Serious Warnings and Precautions

d allergenic extract is intended for use by physicians who are experienced
istration of standardized (BAU/mL) allergenic extracts for immunotherapy
rgency care of anaphylaxis, or for use under the guidance of an allergy
Standardized grass pollen extracts labeled in BAU/mL are not
ıable with non-standardized grass pollen extracts labeled in AU/mL.
ed allergenic extracts are not directly interchangeable with allergenic
f the same labeled potency from different manufacturers. For
untreated patients or patients switching from non-standardized to
, see **WARNING and PRECAUTIONS** section. For previously untreated
initial dose of standardized extract must be based on skin testing as
the warnings, dosage and administration section. Patients should be
recognize adverse reaction symptoms and cautioned to contact the
ffice if reaction symptoms occur. **As with all allergenic extracts, severe**
eactions may occur. In certain individuals, these life-threatening
ay be fatal. Patients should be observed for at least 20 - 30 minutes
atment, and emergency measures, as well as personnel trained in their
be immediately available in the event of a life-threatening reaction.
h unstable asthma or steroid dependent asthmatics and patients with
cardiovascular disease are at greater risk to a fatal outcome from a
rgic reaction.
I should not be injected intravenously. Deep subcutaneous routes have
safe.
atients may experience severe anaphylactic reactions resulting in
bstruction, shock, coma and/or death. Adverse events are to be reported
nada, Tel: 866-234-2345 or by Fax: 866-678-6789.
eiving beta-blockers may not be responsive to epinephrine or inhaled
ors. Respiratory obstruction not responding to parenteral or inhaled
ors may require theophylline, oxygen, intubation and the use of life
tems. Parenteral fluid and/or plasma expanders may be utilized for
f shock. Adrenocorticosteroids may be administered parenterally or
y. Refer to the warnings, precautions and adverse reaction sections

Standardized Grass Pollen Extracts

DUCT INFORMATION

	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
	Liquid 100,000 BAU/mL	Phenol, Glycerin, Sodium Chloride, Sodium bicarbonate *For a complete listing see Dosage Forms, Composition and Packaging section.*

rgenic extract of grass pollens from Timothy (*Phleum pratense*), Orchard
rata), June (*Poa pratensis*), Redtop (*Agrostis alba*), Sweet Vernal
odoratum), Meadow Fescue (*Festuca elatior*), Perennial Rye (*Lolium*
e of 4 Standard grass pollen (Timothy, Orchard, June and Redtop) and
dard grass pollen (Timothy, Orchard, June, Redtop and Sweet Vernal) in the
al are sterile, and contain glycerine 50% v/v and phenol 0.4% (preservative).
may include sodium chloride for isotonicity and sodium bicarbonate buffer.

llen extracts, for subcutaneous injection for immunotherapy and/or
intracutaneous testing (see **Dosage and Administrative** section), are
defatted dried pollen extracted in glycerinated Coca's Fluid, filtered
dispensed into multiple dose vials. These are subsequently tested for
nd potency.

are the specific pollens collected from their respective plants. Allergenic
posites of the extractable allergenic and non-allergenic substances from the
g pollen. The allergenic moiety varies, qualitatively and quantitatively, from
s and can be a small or large portion of the total extractable material. Due
y of the solution and the physico-chemical properties of the individual
s, insoluble compounds can form. For this reason extracts may exhibit
of opacity, crystalline or amorphous particles and/or sediment.

grass pollen extracts labelled in BAU/mL are not directly
with grass pollen extracts labelled in AU/mL or non-standardized
racts.

and for lot-to-lot consistency, the potency is expressed in Bioequivalent
(Us) per millilitre. A value of 10,000 BAU/mL is assigned to the U.S. Food
stration, Center for Biologics Evaluation and Research (CBER) reference
be diluted 1:0.5 million to produce intradermal ∑E (sum of Erythema) of 50
ncture reactive subjects[1]. A value of 100,000 BAU/mL is assigned to the
standard that can be diluted 1:5 million to produce intradermal ∑E (sum of
mm in highly puncture reactive subjects. The relative potency of each lot of
ract has been compared to the official CBER reference standard by an
y such as ELISA Inhibition.[2] When the potency is equivalent by ELISA
eference, the product is assigned 10,000 BAU/mL or 100,000 BAU/mL.

bition assay, a competitive binding assay, the wells of microtiter plates are
haracterized allergenic extract. Allergic sera is added to each well. The
ecific for the coating allergen is inhibited by concentrations of a test sample
e same allergen. The amount of IgE bound to the solid phase allergen (and
degree of inhibition) is determined using enzyme-labeled anti-human IgE
e appropriate substrate. The potency relative to a reference is determined
ne bioassay method.

ND CLINICAL USE

ass Pollen Extracts is indicated for:
f treatment (hyposensitization therapy) of patients who experience allergic
e to exposure to grass pollen and who exhibit Type I skin sensitivity when
e specific allergens.

n (injection) therapy is a treatment for patients exhibiting allergic reactions
ens, dust mites, molds, animal danders, and various other inhalants in
the offending allergen cannot be avoided.

reated patients, prior to the initiation of therapy, clinical sensitivity to the
ss pollen extract should be established by careful evaluation of the patient's
l by diagnostic skin testing. Hyposensitization should not be prescribed for

WARNINGS AND PRECAUTIONS, Special Populations).

Extract usage in children should follow the same precautions as in adults.

CONTRAINDICATIONS

There are no known absolute contraindications to the use of Standardized Grass Pollen Extracts for immunotherapy. Immunotherapy with specific antigens is contraindicated in those individuals who do not exhibit skin test and clinical sensitivity to the particular antigens. (See **WARNINGS** and **PRECAUTIONS**).

Allergenic extract injections should not be administered in the presence of diseases characterized by a bleeding diathesis.

Children with nephrotic syndrome (immunization, can cause an exacerbation of their nephrotic disease).

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.

General contraindications include:

EXTREME SENSITIVITY TO THE SPECIFIC ALLERGEN - Determined from previous anaphylaxis following exposure.

AUTOIMMUNE DISEASE - Individuals with autoimmune disease may be at risk, due to the possibility of routine immunizations exacerbating symptoms of the underlying disease[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 AND PRECAUTIONS

General

Standardized extracts may be more, less, or equivalently potent compared to non-standardized extracts (See Table 3 in **CLINICAL PHARMACOLOGY** Section).

Conversion from non-standardized to standardized Grass Pollen Extracts:

There is no one specific formula to convert immunotherapy patients from non-standardized to standardized extracts. However, you may wish to consider the following as part of your overall plan:

A. Time your conversion outside of the height of the grass pollen season.

B. Table 3 describing potency of non-standardized extracts in **CLINICAL PHARMACOLOGY** section can be used as a guide in selection dose. **CAUTION: By the very nature of non-standardized extracts individual lots may vary more than 10-fold from the average value expressed in these tables. Further, you must consider the rapid decline in potency of non-glycerinated concentrates or aqueous dilutions of glycerinated concentrates of grass pollen extract. The BAU/mL expressed in the tables, therefore, may be overstated when compared to actual patient treatment extracts.**

1. Refer to the table in the **CLINICAL PHARMACOLOGY** section and based on the current w/v or PNU, determine an approximate BAU concentration that would be about 1/10 the non-standardized dose that the patient is currently receiving. To compare dose selection by puncture and intradermal testing, compare their wheal and erythema responses. If the reaction to the standardized is equal to or less than the non-standardized, proceed with immunotherapy beginning with 0.05 mL of the standardized extract concentration tested, and proceed to maintenance as described in the **DOSAGE AND ADMINISTRATION** Section.
2. If the intradermal reaction to the standardized extract is greater than the non-standardized dose, dilute 10 fold and repeat until skin response to standardized is equal to or less than nonstandardized, then proceed with immunotherapy.

C. From alum precipitated or modified extracts to standardized extracts: It is recommended that therapy be initiated as if the patient were not previously treated.

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 betablockers 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.

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.
- Evidence of a local or systemic reaction to the preceding extract injection during a course of immunotherapy.

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 **ADVERSE REACTIONS**.

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.

The physician must be prepared to treat anaphylaxis should it occur and have the necessary drugs and equipment on hand to do so. Extracts should not be administered by the patient or other individuals who are not prepared to treat anaphylaxis should it occur.

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. 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 reduced by at least 75% of the amount of the dosage from the previous extract.
6. Use standard aseptic precautions when making dilutions.
7. 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.
8. Standardized concentrates of allergenic extracts must be diluted prior to initiation of immunotherapy.

Carcinogenesis and Mutagenesis

There is no evidence of carcinogenicity, mutagenesis or impairment of fertility in humans from Standardized Grass Pollen Extracts. No long-term studies in animals have been performed to evaluate carcinogenic potential.

Special Populations

Pregnant Women:

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.

Nursing Women:

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.

Pediatrics (< 5 years of age):

Although extracts have not been studied systematically in various age groups, older children appear to tolerate injections of allergenic extracts well. Children less than five years of age on extract immunotherapy may have an increased risk of a severe reaction, but respond well to skin test diagnosis. Studies with pollenosis and asthma have been conducted in children[15-17].

Extract usage in children should follow the same precautions as in 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.

Geriatrics

Although extracts have not been studied systematically in various age groups, geriatric patients appear to tolerate injections of allergenic extracts well. Geriatric patients are more likely to be on medication that could block the effect of epinephrine or they could be more sensitive to the cardiovascular side effect of epinephrine because of preexisting cardiovascular disease.

Monitoring and Laboratory Tests

Patients receiving allergenic extracts should be kept under observation a minimum of twenty minutes so that any adverse reaction can be observed and properly handled. This time should be extended to at least thirty minutes for high-risk patients such as those with labile or steroid-dependent asthma or those suffering an exacerbation of their symptoms. Airway obstruction in high risk patients can be monitored by peak flow measurements before and after administration of allergens.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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] and also more recently by Reid, M.J., 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 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

PRESCRIBING INFORMATION

Allergenic Extracts

Standardized Grass Pollen Extracts

Standardized Timothy Grass
Standardized Orchard Grass
Standardized June Grass
Standardized Redtop
Standardized Sweet Vernal
Standardized Perennial Rye Grass
Standardized Meadow Fescue Grass
Mix of 4 Standardized Grasses (Timothy, Orchard, June, Redtop)
Mix of 5 Standardized Grasses (Timothy, Orchard, June, Redtop, Sweet Vernal)

Liquid, 100,000 BAU/mL

Immunotherapy

ALK ABELLÓ

Date of Preparation:
May 8, 2009

ALK-Abelló, Inc.
35 Channel Drive
Port Washington
New York, USA 11050

Distributed in Canada By:

ALK- Abelló Pharmaceuticals, Inc.
#35-151 Brunel Road
Mississauga, ON
Canada, L4Z 2H6

739A

Submission Control No: 123862

Rarely: Severe reactions caused shock and loss of consciousness, and fatalities.

DRUG INTERACTIONS

Overview

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 (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 (see boxed Warnings).

Other Drugs: Short acting steroids, inhaled $beta_2$ agonists, theophylline and cromolyn do not seem to affect skin test response.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

Prior to use for intradermal testing and immunotherapy, extracts must be prepared by diluting

ilient's permanent record. For preferred results, it is recommended that the
ent of the extent of both responses be recorded. This can be accomplished
longest erythema diameter, then selecting the mid-point of that line and
angle to that line to determine the orthogonal diameter. The sum of these
s is the sum of erythema (∑E); the sum of wheal diameters is determined
r

r is graded on the basis of the size of erythema and/or wheal

k/scratch/puncture) test:

r puncture skin tests should be performed initially using a diluted
glycerinated extract to 10,000 BAU/mL

general guidelines for percutaneous testing[14]. Different devices and/or
ce the size of the reaction, therefore it is important to refer to the device
distributor's instructions when grading reactions. As a negative control, the
ested and included in the interpretation in the skin test reactions. Use of a
ich as histamine base at 1 mg/mL should be used to assess skin test

action or less than control
ema greater than control, smaller than a nickel (21 mm diameter)
ema greater than a nickel in diameter, no wheal
l and erythema without pseudopods
l and erythema with pseudopods

device, needle, scalpel blade, or scarifier is used. A separate sterile device
each patient to prevent transmission of infectious agents. If the device
use a separate device for each antigen to prevent crosscontamination.

led only enough to enter the dermis without drawing blood. Follow the
device being used. The antigen may be applied directly with a puncture
uced by applying a drop of extract to the scratch or prick site, taking care
kin with the dropper tip.

) should start with a dilute solution, usually in the range of 0.1 BAU/mL or

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

upper outer aspect of the arm, using a 26 - 27 gauge, short bevel needle,
y 0.05 mL of the intradermal test solution. Skin whealing responses should
20 minutes after administering the test.

est is one where the sum of erythema was 0 or equal to the sum of the
tive control, the diluent should be tested and included in the interpretation
ns. What follows are general guidelines for intradermal testing[14].

action or less than negative control
m wheal with erythema, or erythema alone larger than a nickel (21 mm
eter)
m wheal and erythema without pseudopods
8 mm wheal and erythema without pseudopods
l and erythema with pseudopods

- Starting dose for immunotherapy is related directly to a patient's
ermined by carefully executed skin testing. Degree of sensitivity can be
lermination of D_{50} (the intradermal dose, base three, that produces a ∑E =

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

e of allergenic extract has been established, the initial dose from the new
reduced to 25% of the previously well tolerated dose (see also **WARNINGS**
ONS).

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

ven subcutaneously preferably in the arm. It is advantageous to give
nate arms and routinely in the same area. In some patients, a local
llergen may develop thus preventing a possible severe local reaction.

needle, but before injecting the dose, pull plunger of the syringe slightly. If
ie syringe, discard the syringe and contents and repeat injection at another

l extracts must be diluted for initial therapy and intradermal skin testing. For
uent, refer to DOSAGE AND ADMINISTRATION section.

s slowly become less potent with age. During the course of treatment, it
y to continue therapy with a vial of extract bearing a later expiration date.
f the extract bearing the later expiration date should be lowered to a safe
ing level. When switching one standardized extract with another, at least
dose is suggested.

ptic precautions when making dilutions. The first dose of the new extract
d at least 75% of the amount of the dosage from the previous extract.

or diluted forms of this product are not complete. The undiluted product will
under recommended storage conditions at least until the expiration date on
eached. It is recommended that minimal amounts of the concentrate be
e diluted product is used up within a relatively short period of time; i.e.,
re than four weeks.

ass Pollen Allergenic Extracts are supplied as sterile solutions for
subcutaneous administration:

k extracts, use of Sterile Diluent for Allergenic Extracts or Sterile Diluent for

TABLE II
Ten-Fold Dilution Series

Dilution	Extract	Diluent	BAU/mL
0	Concentrate		100,000
1	0.5 mL concentrate	4.5 mL	10,000
2	0.5 mL dilution 1	4.5 mL	1,000
3	0.5 mL dilution 2	4.5 mL	100
4	0.5 mL dilution 3	4.5 mL	10
5	0.5 mL dilution 4	4.5 mL	1
6	0.5 mL dilution 5	4.5 mL	0.1

*Due to differences such as source material, preservative, potency dilutions, storage conditions, and length of storage, there is no common potency correlation ratio between extracts standardized in Bioequivalent Allergy Units (BAU) and:

1) standardized extracts previously labeled in Allergy Units (AU);
2) non-standardized extracts labeled weight-to-volume (w/v);
3) non-standardized extracts labeled in Protein Nitrogen Units (PNU); or
4) alum-precipitated extracts.

Stock mixtures of grass pollen extracts are compounded from individual grass pollen extracts. The total potency per milliliter (mL) of these mixtures is described in DOSAGE FORMS, COMPOSITION AND PACKING.

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.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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 pollens, 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 (∑ = sum of longest diameter and orthogonal cross diameter).[5]

Table 1: Puncture bifurcated needle data with 10,000 BAU/mL CBER Reference Grass Pollen Extracts.

Reference	FDA		P∑Erythema (mm)		P∑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
Redtop	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 (BAU_{50}) of the CBER (FDA) Grass Pollen Extract Reference Preparation required to produce a 50 mm Sum of Erythema was calculated based on titration in sensitive individuals.

Table 2: Intradermal Dose of CBER Reference Grass Pollen Extracts for 50 mm Sum of Erythema Diameter (BAU_{50})[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
Redtop	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

An analysis of relative potency of the 1:10 w/v unstandardized grass pollen extracts utilizing the ELISA Inhibition method shows the relative potency in BAU/mL in the following table. **CAUTION:** By the very nature of unstandardized extracts, individual lots of the unstandardized extracts may vary more than 1 log from the average value expressed in these tables.

TABLE 3: Estimation of Potency Described in BAU/mL by ELISA-Inhibition of ALK Abello, Inc. 1:10 w/v Non-standardized Grass Pollen Extracts Manufactured and Distributed by ALK-Abello, Inc. (Formerly Center Laboratories, Inc.)

1:10 w/v Extract	# Lots Assayed	Ave PNU/mL	Range PNU/mL	Estimated BAU/mL	Range * BAU/mL	BAU/PNU RATIO

Physicians must exercise care in switching patients from non-standardized to standardized extracts. As with non-standardized extracts, dosage with BAU extracts must be derived based on the patient's sensitivity to the specific pollen. Switching from an extract that was not standardized in BAU cannot be made by a calculated, numerical ratio, but TABLE 3 can be used as a guide. Dose selection can be confirmed by side-by-side testing of non-standardized and standardized extracts at estimated equal doses. See **WARNINGS** section. Patients being switched from non-standardized extracts from another manufacturer to extracts standardized in BAU can be re-evaluated by diagnostic skin testing to judge the dose to start immunotherapy or to build up to new maintenance dosages.

Duration of Effect

The usual duration of treatment has not been established. A period of two or three years of injection therapy constitutes an average minimum course of treatment. Patients should have sufficient treatments before each pollen season.

STORAGE AND STABILITY

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.

SPECIAL HANDLING INSTRUCTIONS

Clinicians should be aware that diluted extracts are inherently less stable than concentrates. Dilutions of glycerinated extracts which result in glycerin below 50% may also be less stable. Potency of a particular dilution can be checked by skin test in comparison to a fresh dilution of the extract on an individual known to be allergic to the specific antigen.

DOSAGE FORMS, COMPOSITION AND PACKAGING

For percutaneous testing, 5 mL vial, 100,000 BAU/mL in glycerin 50% (v/v).

For immunotherapy, 10 mL and 50 mL vials 100,000 BAU/mL in glycerin 50% (v/v).

Composition of Standardized Grasses in each product:

Individual standardized grass pollen includes 100,000 BAU/mL of either one of the following grasses: June (Poa pratensis), Meadow Fescue (Festuca elatior), Orchard (Dactylis glomerata), Perennial Rye (Lolium perenne), Redtop (Agrostis alba), Sweet Vernal (Anthoxanthum odoratum), and Timothy (Phleum pratense).

Mixture of 4 standardized grass pollen:

June (Poa pratensis)	25,000 BAU/mL
Orchard (Dactylis glomerata)	25,000 BAU/mL
Redtop (Agrostis alba)	25,000 BAU/mL
Timothy (Phleum pratense).	25,000 BAU/mL

Mixture of 5 standardized grass pollen:

June (Poa pratensis)	20,000 BAU/mL
Orchard (Dactylis glomerata)	20,000 BAU/mL
Redtop (Agrostis alba)	20,000 BAU/mL
Sweet Vernal (Anthoxanthum odoratum)	20,000 BAU/mL
Timothy (Phleum pratense).	20,000 BAU/mL

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:

Standardized Timothy Grass
Standardized Orchard Grass
Standardized June Grass
Standardized Redtop
Standardized Sweet Vernal
Standardized Perennial Rye Grass
Standardized Meadow Fescue Grass

Product Characteristics

Standardized allergenic extract of grass pollens from Timothy (*Phleum pratense*), Orchard (*Dactylis glomerata*), June (*Poa pratensis*), Redtop (*Agrostis alba*), Sweet Vernal (*Anthoxanthum odoratum*), Meadow Fescue (*Festuca elatior*), Perennial Rye (*Lolium perenne*), mixture of 4 Standard grass pollen (Timothy, Orchard, June and Redtop) and mixture of 5 Standard grass pollen (Timothy, Orchard, June, Redtop and Sweet Vernal) in the accompanying vial are sterile, and contain glycerine 50% v/v and phenol 0.4% (preservative). Inert ingredients may include sodium chloride for isotonicity and sodium bicarbonate buffer.

DETAILED PHARMACOLOGY

The allergic reaction is dependent upon the presence of antigen-specific immunoglobulin E (IgE) antibodies that are bound to specific receptors on mast cells and basophils. The presence of IgE antibodies on mast cells and basophils sensitizes these cells and--upon interaction with the appropriate allergen--histamine and other mediators are released. IgE antibody has been shown to correlate with atopic diseases such as allergic rhinitis and allergic asthma. In the skin these mediators are responsible for the characteristic wheal and flare (erythema) reactions upon allergenic extract skin testing in persons with the specific allergies.

Specific immunotherapy with pollen extracts as employed for many years is helpful in reducing symptoms associated with exposure to the offending allergens. A summary of effectiveness by the Panel on Review of Allergenic Extracts, an advisory committee to the U. S. Food and Drug Administration, has been published. Several mechanisms have been proposed to explain the effectiveness of immunotherapy: an increase in antigen-specific IgG antibodies is frequently associated with clinical effectiveness, although correlation is not consistent in all studies; there is a decrease in specific IgE; and IgE production is suppressed during periods of seasonal or high exposure to the antigen. Other changes following immunotherapy have been noted including development of auto-anti-idiotypic antibodies, a decrease in blood basophil sensitivity to allergen, a decrease in lymphokine production and lymphocyte proliferation by cells exposed to allergen, and development of allergen-specific suppressor cells. The complete mechanisms of immunotherapy are not known and remain the subject of investigation.

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