

ALLERGENIC EXTRACTS

Standardized Grass Pollen Extracts

U.S. Government License No. 308



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USA

Revised 10/04

WARNING

THIS ALLERGENIC 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.

THIS PRODUCT SHOULD NOT BE INJECTED INTRAVENOUSLY.

STANDARDIZED GRASS POLLEN EXTRACTS LABELED IN BIOEQUIVALENT ALLERGY UNITS (BAU)/ML ARE NOT INTERCHANGEABLE WITH GRASS POLLEN EXTRACTS LABELED IN ALLERGY UNITS (AU)/ML OR WITH NONSTANDARDIZED GRASS POLLEN EXTRACTS. FOR PREVIOUSLY UNTREATED PATIENTS OR PATIENTS PREVIOUSLY RECEIVING EXTRACTS FROM ANOTHER MANUFACTURER, 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 EXTRACTS SHOULD BE INSTRUCTED TO RECOGNIZE ADVERSE REACTION SYMPTOMS AND CAUTIONED TO CONTACT THE PHYSICIAN'S OFFICE IF REACTION SYMPTOMS OCCUR. IN CERTAIN INDIVIDUALS THESE REACTIONS COULD BE FATAL. PATIENTS SHOULD BE OBSERVED FOR AT LEAST 20 MINUTES FOLLOWING TREATMENT. PATIENTS WITH LABILE OR STEROID-DEPENDENT ASTHMA ARE "HIGH RISK PATIENTS" WHO REQUIRE SPECIAL CAUTION IN DOSE ADMINISTRATION AND SHOULD REMAIN IN THE OFFICE FOR AT LEAST 30 MINUTES. AIRWAY OBSTRUCTION IN HIGH RISK PATIENTS CAN BE MONITORED BY PEAK FLOW MEASUREMENTS BEFORE AND AFTER ADMINISTRATION OF ALLERGENS. EMERGENCY MEASURES AS WELL AS PERSONNEL TRAINED IN THEIR USE SHOULD BE IMMEDIATELY AVAILABLE IN THE EVENT OF A LIFE THREATENING REACTION. TO REPORT SERIOUS ADVERSE EVENTS, THE FOOD AND DRUG ADMINISTRATION MED-WATCH NUMBER IS 1-800-332-1088. PATIENTS BEING SWITCHED FROM ONE LOT OF EXTRACT TO ANOTHER FROM THE SAME MANUFACTURER SHOULD HAVE THEIR DOSE REDUCED BY 75%.

RISK OF ANAPHYLAXIS SHOULD BE WEIGHED AGAINST BENEFITS: IN PATIENTS RECEIVING BETA BLOCKERS AS THEY MAY NOT BE RESPONSIVE TO BETA ADRENERGIC DRUGS SHOULD ANAPHYLAXIS OCCUR; IN PATIENTS WITH UNSTABLE OR STEROID-DEPENDENT ASTHMA; OR IN PATIENTS WITH CARDIOVASCULAR DISEASE.

REFER ALSO TO THE WARNINGS, PRECAUTIONS, ADVERSE REACTIONS AND OVERDOSAGE SECTIONS BELOW.

DESCRIPTION

Standardized Grass Pollen Allergenic Extracts are supplied as sterile solutions for intracutaneous or subcutaneous administration. Standardized Grass Pollen Allergenic Extracts include Bermuda (*Cynodon dactylon*), Kentucky Blue (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*). Glycerinated concentrates contain the soluble extractants of the source material with 0.25% sodium chloride, 0.27% sodium bicarbonate, and 50% glycerin v/v. All extracts contain 0.4% phenol as the preservative. Source materials for each extract are the specific pollens collected from the respective plants.

Standardized Grass Pollen Extracts are labeled in Bioequivalent Allergy Units (BAU)/mL. STANDARDIZED GRASS POLLEN EXTRACTS LABELED IN BAU/ML ARE NOT INTERCHANGEABLE WITH GRASS POLLEN EXTRACTS LABELED IN AU/ML OR WITH NONSTANDARDIZED GRASS POLLEN EXTRACTS. Bioequivalent allergy units are assigned based on comparison by enzyme linked immunosorbent assay (ELISA) to references from the U. S. Food and Drug Administration, Center for Biologics Evaluation and Research (CBER). CBER References are assigned unitage based on quantitative skin testing.¹⁻⁴ CBER references which can be diluted 1:5,000,000 to intradermally elicit a 50 mm sum of erythema diameter response in highly puncture reactive subjects are assigned 100,000 BAU/mL, whereas references diluted 1:500,000 which elicit the same 50 mm sum of erythema diameter response are assigned 10,000 BAU/mL.

CLINICAL 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.⁵⁻⁸ 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.⁷⁻¹¹

Puncture test results with eight US reference extracts at 10,000 BAU/mL (15 grass-specific allergic subjects per extract) are shown in TABLE 1.³⁰ For the eight grass pollens, there was a mean sum-of-diameter wheal of 15.2 mm (SD = 1.8) and a mean sum-of-diameter erythema of 84.0 mm (SD = 5.8).

TABLE 1

Puncture Skin Tests with 10,000 BAU/mL Grass Extracts
(Bifurcated Needle)

Reference Pollen	Puncture Sum of Wheal (mm)		Puncture Sum of Erythema (mm)	
	Mean	Range	Mean	Range
Bermuda	15.7	7 - 31	90.3	43 - 123
Kentucky Blue/June	15.9	6 - 28	77.3	47 - 107
Meadow Fescue	11.9	7 - 22	81.1	57 - 115
Orchard	14.1	9 - 19	84.3	57 - 111
Perennial Rye	17.5	6 - 36	92.3	73 - 135
Redtop	14.1	8 - 19	77.1	42 - 98
Sweet Vernal	15.7	8 - 30	81.2	28 - 123
Timothy	16.9	8 - 40	88.3	51 - 109

Intradermal skin tests with eight U.S. reference extracts (TABLE 2) in highly puncture reactive subjects (TABLE 1) indicate that a calculated dose of 0.02 BAU/mL should yield an average sum of erythema reaction of 50 mm, as tested in subjects sensitive to the specific grass pollen extract. However in the more sensitive subjects, the dose was as low as 0.0003 BAU/mL for one grass to 0.002 BAU/mL for several others. Conversely, doses of from 0.1 to 1.9 BAU/mL were calculated to yield the same reaction in the least-sensitive subjects.

TABLE 2

Intradermal Skin Test Doses
(Calculated BAU/mL Required for 50 mm Sum of Erythema)

Reference Pollen	Bioequivalent Allergy Units/mL			
	Mean	Range		
Bermuda	0.02	0.0003	-	0.4
Kentucky Blue/June	0.02	0.004	-	0.1
Meadow Fescue	0.02	0.002	-	0.9
Orchard	0.02	0.002	-	1.9
Perennial Rye	0.02	0.002	-	0.7
Redtop	0.02	0.004	-	0.8
Sweet Vernal	0.02	0.002	-	1.0
Timothy	0.02	0.002	-	0.6

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.¹² 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.¹³ 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.¹⁴ The complete mechanisms of immunotherapy are not known and remain the subject of investigation.

Standardized versus nonstandardized extracts: Standardized grass pollen extracts cannot be directly compared to the previously marketed nonstandardized extract concentrates of the same grass pollens such as those labeled at 1:10 w/v or 1:20 w/v or at 20,000 to 40,000 PNU. The potency of the nonstandardized extracts vary from species to species. Some nonstandardized grass pollen concentrates have been from a few thousand BAU/mL to several hundred thousand BAU/mL as measured by in vitro ELISA testing. Extracts of some lots of Greer nonstandardized glycerinated 1:20 w/v extracts such as Meadow Fescue and Redtop have tested over 200,000 BAU/mL. Two Timothy aqueous nonstandardized 1:10 w/v aqueous extract lots were over 200,000 BAU/mL. Several lots of nonstandardized concentrates of Kentucky Blue/June, Orchard, Perennial Rye, and Sweet Vernal varied around 100,000 BAU/mL. Bermuda grass is not as potent. The FDA Bermuda reference is assigned 10,000 BAU/mL, a value similar to that found in several Greer lots of nonstandardized Bermuda. This is the maximum available strength of standardized Bermuda grass pollen extract. See TABLE 3 for examples of BAU potency by in vitro ELISA testing for nonstandardized grass pollen extracts.

TABLE 3
BAU/mL of Previously Marketed, Nonstandardized,
Grass Pollen Extracts BAU/mL Range by In Vitro ELISA*

Pollen	# of Lots Tested	1:10 w/v Aqueous	# of Lots Tested	1:20 w/v
				glycerinated
Bermuda	1	10,740	5	4,000 to 14,500
Meadow Fescue	3	287,300 to 666,000	4	169,200 to 378,200
Kentucky Blue/June	3	56,100 to 145,400	4	56,100 to 91,500
Orchard	2	134,000 to 139,200	5	71,200 to 110,500
Redtop	3	141,900 to 425,000	4	134,600 to 219,200
Perennial Rye	4	59,100 to 302,000	4	52,900 to 80,400
Sweet Vernal	2	171,900 to 234,800	5	63,900 to 201,200
Timothy	3	186,300 to 291,000	3	63,000 to 104,800

Extracts testing between 67,300 and 148,600 are not statistically different from 100,000 BAU/mL. Extracts which test between 6,730 to 14,860 are not statistically different from 10,000 BAU/mL.

***CAUTION:** Only a few lots of each nonstandardized pollen species have been tested by ELISA. The lots tested varied from fresh extracts to extracts more than three years old. Do not assume that these values apply to specific lots that are in distribution. In addition to age, storage temperatures influence potency.

Physicians must exercise care in switching patients from nonstandardized to standardized extracts. As with nonstandardized 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 nonstandardized and standardized extracts at estimated equal doses. See WARNINGS section.

The potency of nonstandardized grass pollen extracts have varied enough so that the strength of any extract previously used in a specific patient cannot be related to a particular potency in switching to BAU extracts. Therefore, patients being switched from nonstandardized extracts from another manufacturer to extracts standardized in BAU can be reevaluated by diagnostic skin testing to judge the dose to start immunotherapy or to build up to new maintenance dosages.

INDICATIONS AND USAGE

Standardized Grass Pollen Extracts are indicated for the skin-test diagnosis of allergy and immunotherapy treatment of patients with a history of allergy to the respective pollen. The diagnosis of IgE-mediated allergy may be established by the allergy history, clinical evaluation, and skin test reactivity.^{8,11,15} Extracts at 10,000 BAU/mL are indicated for use in scratch, prick, or puncture skin test diagnosis. Extracts at 100,000 BAU/mL are indicated for use in scratch, prick, or puncture skin test diagnosis in less sensitive subjects, such as those negative or indeterminate upon scratch, prick, or puncture testing at 10,000 BAU/mL. Extracts at 10,000 BAU/mL or 100,000 BAU/mL are indicated for intradermal skin test diagnosis only when appropriately diluted.

Immunotherapy with Standardized Grass Pollen Extracts is indicated when testing and patient history have identified the offending allergens and when it is not possible or practical to avoid these allergens.¹⁶⁻¹⁸ Extracts at 10,000 BAU/mL or 100,000 BAU/mL are indicated for immunotherapy only when appropriately diluted. 10,000 BAU/mL extracts are indicated for immunotherapy on previously untreated patients. 100,000 BAU/mL extracts are indicated if a higher dose is needed. (See DOSAGE AND ADMINISTRATION) **STANDARDIZED GRASS POLLEN EXTRACTS LABELED IN BAU/mL ARE NOT INTERCHANGEABLE WITH GRASS POLLEN EXTRACTS LABELED IN AU/mL OR WITH NONSTANDARDIZED GRASS POLLEN EXTRACTS.** The use of Standardized Grass Pollen Extracts for the above purposes should be made only by physicians with special familiarity and knowledge of allergy. (See DOSAGE AND ADMINISTRATION)

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 require careful consideration and probably should not receive injection therapy because a variety of seemingly unrelated events, such as immunization, can cause an exacerbation of their nephrotic disease.

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.

WARNINGS

All concentrates of Standardized Grass Pollen Extracts are manufactured to assure high potency and have the ability during skin testing and immunotherapy to cause serious local and systemic reactions including death in extremely sensitive patients. Most reactions occur within 20 minutes after injection, but may occur later.¹⁹ To minimize the potential for local or systemic reactions, the relative sensitivity of the patient must be assessed from the allergic history and from clinical observations. Patients should be informed of these risks prior to skin testing and immunotherapy. (See PRECAUTIONS and ADVERSE REACTIONS)

Concentrated extracts at 10,000 and 100,000 BAU/mL, must be diluted with a sterile diluent prior to use in a patient for intradermal testing or for immunotherapy.

Skin testing should be initiated only with 10,000 BAU/mL extracts. If several concentrated extracts at 100,000 BAU/mL are administered concurrently to a sensitive patient, the additive effects of cross-reacting allergens may cause a systemic anaphylactic reaction.

Allergenic extracts should be temporarily withheld from patients or the dose adjusted downward if any of the following conditions exist:

1. severe symptoms of rhinitis and/or asthma
2. infection or flu accompanied by fever
3. exposure to excessive amounts of clinically relevant allergen prior to a scheduled injection
4. evidence of a local or systemic reaction to the preceding extract injection during a course of immunotherapy

The dosage must be reduced: 1) when starting a patient on fresh extract; 2) when transferring a patient from another form of extract to a BAU standardized extract; or 3) when modifying dosages or components in a mixture or an individual prescription, even though the labeled strength of the old and new vials may be the same. This reduction in dosage may be necessary: 1) due to the previously used extract having lost potency during storage; 2) due to the fact that standardized extracts labeled in BAU/mL differ in potency in comparison to nonstandardized extracts of the same species (see TABLE 3); or 3) due to different patient sensitivity to different components. The amount of new extract given should not exceed 25% of the last dose given from the old vial, assuming both extracts contain comparable amounts of allergen. Any evidence of a local or generalized reaction requires a reduction in dosage during the initial stages of immunotherapy, as well as during maintenance therapy. The information about nonstandardized extracts shown in TABLE 3 may be helpful in confirming the appropriateness of the initial dose. When a patient is first being administered a standardized extract labeled in BAU/mL, the new dose can be selected based on a side-by-side comparison with the previously used nonstandardized extract. The availability of 10,000 BAU/mL and 100,000 BAU/mL doses is intended to facilitate safe switching by providing the physicians access to lower and higher dosages.

Patients receiving beta blocker drugs may not be responsive to beta adrenergic drugs used to treat anaphylaxis. The risks of anaphylaxis in these patients should be carefully weighed against the benefits of immunotherapy.

PRECAUTIONS

GENERAL

Not for intravenous use!

Systemic allergic reactions may occur as a result of immunotherapy. The risk can be minimized by adherence to a careful injection schedule, which starts with a low concentration of extract and is increased slowly. Because of the danger of serious reactions, caution is needed in testing exquisitely sensitive patients or patients with labile or steroid-dependent asthma. Review the patient's history of reactions to previous injections and adjust dosages accordingly.

The physician must be prepared to treat anaphylaxis should it occur and have the necessary drugs and equipment on hand to do so.^{20,21,31} Extracts should not be administered by the patient or other individuals who are not prepared to treat anaphylaxis should it occur.

Patients receiving allergenic extracts should be kept under observation a minimum of twenty²⁰ minutes so that any adverse reaction can be observed and properly handled.²² This time should be extended to at least 30 minutes for high-risk patients such as those with labile or steroid-dependent asthma or those suffering an exacerbation of their symptoms.³² Airway obstruction in high risk patients can be monitored by peak flow measurements before and after administration of allergens.

Check the prescription or lot number, vial number, strength, and verify the dosage schedule of the prescription for the specific patient. Only after this verification has been made should an injection be given.

A separate, sterile syringe and needle or sterile disposable unit must be used for each patient to prevent the transmission of hepatitis or other infectious agents from person to person. Needles should not be recapped and should be disposed of properly.

Do not use the same syringe for different extracts, nor for the diluent after using it for an extract.

INFORMATION FOR PATIENTS

Most serious reactions following the administration of allergenic extracts occur within 30 minutes. The patient should remain under observation for this period of time or longer if instructed by the physician. The size of any local reaction should be recorded. Large local reactions may be indicative of subsequent systemic reactions as dosages increase. The patient should be instructed to report any unusual reactions. In particular, this includes unusual swelling and/or tenderness at the injection site or reactions such as rhinorrhea, sneezing, coughing, wheezing, shortness of breath, nausea, dizziness, or faintness. Reactions may occur some time after leaving the physician's office, in which case medical attention should be sought immediately.

DRUG INTERACTIONS

Skin test diagnosis with Allergenic Extracts may result in false negative responses when used within 3-10 days of H1 -Blockers such as cetirizine, loratadine, and terfenadine. The inhibitory effect of astemizole may last up to 60 days.³³ These products suppress histamine skin test reactions and could mask a positive response. The suppressive action of other drugs should be considered and emphasizes the need for a histamine positive-control test.

Patients receiving beta blocker drugs may not be responsive to beta adrenergic drugs used to treat anaphylaxis. The risks of anaphylaxis in these patients should be carefully weighed against the benefits of immunotherapy.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

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.

PREGNANCY

TERATOGENIC EFFECTS

PREGNANCY CATEGORY C - Animal reproduction studies have not been conducted with Standardized Grass Pollen Extracts. It is also not known whether Standardized Grass Pollen Extracts can cause fetal harm when administered to a pregnant woman or whether they can affect reproduction capacity. Standardized Grass Pollen Extracts should be given to a pregnant woman only if clearly needed.

There is no evidence of adverse effects of allergenic extracts on the fetus.¹² Studies have not been performed in animals to determine whether extracts affect fertility in males or females, have teratogenic potential, or have other adverse effects on the fetus. Caution should be exercised in testing or treating pregnant females because a systemic reaction may cause an abortion as a result of uterine muscle contractions.

LABOR AND DELIVERY

There is no known information of adverse effects during labor and delivery.

NURSING MOTHERS

It is not known whether allergenic extracts or their antigens are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when extracts are administered to a nursing woman.

PEDIATRIC AND GERIATRIC USE

Although extracts have not been studied systematically in various age groups, older children and geriatric patients 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.²⁹ Studies with pollenosis and asthma have been conducted in children e.g. refs. 23-25. Extract usage in children should follow the same precautions as in adults.

ADVERSE REACTIONS

Adverse systemic reactions may occur within minutes upon use of an allergenic extract to which a person has specific sensitivity. These reactions consist primarily of allergic symptoms such as generalized skin erythema, urticaria, pruritus, angioedema, rhinitis, wheezing, laryngeal edema, and hypotension. Less commonly, nausea, emesis, abdominal cramps, diarrhea and uterine contractions may occur. Systemic reactions occur with varying frequency in different clinics and are usually less than 1%. To some extent, the reaction rate is related to the type and dose of administered extract and to the degree of sensitivity of the patient. Severe reactions may cause shock and loss of consciousness. Fatalities have occurred rarely.^{12,26,27} Fatal reactions are often associated with high-risk patients such as those with labile or steroid-dependent asthma, particularly in those suffering an exacerbation of their symptoms at the time of extract administration. In general, immunotherapy with allergenic extracts is considered to be safe.²⁸ Despite all precautions occasional reactions are unavoidable.

Adverse systemic / anaphylactic reactions should be treated as follows:

- A. If the injection site is an arm, a tourniquet should be immediately applied above the site. Release the tourniquet every few minutes for a few seconds.
- B. Epinephrine 1:1000 should be injected immediately in the opposite arm in amounts of 0.3 to 0.5 mL and 0.2 mL epinephrine should be administered at the site of injection. For children below the age of 6 years, adjust the initial dose of epinephrine to 0.005 mL per pound (0.01 mL/kg) of body weight. Repeat epinephrine dosage in 15 minutes if necessary and if symptoms persist.
- C. Adverse reactions not responding to epinephrine therapy may require other measures such as the use of inhaled, parenteral bronchodilators, vasopressors, oxygen, or volume replacement therapy. Proper equipment and trained personnel should be available.^{20,21,31}

Local reactions consisting of erythema, itching, swelling, tenderness and sometimes pain may occur at the injection site. These reactions may appear within a few minutes to hours and persist for several days. Local cold applications and oral antihistamines may be effective treatment. For marked and prolonged local reactions, steroids may be helpful.

Reporting of Adverse Events

Reporting of serious or unexpected adverse events occurring after extract administration is encouraged. MedWatch Forms, FDA Form 3500, are available from FDA, 1-800-332-1088. Health-care providers also should report these events to the Regulatory Affairs adverse reaction monitor, Greer, P.O. Box 800, Lenoir NC 28645-0800 or call 1-800-438-0088.

OVERDOSAGE

Systemic reactions are uncommon after injection, but if the patient receives more extract than can be tolerated at that particular time and begins to experience immediate hypersensitivity anaphylaxis, the procedures listed under ADVERSE REACTIONS should be instituted.

Overdosage may occur because of an error in the volume of extract injected, an incorrect dilution injected, or because the patient may be exposed to airborne or environmental antigens simultaneously with injection of the same antigens. In the event of a systemic reaction occurring, the dosage schedule should be carefully reviewed and if necessary adjusted as outlined above under WARNINGS.

DOSAGE AND ADMINISTRATION

1. DIAGNOSTIC TESTING

For the patient with a suspected diagnosis of allergy to more than one antigen, initial screening skin tests should include the individual extracts. If a screening skin test with a mixture is used, a positive response should be followed by testing with the individual extracts to determine the degree of sensitivity to each and to guide in the selection of extracts and their concentration for immunotherapy if indicated. However, because a negative skin test with a mixture may not be indicative of the absence of allergy to one or more of the components due to their

dilution, testing with individual extracts is more precise. False negative responses may occur if serum levels of antihistamines remain from prior medication administration. (See PRECAUTIONS) The use of a histamine positive control is especially recommended for patients on prior medications which may decrease the histamine skin test response.

Skin tests read after 15 to 20 minutes are graded in terms of the induration (wheal) and erythema (flare) response compared to the appropriate controls. Wheal and flare sizes may be recorded by actual measurements. The largest diameter of the wheal and flare may be recorded, or the sum of the largest diameter and the orthogonal (right angle) diameter wheal or flare may be used as in the studies in TABLE 1 and TABLE 2.

Scratch or Prick-puncture Skin Testing:

For puncture, prick, or scratch skin test, the 10,000 BAU/mL strength is recommended and will detect the more sensitive patients. Inconclusive results at 10,000 BAU/mL may be followed by a puncture, prick, or scratch skin test at 100,000. At the higher concentration, some nonspecific positives may occur.

Controls for Scratch, Prick-Puncture Testing:

As a positive control, glycerinated histamine phosphate 5 mg/mL (1.8 mg/mL histamine base) or aqueous histamine phosphate 2.75 mg/mL (1 mg/mL (1:1,000 w/v) histamine base) may be used as a positive control. A 50% glycerosaline solution may be used as the negative control.

Intradermal Skin Testing:

Extracts for intradermal testing must be prepared by diluting the concentrated extract with sterile diluent (such as normal or buffered saline, or normal saline with human serum albumin).

Intradermal skin tests with eight U.S. reference extracts (TABLE 2) indicate that a calculated dose of 0.02 BAU/mL should yield an average sum of erythema reaction of 50 mm, as tested in subjects with similar puncture reactivities described in TABLE 1 to that specific grass pollen extract. However in the more sensitive subjects, the dose was as low as 0.0003 BAU for one grass to 0.002 BAU for several others. Conversely, doses of from 0.1 to 1.9 BAU were calculated to yield the same reaction in the least-sensitive subjects.

Controls for Intradermal Testing:

As a positive control, use glycerinated histamine phosphate diluted to 0.5 mg/mL (0.18 mg/mL histamine base) or aqueous histamine phosphate 0.275 mg/mL (0.1 mg/mL histamine base). As a negative control, use 0.5% to 1% glycerin in 0.9% saline.

A. Patients with a negative scratch or prick-puncture test:

Patients who do not react to a scratch or prick-puncture test should be tested intradermally, using a 26 or 27 gauge 1/4 inch needle, with 0.02 to 0.05 mL of a 50 BAU/mL extract dilution. A negative test should be followed by repeat tests using progressively stronger concentrations until significant wheal and flare reaction sizes are attained or until the maximum

recommended strength of 200 BAU/mL is reached. As a positive control, use glycerinated histamine phosphate diluted to 0.5 mg/mL (0.18 mg/mL histamine base) or aqueous histamine phosphate 0.275 mg/mL (0.1 mg/mL histamine base). As a negative control use 0.5% to 1% glycerosaline solution.

B. Patients tested only by the intradermal method:

Since highly reactive individuals may react intracutaneously at doses even smaller than indicated above, it is recommended that intradermal testing be preceded by a puncture test and the dose adjusted accordingly. Other patients suspected of being moderately allergic may be tested with an intradermal test dose of 0.02 to 0.05 mL of a 0.05 BAU/mL dilution. A negative test should be followed by repeat tests using progressively stronger concentrations until the maximum recommended strength of 200 BAU/mL is reached. As a negative control use 0.5% to 1% glycerosaline solution. As a positive control, use glycerinated histamine phosphate diluted to 0.5 mg/mL (0.18 mg/mL histamine base) or aqueous histamine phosphate 0.275 mg/mL (0.1 mg/mL histamine base).

2. THERAPY

Standardized versus Nonstandardized Extracts:

Dosage with extracts standardized in BAU must be derived from a knowledge of the patient's sensitivity to the specific pollen. Switching from an extract not standardized in BAU cannot be made by a calculated ratio. There are no equivalent dosages in bioequivalent allergy units applicable to all the grass species that can be related to previously marketed nonstandardized extracts labeled in weight-to-volume (w/v), Protein Nitrogen Units (PNU), or Allergy Units (AU). The information about nonstandardized extracts shown in TABLE 3 may be helpful in selecting the initial dose for the side-by-side skin test comparison. Patients being switched from nonstandardized extracts to extracts standardized in BAU can be reevaluated by diagnostic skin testing to judge the dose for starting immunotherapy or building up to new maintenance dosages. When a patient is first being administered a standardized extract labeled in BAU/mL, the new dose can be selected based on a side-by-side comparison with the previously used nonstandardized extract.

Immunotherapy is administered by subcutaneous injection. Dosage is individualized according to the patient's sensitivity, the clinical response, and tolerance to the extract administered during the early phases of an injection regimen. Extracts for immunotherapy must be prepared by diluting the concentrate with sterile diluent (such as normal or buffered saline, or normal saline with human serum albumin).

The initial dose of an extract in BAU should be calculated based on the puncture test reactivity. Note in TABLE 1 and TABLE 2 the puncture and intradermal skin test reactivity of sensitive subjects evaluated with the US reference extracts.

The initial dose of the extract may be as low as 0.1 mL of a 0.005 to 0.05 BAU/mL dilution (0.0005 to 0.005 BAU) (dilution 5 or 6 in TABLE 4 below) or even less for the exquisitely sensitive patient. Patients with lesser sensitivity may be started at 0.1 mL of a 0.5 to 5 BAU/mL dilution (0.05 to 0.5 BAU).

The amount of allergenic extract is increased at each injection by no more than 50% of the previous amount, and the next increment is governed by the response to the last injection. Large local reactions which persist for longer than 24 hours are generally considered an indication for repeating the previous dose or reducing the dose at the next administration. Any evidence of systemic reaction is an indication for a reduction of 75% in the subsequent dose. The upper limits of dosage in BAU have not been established. Doses larger than 0.2 mL of an extract in 50% glycerin may cause discomfort upon injection. The dosages of allergenic extracts do not vary significantly with the allergic disease under treatment.

To prepare dilutions starting from a 100,000 BAU/mL concentrate, proceed as in TABLE 4. The 50,000 BAU/mL concentrate can be made by using equal parts of the 100,000 BAU/mL extract and the sterile diluent. The ten-fold dilution series uses 0.5 mL of concentrate to 4.5 mL of sterile diluent with additional dilutions made in the same manner.

TABLE 4
Ten-Fold Dilution Series*

Dilution	Extract	Diluent	BAU/mL	BAU/mL
0	Concentrate		100,000	10,000
1	0.5 mL concentrate	4.5 mL	10,000	1,000
2	0.5 mL dilution 1	4.5 mL	1,000	100
3	0.5 mL dilution 2	4.5 mL	100	10
4	0.5 mL dilution 3	4.5 mL	10	1
5	0.5 mL dilution 4	4.5 mL	1	0.1
6	0.5 mL dilution 5	4.5 mL	0.1	0.01

*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) nonstandardized extracts labeled weight-to-volume (w/v); 3) nonstandardized extracts labeled in Protein Nitrogen Units (PNU); or 4) alum-precipitated extracts.

The optimal interval between doses of allergenic extracts has not been established. Injections usually are given 1 or 2 times per week until the maintenance dose is reached. The injection interval is then increased to 2 weeks, then to 3 weeks and finally to 4 weeks. If the patient does not return for 6 to 8 weeks, 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 considering 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 25% of the previous dose.

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.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Some concentrated extracts naturally develop a cloudy appearance over time under refrigeration, the material settling to the bottom on standing.

HOW SUPPLIED

Stock concentrate extracts containing 10,000 BAU/mL and 100,000 BAU/mL are supplied in 10, 30 and 50 mL multiple-dose vials in 50% glycerin. (Standardized Bermuda grass pollen extract is supplied at a maximum strength of 10,000 BAU/mL.) Extracts for puncture, prick or scratch testing are supplied in 5 mL dropper vials at 10,000 BAU/mL or in multiple-dose vials at 100,000 BAU/mL (except Bermuda) in 50% glycerin. Intradermal strengths should be prepared by dilution of stock concentrates with normal saline or saline containing HSA.

STORAGE

All allergenic extracts should be stored at 2-8°C and kept in this temperature range during office use. Refer to vial labels for expiration dates. 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.

REFERENCES

- 1 Turkeltaub, P.C., Rastogi, S.C., Baer, H., Anderson, M.C., Norman, P.S.: A standardized quantitative skin-test assay of allergen potency and stability: Studies on the allergen dose-response curve and effect of wheal, erythema, and patient selection on assay results. *J. Allergy Clin. Immunol.* 1982;70:343-352.
- 2 ELISA competition assay. Methods of the Allergenic Products Testing Laboratory, Laboratory of Immunobiochemistry, Division of Allergenic Products and Parasitology, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, 1994.
- 3 Turkeltaub, P.C., Rastogi, S.C.: Quantitative intradermal procedure for evaluation of subject sensitivity to standardized allergenic extracts and for assignment of bioequivalent allergy units to reference preparations. *Ibid.*
- 4 Turkeltaub, P.C.: Assignment of bioequivalent allergy units based on biological standardization methods. *Arbeiten aus dem Paul-Ehrlich-Institut* (Bundesamt für Sera und Impfstoffe), Band 52, Gustav Fischer Verlag, Stuttgart-New York, 1988.
- 5 Lichtenstein, L.M., Ishizaka, K., Norman, P.S., et al.: IgE antibody measurements in ragweed hay fever: relationship to clinical severity and the results of immunotherapy. *J. Clin. Invest.* 1973;52:472.

- 6 Elgefors, B., Julin, A., Johansson, S.G.O.: Immunoglobulin E in bronchial asthma. *Acta Allergol* 1974;29:327.
- 7 Norman, P.S., The clinical significance of IgE. *Hosp. Pract.* 1975;10:41-49.
- 8 Bryant, D.A., Burns, M.W., Lazarus, L.: The correlation between skin tests, bronchial provocation tests and the serum level of IgE specific for common allergens in patients with asthma. *Clin. Allergy* 1975;5:145.
- 9 Loeffler, J.A., Cawley, L.P., Moeder, M.: Serum IgE levels - correlation with skin test sensitivity. *Ann. Allergy* 1973;31:331.
- 10 Pepys, J.: Skin tests in diagnosis. In Gell, P.G.H., Coombs, R.R.A., Lachman, P.J., editors: *Clinical aspects of Immunology*. Blackwell Scientific Publications, Ltd., Oxford, 1975.
- 11 Burrows, B., et al.: Respiratory disorders and allergy skin test reactions. *Ann. Intern. Med.* 84:134, 1976.
- 12 Implementation of Efficacy Review, Allergenic Extracts. Federal Register 1985;50:3082-3288.
- 13 Levy, D.A., Lichenstein, L.M., Goldstein, E.O., Ishizaka, K.: Immunologic and cellular changes accompanying the therapy of pollen allergy. *J. Clin. Invest.* 1973;50:360.
- 14 Gurka, G., Rocklin, R.: Immunologic responses during allergen-specific immunotherapy for respiratory allergy. *Annals of Allergy* 1988;61:239-43.
- 15 Zeiss, C.R., Jr.: Patient evaluation. In *Allergy and Clinical Immunology*, p.616, edited by R.F. Lockey, Medical Examination Publishing Co., Garden City, New York, 1976.
- 16 Frankland, A.W., Augustin, R.: Prophylaxis of summer hay-fever and asthma: a controlled trial comparing crude grass-pollen extracts with the isolated main protein component. *Lancet* 1954;1:1055.
- 17 Frankland, A.W., Augustin, R.: Grass pollen antigens effective in treatment. *Clin. Sci.* 1962;23:95.
- 18 Rohr, A.S., Marshall, N.A., Saxon, A.: Successful immunotherapy for *Triatoma protracta*-induced anaphylaxis. *J. Allergy Clin. Immunol.* 1984;73:369-75.
- 19 Greenberg, M.A., Kaufman, C.R., Gonzalez, G.E., Rosenblatt, C.D., Smith, L.J., Summers, R.J.: Late and immediate systemic-allergic reactions to inhalant allergen immunotherapy. *J. Allergy Clin. Immunol.* 1986;77:865-70.
- 20 Ouellette, J.J.: Emergency management of the allergic reactions. *Modern Medicine* 1975;99.
- 21 Anderson, J.A., et al.: Personnel and equipment to treat systemic reactions caused by immunotherapy with allergenic extracts. *J. Allergy Clin. Immunol.* 1986;77:271-3.
- 22 Executive Committee, American Academy of Allergy and Immunology. The waiting period after allergen skin testing and immunotherapy (Position statement). *J. Allergy Clin. Immunol.* 1990;85:526-7.
- 23 Sadan, N., Rhyne, M.B., Mellits, E.D., et al.: Immunotherapy of pollenosis in children: investigation of the immunologic basis of clinical improvement. *N. Eng. J. Med.* 1969;280:623.
- 24 Johnstone, D.E.: Value of hyposensitization therapy for perennial bronchial asthma in children. *Pediatrics* 1961;27:39.

- ²⁵ VanAsperin, P.P., Kemp, A.S., Mellis, C.M.: Skin test reactivity and clinical allergen sensitivity in infancy. *J. Allergy Clin. Immunol.* 73:381-6.
- ²⁶ Committee on Safety of Medicine: Desensitizing vaccines. *Br. Med. J* 1986;293:948.
- ²⁷ Lockey, R.F., Benedict, L.M., Turkeltaub, P.C., Bukantz, S.C.: Fatalities from immunotherapy (IT) and skin testing (ST). *J. Allergy Clin. Immunol.* 1987;79:660-7.
- ²⁸ Norman, P.S., Van Metre, T.E., Jr: The safety of allergenic immunotherapy. *J. Allergy Clin. Immunol.* 1990;85:522-5.
- ²⁹ Ownby, D.R., Adinoff, A.D.: The appropriate use of skin testing and allergen immunotherapy in young children. *J. Allergy Clin. Immunol.* 1994;94:662-5.
- ³⁰ Data on File - Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, MD.
- ³¹ Board of Directors, American Academy of Allergy and Immunology Guidelines to minimize the risk from systemic reactions caused by immunotherapy with allergenic extracts. (Position statement). *J. Allergy Clin. Immunol.* 1994;93:811-12.
- ³² Reid, M.J., Lockey, R.F., Turkeltaub, P.C., and Platts-Mills, T.A.E.: Survey of fatalities from skin testing and immunotherapy 1985-1989. *J. Allergy Clin. Immunol.* 1993;92:6-15.
- ³³ Bousquet, J.: In Vivo Methods For Study of Allergy: Skin tests, techniques, and interpretation. In *Allergy Principles and Practice*, 4th Edition, Middleton, et al eds., C.V. Mosby, St. Louis, MO, 1993.

