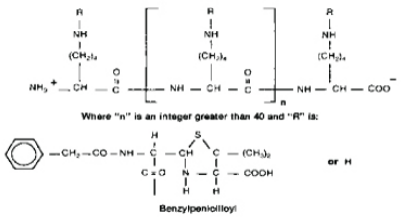
PACKAGE INSERTS

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

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

DESCRIPTION:
PRE-PEN® (benzylpenicilloyl polylysine) injection is a sterile solution of benzylpenicilloyl polylysine in a concentration of 6.0 X 10-5M (benzylpenicilloyl) in 0.01 M monobasic sodium phosphate and 0.15 M sodium chloride.Benzylpenicilloyl polylysine 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 nonbenzylpenicilloyl 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 PREPEN 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:
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 antigeninduced 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 3 mm in diameter, in duplicate at least 2 cm 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 5 mm. 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 is a clear, colorless, sterile solution in a concentration of 6.0 X 10-5M (benzylpenicilloyl) 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.

Store PRE-PEN refrigerated at 2°C to 8°C (36°F to 46°F). If removed from refrigerator, PRE-PEN should be kept at room temperature up to 25°C (77°F) and must be used within 24 hours. Discard any unused portion. As with all parenteral drug products, PRE-PEN should be inspected visually for particulate matter and discoloration prior to administration. Report presence of particulate matter or discoloration to Manufacturer.

Rx only

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You are encouraged to report patient reactions to skin testing and/or immunotherapy to ALK. Our contact information is toll-free 1-855-216-6497 or email AdverseEvents@alk.net. Reports can be made directly to FDA as well at www.fda.gov/medwatch or 1-800-FDA-1088.

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 anaphlactic 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, woolens, 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.1 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[2,3]. See also **PRECAUTIONS** and **ADVERSE REACTIONS.**

WARNINGS

Severe Allergic Reactions:

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.

Anaphylaxis Following False Negative Food Allergen Skin Test Results:

False negative skin test results associated with anaphylaxis from subsequent exposure to the allergen have been reported during postmarketing diagnostic use of some food allergenic extracts. Based on the patient's clinical history and the index of suspicion, healthcare providers should consider confirming negative skin testing with serologic testing by measuring specific serum IgE or with a medically-supervised oral food challenge.

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:

1. 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.
2. Store allergenic extracts between 2°-8°C at all times, even during use.
3. Care must be taken to avoid drawing blood.
   A. For percutaneous testing, if blood is observed, immediately wipe the allergen from the site.
   B. 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**).
4. 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.
5. Use standard aseptic precautions if making dilutions from stock concentrates to intradermal strength.
6. 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[4]. 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[5].

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$_2$ 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$_2$ 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.[2] 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 overdosage 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:

1. 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: IIn both percutaneous and intracutaneous tests, a negative control test with diluent alone should be performed because some patients exhibit dermographia, 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.[6] 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 2º to 8ºC 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
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.1 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).2 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.10

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.3,4,5 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.[6]

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 $beta_2$ 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.[7] Fatalities from immunotherapy in the United States since 1945 have been extensively reviewed by Lockey, R. F., et al[8] and more

recently by Reid, M. J. et al.[9]

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 yield5 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 ≥ 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 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.

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.[1] 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).[2] 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.[3]

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[3]. 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.[9] 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.[6,10-12] 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.[3,7,8,11]

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.[13] Fatalities from immunotherapy in the United States since 1945 have been extensively reviewed by Lockey, R.F., et al.[14] and also more recently by Reid, M.J., et al.[15] 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-Al** 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-Al** 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-Al** Alum Precipitated extracts. In order to avoid untoward reactions, it is recommended that previous therapy be disregarded and therapy with **Center-Al** be initiated as though the patient were previously untreated. The first dose of **Center-Al** should be related to the patient's sensitivity, determined by history and confirmed by skin testing. CAUTION: **Center-Al** 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-Al** 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:

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

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% glycinerated 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-Al** 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-Al** 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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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 $C_5H_9N_3 \cdot 2H_3PO_4$; 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 ephedrine, in general, have been shown to decrease allergen induced wheal. Theoretically, this may also reduce wheal 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, anginal 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.

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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% (preserva¬tive). 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 ΣE (sum of Erythema) of 50 mm in highly puncture reactive subjects[1]. A value of 100,000 BAU/mL is assigned to the CBER reference standard that can be diluted 1:5 million to produce intradermal ΣE (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.[2] 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.[3] 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.[4] 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 (Σ = sum of longest diameter and orthogonal cross diameter).[5]

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)[5].

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, **DOSAGE 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.[6,7,8] 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[12].

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[13]. 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.[9]

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.[10] Fatalities from immunotherapy in the United States since 1945 have been extensively reviewed by Lockey, R. F., et al.[11] Reid, M.J., et al.[12] and also more recently by Bernstein, D. I. et al.[15] . 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[14]. 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 wheaing 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 [14].

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).

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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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.[1] 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).[2] 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.[3] 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 hyposensitization therapy.

Numerous controlled studies have demonstrated the clinical efficacy of immunotherapy with cat, dust mites and some pollen extracts.[4] 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.[5,6,7] 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 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 of hyposensitization 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.[8]

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.[9] Fatalities from immunotherapy in the United States since 1945 have been extensively reviewed by Lockey, R F, et al[10], Reid M J et al.[11] and more recently by Bernstein, D. I. et al[12] . 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).[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 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[1]. 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[2]. 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 testing3. 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[4].

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

CLINICAL PHARMACOLOGY[5]
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.[6,7]

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 ∑ E of 82.4 mm with a range of 61 to 110 mm and a mean ∑ 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 ß-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 equipment8: 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 patients9, and because the beta-blocker may impair the ability to reverse the reaction[10] 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[11]:

- 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 patients9, and because the beta-blocker may impair the ability to reverse the reaction[10].

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[12]. 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 intervalInject 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 glococorticoids (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[8].

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 concentrate, 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[12]

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[13]

	Mean Diameters (mm)	
Grade	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[12],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[13].

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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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 or parents/guardians on its appropriate use, and instruct patients or parents/guardians to seek immediate medical care upon its use. (5.1)**
- **ODACTRA may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. (5.1)**
- **ODACTRA may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers. (5.1)**

----------RECENT MAJOR CHANGES----------

Indications and Usage (1) --------- ---------- 1/2023

Warnings and Precautions (5.1 Severe Allergic Reactions)--- 1/2023

----------INDICATIONS AND USAGE----------
ODACTRA is an allergen extract indicated as immunotherapy for the treatment of house dust mite (HDM)-induced allergic rhinitis, with or without conjunctivitis, confirmed by positive *in vitro* testing for IgE antibodies to *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* house dust mites or by positive skin testing to licensed house dust mite allergen extracts. ODACTRA is approved for use in persons 12 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. Allow it to remain there until completely dissolved. 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 or parents/guardians 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. (5.6)

---------- ADVERSE REACTIONS ----------
- The most common solicited adverse reactions reported in ≥10% of adult subjects (18 through 65 years of age) treated with ODACTRA were: throat irritation/tickle, itching in the mouth, itching in the ear, swelling of the uvula/back of the mouth, swelling of the lips, swelling of the tongue, tongue pain, nausea, throat swelling, stomach pain, tongue ulcer/sore on the tongue, mouth ulcer/sore in the mouth, and food tastes different. The most common solicited adverse reactions reported in ≥10% of adolescent subjects (12 through 17 years of age) treated with ODACTRA were: throat irritation/tickle, itching in the mouth, itching in the ear, tongue pain, stomach pain, swelling of the uvula/back of the mouth, swelling of the lips, swelling of the tongue, throat swelling, nausea, tongue ulcer/sore on the tongue, and mouth ulcer/sore in the mouth, and diarrhea. (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.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 1/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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 or parents/guardians on its appropriate use, and instruct patients or parents/guardians to seek immediate medical care upon its use. (5.1)**
- **ODACTRA may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. (5.1)**
- **ODACTRA may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers. (5.1)**

1 INDICATIONS AND USAGE

ODACTRA™ is an allergen extract indicated as immunotherapy for the treatment of house dust mite (HDM)-induced allergic rhinitis, with or without conjunctivitis, confirmed by positive *in vitro* testing for IgE antibodies to *Dermatophagoides farinae* or *Dermatophagoides pteronyssinus* house dust mites, or by positive skin testing to licensed house dust mite allergen extracts. ODACTRA is approved for use in persons 12 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 (or their parents/guardians) in the proper use of auto-injectable epinephrine *[see Warnings and Precautions (5.1)]*.

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.

Allergic reactions may require treatment with epinephrine. Prescribe auto-injectable epinephrine to patients receiving ODACTRA. Instruct patients or their parents/guardians to recognize the signs and symptoms of a severe allergic reaction and in the proper use of emergency auto-injectable epinephrine. Instruct patients or their parents/guardians to seek immediate medical care and to stop treatment with ODACTRA upon use of auto-injectable epinephrine *[see Patient Counseling Information (17).]* See Prescribing Information for epinephrine 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 that may 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); severe mast cell disorder; or cardiovascular disease including unstable angina, recent myocardial infarction, significant arrhythmia, and uncontrolled hypertension. In addition, ODACTRA may not be suitable for patients who are taking medications that can potentiate or inhibit the effects of epinephrine (see Prescribing Information for epinephrine for information on drug interactions).

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 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.

5.3 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.

5.4 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.

5.5 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.

5.6 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

The most common solicited adverse reactions reported in ≥10% of adult subjects (18 through 65 years of age) treated with ODACTRA were: throat irritation/tickle, itching in the mouth, itching in the ear, swelling of the uvula/back of the mouth, swelling of the lips, swelling of the tongue, tongue pain, nausea, throat swelling, stomach pain, tongue ulcer/sore on the tongue, mouth ulcer/sore in the mouth, and food tastes different. The most common solicited adverse reactions reported in ≥10% of adolescent subjects (12 through 17 years of age) treated with ODACTRA were: throat irritation/tickle, itching in the mouth, itching in the ear, tongue pain, stomach pain, swelling of the uvula/back of the mouth, swelling of the lips, swelling of the tongue, throat swelling, nausea, tongue ulcer/sore on the tongue, and mouth ulcer/sore in the mouth, and diarrhea.

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 (18 through 65 years of age)

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

Adverse Reaction	Any Intensity		Severe†	
	ODACTRA (N=640)	Placebo (N=631)	ODACTRA (N=640)	Placebo (N=631)
Ear and labyrinth disorders				
Itching in the ear	51.7%	11.7%	0.3%	-
Gastrointestinal disorders				
Itching in the mouth	61.3%	14.1%	0.2%	-
Swelling of the uvula/back of the mouth‡	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%	-	-
Nervous system disorders				
Taste alteration/food tastes different	10.0%	3.6%	-	-
Respiratory, thoracic and mediastinal disorders				
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.
†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.
‡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 recurred 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.

Adolescents (12 through 17 years of age)

In two clinical studies, a total of 347 adolescent subjects were treated with at least one dose of ODACTRA. Study 1 (NCT01700192) was a double-blind, placebo-controlled, randomized clinical study. Study 5 (NCT04541004) was a single arm, open-label safety study. Because the study design and safety data presentation differ in the studies, adverse reaction rates cannot be directly compared. Overall, the safety profile in adolescents was consistent with the safety profile in adults.

Study 1 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, 94 subjects 12 through 17 years of age received at least one dose of ODACTRA, with a median treatment duration of 279 days (range 1 to 353 days). 95 subjects received placebo. Of the adolescent subjects treated with ODACTRA, 53% were male, 39% had asthma, and 72% were polysensitized to other allergens in addition to HDM. The adolescent subject population was 69% White, 13% Black or African American, 10% multiple race, 5% Asian, and 3% American Indian or Alaska Native. Subject demographics in placebo-treated subjects were similar to the active treatment group.

In Study 1, 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. The solicited adverse reactions reported in adolescent subjects 12 through 17 years of age are summarized in Table 2.

Table 2: Solicited* Adverse Reactions Within 28 Days After Initiation of Treatment with ODACTRA or Placebo (Study 1, Safety Analysis Set) in Subjects 12 through 17 Years of Age (NCT01700192)

Adverse Reaction (Any Intensity‡)	ODACTRA (N=94)	Placebo (N=95)
Ear and labyrinth disorders		
Itching in the ear	50.0%	11.6%
Gastrointestinal disorders		
Itching in the mouth‡	73.4%	14.7%
Tongue pain	24.5%	4.2%
Stomach pain	23.4%	15.8%
Swelling of the uvula/back of the mouth†	20.2%	3.2%
Swelling of the lips	20.2%	1.1%
Swelling of the tongue	19.1%	3.2%
Nausea‡	17.0%	9.5%
Tongue ulcer/sore on the tongue	12.8%	4.2%
Mouth ulcer/sore in the mouth	10.6%	3.2%
Diarrhea	7.7%	2.1%
Vomiting‡	4.3%	-
Nervous system disorders		
Taste alteration/food tastes different	4.3%	4.2%
Respiratory, thoracic and mediastinal disorders		
Throat irritation/tickle‡	73.4%	35.8%
Throat swelling	18.1%	8.4%

In Table 2, 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.
†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, and/or mouth swelling/edema (which can be anywhere in the mouth, not specifically back of the mouth).
‡Of those subjects reporting any intensity of: itching in the mouth, nausea, throat irritation/tickle, or vomiting in the ODACTRA group, 1 subject (1.1%) reported severe intensity of the reaction. Adverse reactions were categorized as severe according to the definition 'incapacitating with inability to work or do usual activity', as assessed by the investigator.

In Study 1, participants were monitored for unsolicited adverse events and serious adverse events (SAEs) for the duration of treatment (up to 52 weeks). Unsolicited adverse events that were reported in numerically more subjects treated with ODACTRA than with placebo and occurred in ≥1% of subjects 12 through 17 years of age within 28 days after initiation of treatment with ODACTRA aresummarized in Table 3.

In Study 1, 94 adolescent subjects received at least one dose of ODACTRA, of whom 81 (86%) completed at least 4 months of treatment.

The percentage of adolescent subjects who discontinued from the study because of an adverse reaction while exposed to ODACTRA or placebo was 10% and 1%, respectively. The most common adverse reaction that led to study discontinuation in adolescent subjects who were exposed to ODACTRA were throat irritation (4%), swollen tongue (2%) and nausea (2%).

No adolescent subjects treated with ODACTRA in Study 1 reported serious adverse events, treatment-related systemic allergic reactions, or adverse reactions treated with epinephrine.

Table 3: Unsolicited Adverse Reactions occurring During the Entire Trial After Initiation of Treatment with ODACTRA or Placebo (Study 1, Safety Analysis Set) Reported in ≥1% of Subjects 12 through 17 Years of Age (NCT01700192)

Adverse Reaction	ODACTRA (N=94)†	Placebo (N=95)†
Ear and labyrinth disorders		
Ear discomfort	1.1%	-
Ear pain	1.1%	-
Eye disorders		
Eye pruritus	1.1%	-
Eye swelling	1.1%	-
Gastrointestinal disorders		
Paraesthesia oral	5.3%	-
Oral pain	4.3%	-
Tongue pruritus	3.2%	-
Stomatitis	2.1%	1.1%
Aphthous ulcer	1.1%	-
Dysphagia	1.1%	-
Eosinophilic esophagitis	1.1%	-
Salivary gland enlargement	1.1%	-
Tongue discomfort	1.1%	-
General disorders and administration site conditions		
Chest discomfort	2.1%	-
Chest pain	1.1%	-
Non-cardiac chest pain	1.1%	-
Infections and infestations		

Adverse Reaction	ODACTRA (N=94)†	Placebo (N=95)†
Acute sinusitis	1.1%	-
Musculoskeletal and connective tissue disorders		
Arthralgia	1.1%	-
Neck pain	1.1%	-
Respiratory, thoracic and mediastinal disorders		
Oropharyngeal pain	1.1%	-
Rhinorrhea	1.1%	-
Throat tightness	1.1%	-
Tonsillar hypertrophy	1.1%	-
Skin and subcutaneous tissue disorders		
Pruritus	2.1%	1.1%
Vascular disorders		
Flushing	1.1%	-

In Table 3, the dashes represent no subjects.
† Due to the population size (ODACTRA; N=94; and placebo; N=95), 1.1% represents one subject.

Study 5 was a single-arm, open label study conducted in Europe, and exposed 253 subjects 12 through 17 years of age with house dust mite-induced allergic rhinitis with or without conjunctivitis and with or without asthma to at least one dose of ODACTRA. The median treatment duration was 28 days (range 11 to 32 days). Of the subjects, 60% were male, 43% had asthma, and 56% were polysensitized to other allergens in addition to HDM. The subject population was 99.6% White and 0.4% Native Hawaiian or Other Pacific Islander.

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. Participants were monitored for unsolicited adverse events and serious adverse events (SAEs) for the duration of the study.

In Study 5, the proportions of subjects reporting solicited adverse reactions during the first 28 days following initiation of treatment with ODACTRA were comparable to those reported during the first 28 days following initiation of treatment with ODACTRA in Study 1.

In Study 5, the following unsolicited adverse reactions occurred in ≥1% of subjects 12 through 17 years of age during the entire study [median treatment duration 28 days (range 11 to 32 days)] after initiation of treatment with ODACTRA: oral pain (3.2%), oral pruritus (2.8%), throat irritation (1.6%), ear pruritus (1.2%), and mouth ulceration (1.2%).

In Study 5, 253 adolescent subjects received at least one dose of ODACTRA, of whom 248 (98%) completed 28 days of treatment. The percentage of subjects who discontinued from the study because of an adverse reaction while exposed to ODACTRA was 1%.

Across eight clinical studies of varying durations which enrolled individuals 5 through 85 years of age and which were 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. Of these eight clinical studies, 2416 subjects received different doses of ODACTRA in four clinical studies with durations of 12 months or longer [2 cases/2416 subjects (0.08%) who received ODACTRA for 12 months or longer]. One case of eosinophilic esophagitis assessed as related to treatment occurred on Day 99 in an adult subject receiving ODACTRA. One case of eosinophilic esophagitis assessed as related to treatment occurred on Day 204 in an adolescent subject receiving ODACTRA.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ODACTRA. 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.

- *Skin and Subcutaneous Tissue Disorders:* erythema.
- *Immune System Disorders:* serious systemic allergic reactions, including anaphylaxis.
- *Respiratory, Thoracic and Mediastinal Disorders:* cough.

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 an embryo/fetal 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 doses up to 5 times the human sublingual dose. There were no ODACTRA-related post-implantation losses, fetal malformations or variations.

8.2 Lactation

Risk Summary

It is not known whether ODACTRA is excreted in human milk. 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

The safety and effectiveness of ODACTRA have been established in adolescents 12 through 17 years of age. The safety and effectiveness have not been established in persons below 12 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 (5.1)]*.

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.

Adolescents and Adults

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 5. Consistent results across age groups were observed, supporting a similar treatment effect in adolescent and adult subgroups.

Table 5: 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)† Score‡	Placebo (n=620)† Score‡	Treatment Difference (ODACTRA-Placebo)	Difference Relative to Placebo§ Estimate (95% CI)
Primary Endpoint				
TCRS¶	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.
†Number of subjects in analyses.
‡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.
§Difference relative to placebo computed as: (ODACTRA – placebo)/placebo x 100.
¶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.

Adults

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. farinae* 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 6.

Table 6: 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 (n)† Score‡	Placebo (n)† Score‡	Treatment Difference (ODACTRA - Placebo)	Difference Relative to Placebo§ Estimate (95% CI)
Primary Endpoint				
TCRS¶	(318) 5.71	(338) 6.81	-1.09	-16.1% (-25.8%, -5.7%)
Secondary Endpoints				
Rhinitis DSS¶	(318) 2.84	(338) 3.31	-0.47	-14.1% (-23.8%, -3.9%)
Rhinitis DMS¶	(318) 2.32	(338) 2.86	-0.54	-18.9% (-34.7%, -1.3%)
TCS#	(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.
†Number of subjects in analyses.
‡The estimated group least squares means are reported. Treatment difference and that relative to placebo is based on estimated group least squares means.
§Difference relative to placebo computed as: (ODACTRA – placebo)/placebo x 100.
¶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%).
#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. farinae* 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 7.

Table 7: Total Nasal Symptom Score (TNSS) and Total Symptom Score (TSS) During HDM-Allergen Challenge (Study 3, Environmental Exposure Chamber Study) (NCT01644617)

Endpoint*	ODACTRA (n)† Score‡	Placebo (n)† Score‡	Treatment Difference (ODACTRA - Placebo)	Difference Relative to Placebo§ 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.
†Number of subjects in analyses.
‡The estimated group least squares means are reported. Treatment difference and that relative to placebo is based on estimated group least squares means.
§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, 20ºC-25ºC (68ºF-77ºF). Store in the original package until use to protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise patients (or their parents/guardians) 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 (or their parents/guardians) that ODACTRA may cause life-threatening systemic or local allergic reactions, including anaphylaxis. Educate patients (or their parents/guardians) 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 (or their parents/guardians) have auto-injectable epinephrine and instruct patients (or their parents/guardians) in its proper use. Instruct patients (or their parents/guardians) 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 (5.1).]*
- Advise patients to read the patient information for epinephrine.
- Inform patients (or their parents/guardians) 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 (or their parents/guardians) with persistent and escalating adverse reactions in the mouth or throat to discontinue ODACTRA and to contact their healthcare professional *[see Warnings and Precautions (5.2)]*.
- Because of the risk of eosinophilic esophagitis, instruct patients (or their parents/guardians) with severe or persistent symptoms of esophagitis to discontinue ODACTRA and to contact their healthcare professional *[see Warnings and Precautions (5.3)]*.

Asthma

- Instruct patients (or their parents/guardians) 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 (5.4)]*.

Administration Instructions

- Instruct patients (or their parents/guardians) 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:
Catalent Pharma Solutions Limited, Blagrove,
Swindon, Wiltshire, SN5 8RU UK

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 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 1-855-216-6497 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 03/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SEVERE ALLERGIC REACTIONS

- **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)**

1 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.

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

2 DOSAGE AND ADMINISTRATION

For sublingual use only.

2.1 Dose

One GRASTEK tablet daily.

2.2 Administration

Administer the first dose of GRASTEK 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 GRASTEK, 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.

Administer GRASTEK to children under adult supervision.

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 each grass pollen season and continue treatment throughout the season. For sustained effectiveness for one grass pollen season after cessation of treatment, GRASTEK may be taken daily for three consecutive years (including the intervals between the grass pollen seasons). 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 GRASTEK are limited. In the clinical trials, treatment interruptions for up to seven days were allowed.

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

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 ≥1% of subjects treated with GRASTEK are shown in Table 1.

Table 1: Adverse Reactions Reported in ≥1% of Adults Treated with GRASTEK

Adverse Reaction	GRASTEK (N=1669)	PLACEBO (N=1645)
Nervous System Disorders		
Headache	2.1%	1.3%
Ear and Labyrinth Disorders		
Ear pruritus	12.5%	1.1%
Respiratory, Thoracic and Mediastinal Disorders		
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%
Gastrointestinal Disorders		
Oral pruritus	26.7%	3.5%
Mouth edema	11.1%	0.8%
Paresthesia 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	1.9%	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%
Skin and Subcutaneous Tissue Disorders		
Pruritus	2.4%	1.0%
Urticaria	1.7%	0.9%
General Disorders and Administration Site Conditions		
Chest discomfort	1.6%	0.5%
Fatigue	1.4%	0.4%

Adverse reactions of interest that occurred in ≤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 ≥1% of subjects treated with GRASTEK are shown in Table 2.

Table 2: Adverse Reactions Reported in ≥1% of Pediatric Subjects Treated with GRASTEK

Adverse Reaction	GRASTEK (N=447)	PLACEBO (N=434)
Nervous System Disorders		
Headache	3.4%	1.8%
Ear and Labyrinth Disorders		
Ear pruritus	7.2%	0.5%
Eye Disorders		
Eye pruritus	3.4%	2.1%
Respiratory, Thoracic and Mediastinal Disorders		
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%
Gastrointestinal Disorders		
Oral pruritus	24.4%	2.1%
Mouth edema	9.8%	0.2%
Tongue pruritus	9.2%	0.9%
Lip swelling	7.2%	0.5%
Paresthesia 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%
Skin and Subcutaneous Tissue Disorders		
Urticaria	1.8%	0.2%
General Disorders and Administration Site Conditions		
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:

- Ear and Labyrinth Disorders: ear discomfort, ear swelling
- Eye Disorders: eye swelling
- Gastrointestinal Disorders: cheilitis, diarrhea, dry mouth, enlarged uvula, eosinophilic esophagitis, gastritis, lip blister, oral pain, salivary hypersecretion, vomiting
- General disorder and administration site conditions: chest pressure, face edema, sensation of foreign body, swelling of neck
- Immune System Disorders: serious systemic allergic reactions, including anaphylaxis, anaphylactic shock
- Infections and Infestations: pneumonia
- Investigations: heart rate increased, heart rate irregular, oxygen saturation decreased, peak expiratory flow rate decreased
- Nervous System Disorders: altered state of consciousness, dizziness, drowsiness, dysgeusia, paresthesia, tremor, difficulty speaking, paresthesia (including hypoesthesia and burning sensation in extremities)
- Respiratory, Thoracic and Mediastinal Disorders: asthma exercise induced, bronchospasm, hyperventilation, laryngeal discomfort, respiratory distress, status asthmaticus, stridor, throat pruritus, wheezing
- Skin and Subcutaneous Tissue Disorders: angioedema, erythema, erythema facial, rash
- Vascular Disorders: hypotension.

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 approximately 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)† Score‡	Placebo (N)† Score‡	Treatment Difference (GRASTEK – Placebo)	Difference Relative to Placebo§ 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)† Score‡	Placebo (N=158)† Score‡	Treatment Difference (GRASTEK – Placebo)	Difference Relative to Placebo§ 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

	Difference Relative to Placebo* (95% CI)			
Endpoint	**Treatment Year 1 N=568†**	**Treatment Year 2‡ N=316†**	**Treatment Year 3 N=287†**	**Post Treatment Year 1 N=257†**
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%	-45.5%	-40.1%	-28.6%
	(-49.8%, -26.5%)	(-60.4%, -28.2%)	(-55.4%, -21.2%)	(-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 detail on one side.

GRASTEK is supplied as follows:

3 blister packages of 10 tablets (30 tablets total). NDC 52709-1501-3

Store at controlled room temperature 20ºC-25ºC (68ºF-77ºF); excursions permitted between 15ºC-30ºC (59ºF-86ºF). 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

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

U.S. License No. 1292

Manufactured by:
Catalent Pharma Solutions Limited, Blagrove,
Swindon, Wiltshire, SN5 8RU UK

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 or parents/guardians on its appropriate use, and instruct patients or parents/guardians to seek immediate medical care upon its use. (5.1)**
- **RAGWITEK may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. (5.1)**
- **RAGWITEK may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers. (5.1)**

----------RECENT MAJOR CHANGES----------

Indications and Usage (1) ---------- ---------- 04/2021

----------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 persons 5 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 or parents/guardians 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 adults were: throat irritation, oral pruritus, ear pruritus, oral paraesthesia, mouth edema, and tongue pruritus. Adverse reactions reported in ≥5% of children and adolescents 5 through 17 years of age were: throat irritation, oral pruritus, ear pruritus, lip swelling, glossodynia, nausea, oral pain, pharyngeal edema, swollen tongue, abdominal pain upper, stomatitis, and enlarged uvula. (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: 04/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

*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 or parents/guardians on its appropriate use, and instruct patients or parents/guardians to seek immediate medical care upon its use. (5.1)**
- **RAGWITEK may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. (5.1)**
- **RAGWITEK may not be suitable for patients who may be unresponsive to epinephrine or inhaled bronchodilators, such as those taking beta-blockers. (5.1)**

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 persons 5 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 (or their parents/guardians) in the proper use of auto-injectable epinephrine *[see Warnings and Precautions (5.1)]*.

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.

Allergic reactions may require treatment with epinephrine. Prescribe auto-injectable epinephrine to patients receiving RAGWITEK. Instruct patients or parents/guardians to recognize the signs and symptoms of a severe allergic reaction and in the proper use of auto-injectable epinephrine. Instruct patients or parents/guardians to seek immediate medical care and to stop treatment with RAGWITEK upon use of auto-injectable epinephrine *[see Patient Counseling Information (17)]*. See Prescribing Information for epinephrine 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 that may 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); severe mast cell disorder; or cardiovascular disease including unstable angina, recent myocardial infarction, significant arrhythmia, and uncontrolled hypertension. In addition, RAGWITEK may not be suitable for patients who are taking medications that can potentiate or inhibit the effects of epinephrine (see Prescribing Information for epinephrine for information on drug interactions).

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 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.

5.3 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.

5.4 Asthma
Subjects with asthma who participated in clinical trials had asthma of a severity that required, at most, a daily medium dose of an inhaled corticosteroid. RAGWITEK has not been studied in subjects with 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.

5.5 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.

5.6 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 adults were: throat irritation, oral pruritus, ear pruritus, oral paraesthesia, mouth edema, and tongue pruritus. Adverse reactions reported in ≥5% of children and adolescents 5 through 17 years of age were: throat irritation, oral pruritus, ear pruritus, lip swelling, glossodynia, nausea, oral pain, pharyngeal edema, swollen tongue, abdominal pain upper, stomatitis, and enlarged uvula.

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
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 Adults Treated with RAGWITEK or Placebo (28-day pooled analysis)

Adverse Reaction	RAGWITEK* (N=1057)	Placebo† (N=757)
Ear and Labyrinth Disorders		
Ear pruritus	10.4%	1.1%
Respiratory, Thoracic and Mediastinal Disorders		
Throat irritation	16.6%	3.3%
Oropharyngeal pain	1.5%	0.7%
Throat tightness	1.3%	0.5%
Gastrointestinal Disorders		
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%
Skin and Subcutaneous Tissue Disorders		
Pruritus	1.8%	1.3%
General Disorders and Administration Site Conditions		
Chest discomfort	1.0%	0%

* 1036 subjects were 18 through 65 years of age and 21 subjects were older than 65 years of age.
† 746 subjects were 18 through 65 years of age and 11 subjects were older than 65 years of age.

The overall safety profile beyond Day 28 in the two 52-week trials was similar to that observed in the pooled 28-day analysis.

Children and Adolescents (5 through 17 years of age)
In 1 placebo-controlled clinical trial, 513 subjects 5 through 17 years of age with short ragweed pollen-induced rhinitis, with or without conjunctivitis, received at least one dose of RAGWITEK. Of the subjects treated with RAGWITEK, 63% were male, 43% had asthma, and 79% were sensitized to other allergens in addition to ragweed pollen. The subject population was 93% White, 3.1% African American, 2.3% multiple race, 1% Asian, 0.5% Native Hawaiian or Other Pacific Islander, and 0.1% American Indian or Alaska Native. Approximately 40% of subjects were children (5 through 11 years of age) and 60% of subjects were adolescents (12 through 17 years of age). Subject demographics in placebo-treated subjects were similar to the active treatment group.

In the trial in children and adolescents 5 through 17 years of age, parents/ guardians and/ or participants were provided SLIT report cards in which they recorded the occurrence of specific solicited adverse reactions daily for the first 28 days following treatment initiation with RAGWITEK or placebo (summarized in Table 2).

Table 2: Solicited* Adverse Reactions occurring within 28 days of Initiation of Treatment with RAGWITEK or Placebo in Children and Adolescents 5 through 17 Years of Age

Adverse Reaction (Any Intensity)	RAGWITEK (N=513)	Placebo (N=509)
Ear and Labyrinth Disorders		
Itching in the ear	33.9%	6.3%
Gastrointestinal Disorders		
Itching in the mouth	47.8%	11.2%
Mouth pain	18.9%	4.5%
Swelling of the lips	13.8%	1.2%
Nausea	11.5%	3.3%
Swelling of the tongue†	11.3%	0.8%
Stomach pain	10.1%	4.5%
Swelling of the uvula/back of the mouth‡	9.9%	0.4%
Mouth ulcer/sore in the mouth	8.4%	2.2%
Tongue ulcer/sore on the tongue	6.8%	2.2%
Diarrhea	2.7%	1.2%
Vomiting	1.2%	0%
Nervous System Disorders		
Taste alteration/food tastes different	3.9%	2.0%
Respiratory, Thoracic and Mediastinal Disorders		
Throat irritation/tickle	48.3%	17.7%
Throat swelling	10.7%	1.6%

* Solicited adverse reactions (modified from World Allergy Organization [WAO] list of local side effects of sublingual immunotherapy [SLIT]) were those solicited from subjects via SLIT report card within the first 28 days after treatment initiation.
† Of those subjects reporting any intensity of swelling of the tongue in the RAGWITEK group, 1 subject (0.2%) reported severe intensity of swelling of the tongue. Adverse reactions were categorised as severe according to the definition 'incapacitating with inability to work or do usual activity', as assessed by the investigator.
‡ The percentage of subjects reporting "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 at the back of the mouth).

In the clinical trial in children and adolescents, unsolicited adverse reactions occurring throughout the entire duration of the trial were recorded in electronic diaries or reported at study visits. Unsolicited adverse reactions reported by ≥1% of children and adolescents throughout the entire duration of the trial are shown in Table 3.

Table 3: Unsolicited Adverse Reactions occurring during the Entire Trial after Initiation of Treatment, Reported in ≥1% of Children and Adolescents 5 through 17 Years of Age Treated with RAGWITEK or Placebo

Adverse Reaction	RAGWITEK (N=513)	Placebo (N=509)
Ear and Labyrinth Disorders		
Ear pruritus	4.5%	0.2%
Gastrointestinal Disorders		
Oral pruritus	7.8%	1.0%
Tongue pruritus	4.5%	0.4%
Lip swelling	1.9%	-
Paraesthesia oral	1.9%	0.4%
Mouth swelling	1.8%	-
Dysphagia	1.6%	0.2%
Nausea	1.6%	0.4%
Oral pain	1.6%	0.4%
Swollen tongue	1.4%	-
Respiratory, Thoracic and Mediastinal Disorders		
Throat irritation	7.6%	1.6%
Oropharyngeal pain	1.8%	0.4%
Sneezing	1.6%	0.4%
Pharyngeal edema	1.2%	-
Rhinorrhea	1.2%	0.4%
Skin and Subcutaneous Tissue Disorders		
Pruritus	1.2%	0.2%

The percentage of subjects who discontinued from the clinical trial because of an adverse reaction while exposed to RAGWITEK or placebo was 3.9% and 1.0%, respectively. The most common adverse reaction that led to study discontinuation in subjects who were exposed to RAGWITEK was throat irritation.

Three subjects (0.6%) treated with RAGWITEK and one subject (0.2%) treated with placebo experienced treatment-related systemic allergic reactions [adverse reactions marked with an asterisk (*) were included in Table 3].

- One subject treated with RAGWITEK reported hypersensitivity events (skin/face/neck itching*, eye itching/swelling, sneezing*, runny*/itching nose, neck/abdomen redness) beginning on day 6 (i.e., outside the ragweed pollen season) that resolved by day 26. The events resolved within minutes to less than an hour. On two occasions, the subject was treated with antihistamine. This subject subsequently discontinued the trial on day 34 due to persistent local allergic symptoms (swollen tongue).
- The second subject treated with RAGWITEK reported hypersensitivity (generalized rash on body and face) on day 26 (i.e., outside the ragweed pollen season). The event was treated with antihistamine and systemic corticosteroids and resolved in one week; the subject discontinued the trial due to the event.
- The third subject treated with RAGWITEK reported pruritus* (on cheeks, arms and legs) and dyspnea on day 1 (i.e., outside the ragweed pollen season) after administration of the first dose. Both adverse events resolved within 2 hours without treatment and did not reoccur upon restarting trial medication 1 week later. The subject subsequently completed the trial.
- The subject treated with placebo reported hypersensitivity (papular rash with itching on hands, body and lower limbs) on day 7 (i.e. outside the ragweed pollen season). The event was treated with an antihistamine and systemic corticosteroid and resolved in one week; the subject discontinued the trial due to the event.

One subject (0.2%) treated with RAGWITEK and no subjects on placebo, reported adverse reactions that were treated with epinephrine (any route).The one subject treated with RAGWITEK experienced severe laryngitis on day 126 (during the ragweed pollen season), for which the subject was hospitalized and treated with inhaled racemic epinephrine (i.e., not systemic epinephrine); the laryngitis resolved in 2 days.

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.
- *Respiratory, Thoracic and Mediastinal Disorders:* dysphonia.

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 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 excreted 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
Efficacy and safety of RAGWITEK have been established in children and adolescents 5 through 17 years of age. The efficacy and safety in pediatric patients below 5 years of age 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 tablet that dissolves within 10 seconds.
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

Adults
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.

14 CLINICAL STUDIES

Adults
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. 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 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 4.

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 5.
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 4 and 5).

Table 4: Adult Trial 1: Total Combined Scores (TCS), Rhinoconjunctivitis Daily Symptom Scores (DSS), and Daily Medication Scores (DMS) During the Ragweed Pollen Season (Adults 18 through 50 Years of Age)

Endpoint*	RAGWITEK (N)† Score‡	Placebo (N)† Score‡	Treatment Difference (RAGWITEK – Placebo)	Difference Relative to Placebo§ Estimate (95% CI)
TCS Peak Season¶	(159) 6.22	(164) 8.46	-2.24	-26% (-38.7, -14.6)
TCS Entire Season	(160) 5.21	(166) 7.01	-1.80	-26% (-37.6, -13.5)
DSS Peak Season	(159) 4.65	(164) 5.59	-0.94	-17% (-28.6, -4.6)
DSS Entire Season	(160) 4.05	(166) 4.87	-0.82	-17% (-28.5, -4.5)
DMS Peak Season	(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.
* 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: (RAGWITEK - placebo)/placebo x 100. The 95% CI was based on the 2.5th and 97.5th percentiles of the 10,000 bootstrap samples.
¶ Peak ragweed season was defined as maximum 15 days with the highest moving average pollen counts during the ragweed season.

Table 5: Adult Trial 2: Total Combined Scores (TCS), Rhinoconjunctivitis Daily Symptom Scores (DSS), and Daily Medication Scores (DMS) During the Ragweed Pollen Season (Adults 18 through 50 Years of Age)

Endpoint*	RAGWITEK (N)† Score‡	Placebo (N)† Score‡	Treatment Difference (RAGWITEK – Placebo)	Difference Relative to Placebo§ Estimate (95% CI)
TCS Peak Season¶	(152) 6.41	(169) 8.46	-2.04	-24% (-36.5, -11.3)
TCS Entire Season	(158) 5.18	(174) 7.09	-1.92	-27% (-38.8, -14.1)
DSS Peak Season	(152) 4.43	(169) 5.37	-0.94	-18% (-29.2, -4.5)
DSS Entire Season	(158) 3.62	(174) 4.58	-0.96	-21% (-31.6, -8.8)
DMS Peak Season	(152) 1.99	(169) 3.09	-1.10	-36% (-55.8, -14.6)

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: (RAGWITEK - placebo)/placebo x 100. The 95% CI was based on the 2.5th and 97.5th percentiles of the 10,000 bootstrap samples.
¶ Peak ragweed season was defined as maximum 15 days with the highest moving average pollen counts during the ragweed season.

Children and Adolescents (5 through 17 years of age)
The efficacy of RAGWITEK in the treatment of ragweed pollen-induced allergic rhinitis, with or without conjunctivitis, was investigated in a double-blind, placebo-controlled clinical trial in children and adolescents 5 through 17 years of age comparing RAGWITEK (n= 512) and placebo (n= 510) administered as a sublingual tablet daily. Subjects received RAGWITEK or placebo 12-20 weeks prior to the start of the ragweed pollen season and throughout the ragweed pollen season. The subject population was 63% male, 93% White, 3.1% African American, 2.3% multiple race, 1% Asian, 0.5% Native Hawaiian or Other Pacific Islander, and 0.1% American Indian or Alaska Native. Approximately 40% of subjects were children (5 through 11 years of age) and 60% of subjects were adolescents (12 through 17 years of age). Subjects with asthma who participated in clinical trials had asthma of a severity that required, at most, a medium dose of an inhaled corticosteroid. 43% of subjects had asthma at baseline. Treatment groups were balanced with regard to baseline characteristics.

Efficacy was established by self-reporting of rhinoconjunctivitis daily symptom scores (DSS) and daily medication scores (DMS) using a similar methodology to the adult trials.
The sums of the DSS and DMS were combined into the Total Combined Score (TCS) which was averaged over the peak ragweed pollen season. The average TCS over the entire ragweed season was also assessed.
A decrease in TCS during the peak ragweed season for subjects treated with RAGWITEK compared to placebo-treated subjects was demonstrated. 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 Table 6).

Table 6: Pediatric Trial: Total Combined Scores (TCS), Rhinoconjunctivitis Daily Symptom Scores (DSS), and Daily Medication Scores (DMS) During the Ragweed Pollen Season for Children and Adolescents 5 through 17 Years of Age

Endpoint*	RAGWITEK (N)† Score‡	Placebo (N)† Score‡	Treatment Difference (RAGWITEK – Placebo)	Difference Relative to Placebo§ Estimate (95% CI)
TCS Peak Season¶	(460) 4.39	(487) 7.12	-2.73	-38% (-46.0, -29.7)
TCS Entire Season	(466) 3.88	(491) 5.75	-1.86	-32% (-40.7, -23.3)
DSS Peak Season	(468) 2.55	(494) 3.95	-1.40	-35% (-43.2, -26.1)
DMS Peak Season	(460) 2.01	(487) 3.85	-1.84	-48% (-59.8, -32.5)

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: (RAGWITEK® - placebo)/placebo x 100. The 95% CI was based on the 2.5th and 97.5th percentiles of the 10,000 bootstrap samples.
¶ Primary endpoint (pre-specified criteria for success for primary endpoint: a treatment difference relative to placebo of at least -15% and the associated upper bound of the 95% confidence interval (CI) for this difference of at least -10%); peak ragweed season was defined as maximum 15 days with the highest moving average pollen counts during the ragweed season.
Note: All statistical analyses for the 4 endpoints included fixed effects of treatment, baseline asthma status (yes, no), age group (5 through 11 years of age, 12 through 17 years of age), pollen season, and pollen region nested within pollen season.

The average DSS during the entire season was 2.27 (RAGWITEK group) and 3.26 (placebo group) (treatment difference of -0.99) with a relative treatment difference of -30% (95% CI -38.6, -20.7) and the average DMS during the entire season was 1.61 (RAGWITEK group) and 2.48 (placebo group) (treatment difference of -0.87) with a relative treatment difference of -35% (95% CI -45.5, -22.7).

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
Store at controlled room temperature, 20ºC to 25ºC (68ºF to 77ºF); excursions permitted between 15ºC to 30ºC (59ºF to 86ºF). Store in the original package until use to protect from moisture.

17 PATIENT COUNSELING INFORMATION

Advise patients or parents/guardians 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 or parents/guardians that RAGWITEK may cause life-threatening systemic or local allergic reactions, including anaphylaxis. Educate patients or parents/guardians 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 (or their parents/guardians) have auto-injectable epinephrine and instruct patients or parents/guardians in its proper use. Instruct patients (or their parents/guardians) 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 (5.1)]*.
Advise patients or parents/guardians to read the patient information for epinephrine.
Inform patients or parents/guardians 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 (or their parents/guardians) with persistent and escalating adverse reactions in the mouth or throat to discontinue RAGWITEK and to contact their healthcare professional *[see Warnings and Precautions (5.2)]*.
Because of the risk of eosinophilic esophagitis, instruct patients (or their parents/guardians) with severe or persistent symptoms of esophagitis to discontinue RAGWITEK and to contact their healthcare professional *[see Warnings and Precautions (5.3)]*.
Asthma
Instruct patients (or their parents/guardians) 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 (5.4)]*.
Administration Instructions
Instruct patients (or their parents/guardians) 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 (or their parents/guardians) 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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ORDERING INFORMATION

ALK

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:** _____

Bill To: **Ship To:** **Same as Bill To** ☐

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_____ _____

_____ _____

QTY	ITEM DESCRIPTION	VIAL SIZE	CONCENTRATION	AQ	GLY	C-AL	SCR	ID

AQ = Aqueous GLY = Glycerin SCR = Scratch ID = Intradermal

Please Check All That Applies: ☐ **Invoice Account** ☐ **Visa** ☐ **MasterCard** ☐ **American Express** ☐ **Discover**

Card No: _____ **Cardholder Name:** _____ **Exp:** _____

Thank You, We Appreciate Your Business.

A confirmation for this order will be sent to you within 24 hours

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*Pricing is subject to a separate Pricing Agreement with ALK, including ALK's Standard Terms and Conditions.

ALK

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 as otherwise reasonably apparent with 10 business days of delivery. If damage could not reasonably have been discovered within this period, then Buyer must report to ALK with 10 business days of discovery and no later than 30 days from 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. Pictures of damages will be requested. If ALK is unable to remedy or replace the defective or damaged OGS, it shall notify Buyer, and at ALK's sole discretion, ALK shall promptly credit the invoice for the defective or damaged OGS. ALK shall not be responsible for OGS that is damaged, altered, lost or otherwise tampered with after receipt by buyer. Quality Control complaints will be reviewed on a case by case basis. Any product involved in such a complaint must be returned so that a thorough investigation may be completed.

9. **RETURNS**: Buyers 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 ALK error. Subject to Section 8, all items shipped in error or damaged in shipment must be reported to ALK Sales support with accompanying pictures of damages. Sales support will then create a Return Goods Authorization # (RGA). Replacement OGS will be shipped to the Buyer. Returns are permitted ONLY with prior authorization from the Returns Department. Buyer will be notified within 5-10 business days as to the results of all return investigations. Upon investigation and approval of Buyer's return claim, Returns Department will email a return label to Buyer. The Buyer then has 15 days from receipt of the return label to return product. Upon receipt of product, a credit will be issued to the Buyer's account. 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 we have 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 the OGS has 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. Quality Control complaints will be reviewed on a case by case basis. Any product involved in such a complaint must be returned so that thorough investigation may be completed.

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 fulfilment 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 all non-public information, such as, ALK's trade secrets, financial terms, 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. Moreover, Buyer agrees not to reverse engineer any product sold by ALK.

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 §§ 60-1.4(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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