

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Standardized Grass Pollen Allergenic Extracts safely and effectively. See full prescribing information for Standardized Grass Pollen Allergenic Extracts.

Standardized Bermuda Grass Pollen (*Cynodon dactylon*)

Standardized Kentucky Blue (June) Grass Pollen (*Poa pratensis*)

Standardized Meadow Fescue Grass Pollen (*Festuca elatior*)

Standardized Orchard Grass Pollen (*Dactylis glomerata*)

Standardized Perennial Rye Grass Pollen (*Lolium perenne*)

Standardized Redtop Grass Pollen (*Agrostis alba*)

Standardized Sweet Vernal Grass Pollen (*Anthoxanthum odoratum*)

Standardized Timothy Grass Pollen (*Phleum pratense*)

Solutions for percutaneous, intradermal or subcutaneous administration.

Initial U.S. Approval: 1997

### WARNING: SEVERE ALLERGIC REACTIONS

See full prescribing information for complete boxed warning.

- Standardized Grass Pollen Allergenic Extracts can cause severe life-threatening systemic reactions, including anaphylaxis. (5.1)
- Do not administer Standardized Grass Pollen Allergenic Extracts to patients with severe, unstable or uncontrolled asthma. (4)
- Observe patients in the office for at least 30 minutes following treatment. Emergency measures and personnel trained in their use must be available immediately in the event of a life-threatening reaction. (5.1)
- Patients with extreme sensitivity to these products, on an accelerated immunotherapy build-up, switching to another lot, receiving high doses of Standardized Grass Pollen Allergenic Extracts, and patients exposed to similar allergens may be at increased risk of a severe allergic reaction. (5.1)
- Standardized Grass Pollen Allergenic Extracts may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a systemic allergic reaction, and for patients receiving medications such as beta-blockers that may make them unresponsive to epinephrine or inhaled bronchodilators. (5.1, 5.2)

### INDICATIONS AND USAGE

Standardized Grass Pollen Allergenic Extracts are indicated for:

Skin test diagnosis of patients with a clinical history of allergy to one or more of the following grass pollens: Bermuda, Kentucky Blue (June), Meadow Fescue, Orchard, Perennial Rye, Redtop, Sweet Vernal, Timothy. (1)

Immunotherapy for the reduction of grass pollen-induced allergic symptoms confirmed by positive skin test or by *in vitro* testing for pollen-specific IgE antibodies for Bermuda grass pollen, Kentucky Blue (June) grass pollen,

Meadow Fescue grass pollen, Orchard grass pollen, Perennial Rye grass pollen, Redtop grass pollen, Sweet Vernal grass pollen, or Timothy grass pollen. (1)

### DOSAGE AND ADMINISTRATION

For percutaneous, intradermal or subcutaneous use only.

The extracts are diluted with sterile diluents when used for intradermal testing or subcutaneous immunotherapy. For percutaneous testing, the extracts are diluted with sterile diluents in patients expected to be at greater risk for systemic allergic reaction. Dosages vary by mode of administration and by individual response. See full prescribing information for instructions on preparation, administration, and adjustments of dose. (2.1)

### DOSAGE FORMS AND STRENGTHS

Standardized Bermuda Grass Pollen Allergenic Extract solution is available only at 10,000 Bioequivalent Allergy Units (BAU)/milliliter. (3)

Other Standardized Grass Pollen Allergenic Extract solutions are available as stock concentrates at 10,000 and 100,000 BAU/milliliter. (3)

### CONTRAINDICATIONS

- Severe, unstable or uncontrolled asthma. (4)
- History of any severe systemic allergic reaction or any severe local reaction to subcutaneous allergen immunotherapy. (4)

### WARNINGS AND PRECAUTIONS

Severe allergic reactions have occurred following the administration of other allergenic extracts and may occur in individuals following the administration of Standardized Grass Pollen Allergenic Extracts in the following situations:

- Extreme sensitivity to Standardized Grass Pollen Allergenic Extracts, receipt of high doses of Standardized Grass Pollen Allergenic Extracts, or concomitant exposure to similar environmental allergens. (5.1)
- Receiving an accelerated immunotherapy build-up schedule (e.g., “rush” immunotherapy) or changing from one allergenic lot to another. (5.1)

### ADVERSE REACTIONS

The most common adverse reactions, occurring in over 26 to 82% of all patients who receive subcutaneous immunotherapy, are local adverse reactions at the injection site (e.g., erythema, itching, swelling, tenderness, pain). (6)

Systemic adverse reactions, occurring in  $\leq 7\%$  of patients, include generalized skin erythema, urticaria, pruritus, angioedema, rhinitis, wheezing, laryngeal edema, and hypotension. These can be fatal. (6)

To report SUSPECTED ADVERSE REACTIONS, contact GREER Laboratories, Inc. at 1-855-274-1322 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- Antihistamines and other medications that suppress histamine, including topical corticosteroids, topical anesthetics and tricyclic antidepressants can interfere with skin test results. (7)

See 17 for PATIENT COUNSELING INFORMATION

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### WARNING: SEVERE ALLERGIC REACTIONS

#### 1 INDICATIONS AND USAGE

#### 2 DOSAGE AND ADMINISTRATION

2.1 Preparation for Administration

2.2 Diagnostic Testing

2.3 Immunotherapy

#### 3 DOSAGE FORMS AND STRENGTHS

#### 4 CONTRAINDICATIONS

#### 5 WARNINGS AND PRECAUTIONS

5.1 Serious Systemic Adverse Reactions

5.2 Epinephrine

5.3 Cross-Reactions and Dose Sensitivity

#### 6 ADVERSE REACTIONS

#### 7 DRUG INTERACTIONS

7.1 Antihistamines

7.2 Topical Corticosteroids and Topical Anesthetics

7.3 Tricyclic Antidepressants

#### 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

#### 11 DESCRIPTION

#### 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

#### 14 CLINICAL STUDIES

#### 15 REFERENCES

#### 16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

16.2 Storage and Handling

#### 17 PATIENT COUNSELING INFORMATION

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

## FULL PRESCRIBING INFORMATION

### **WARNING: SEVERE ALLERGIC REACTIONS**

- **Standardized Grass Pollen Allergenic Extracts can cause severe life-threatening systemic reactions, including anaphylaxis. (5.1)**
- **Do not administer Standardized Grass Pollen Allergenic Extracts to patients with severe, unstable, or uncontrolled asthma. (4)**
- **Observe patients in the office for at least 30 minutes following treatment. Emergency measures and personnel trained in their use must be available immediately in the event of a life-threatening reaction. (5.1)**
- **Patients with extreme sensitivity, to Standardized Grass Pollen Allergenic Extracts, those on an accelerated immunotherapy build-up schedule, those switching to another allergenic lot, those receiving high doses of the Standardized Grass Pollen Allergenic Extracts, or those also exposed to similar allergens may be at increased risk of a severe allergic reaction. (5.1)**
- **Standardized Grass Pollen Allergenic Extracts may not be suitable for patients with certain underlying medical conditions that may reduce their ability to survive a serious allergic reaction. (5.1)**
- **Standardized Grass Pollen Allergenic Extracts 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**

GREER Standardized Grass Pollen Allergenic Extracts are indicated for:

- Skin test diagnosis of patients with a clinical history of allergy to one or more of the following grass pollens: Bermuda, Kentucky Blue (June), Meadow Fescue, Orchard, Perennial Rye, Redtop, Sweet Vernal, Timothy.
- Immunotherapy for the reduction of grass pollen-induced allergic symptoms confirmed by positive skin test or by *in vitro* testing for pollen-specific IgE antibodies for Bermuda grass pollen, Kentucky Blue (June) grass pollen, Meadow Fescue grass pollen, Orchard grass pollen, Perennial Rye grass pollen, Redtop grass pollen, Sweet Vernal grass pollen, or Timothy grass pollen.

## **2 DOSAGE AND ADMINISTRATION**

**For percutaneous, intradermal or subcutaneous use only.**

The extracts are diluted with sterile diluents when used for intradermal testing or subcutaneous immunotherapy. For percutaneous testing, the extracts are diluted with sterile diluents in patients

expected to be at greater risk for systemic allergic reaction. Dosages vary by mode of administration and by individual response.

## 2.1 Preparation for Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard solution if either of these conditions exist.

The extracts are diluted with sterile diluents when used for percutaneous and intradermal testing, or for subcutaneous immunotherapy.

Undiluted 10,000 BAU/milliliter or 100,000 BAU/milliliter stock concentrates are used for percutaneous testing. To prepare 10-fold dilutions for percutaneous testing in patients suspected to be at greater risk for systemic allergic reaction, start with a 10,000 BAU/milliliter or 100,000 BAU/milliliter stock concentrate. Proceed as shown in [Table 1](#). The 10-fold dilution series uses 0.5 milliliters of concentrate added to 4.5 milliliters of sterile 50% glycerin diluent. Subsequent dilutions are made in a similar manner.

To prepare 10-fold dilutions for intradermal testing and immunotherapy, start with a 10,000 BAU/milliliter or 100,000 BAU/milliliter stock concentrate. Proceed as shown in [Table 1](#). The 10-fold dilution series uses 0.5 milliliters of concentrate added to 4.5 milliliters of sterile diluent (glycerin-free diluents for intradermal testing, glycerin-free or 10% glycerin-saline diluents for immunotherapy). Subsequent dilutions are made in a similar manner.

**Table 1: 10-fold Dilution Series**

Dilution	Extract	Milliliters of Diluent	Dilution Strength (BAU/mL)	Dilution Strength (BAU/mL)
0	Concentrate		100,000	10,000
1	0.5 mL Concentrate	4.5	10,000	1,000
2	0.5 mL Dilution 1	4.5	1,000	100
3	0.5 mL Dilution 2	4.5	100	10
4	0.5 mL Dilution 3	4.5	10	1
5	0.5 mL Dilution 4	4.5	1	0.1
6	0.5 mL Dilution 5	4.5	0.1	0.01

Undiluted 10,000 BAU/milliliter or 100,000 BAU/milliliter stock concentrates are used for percutaneous testing. To prepare 5-fold dilutions for percutaneous testing in patients suspected to be at greater risk for systemic allergic reaction, start with a 10,000 BAU/milliliter or 100,000 BAU/milliliter stock concentrate. Proceed as shown in [Table 2](#). The 5-fold dilution series uses 1 milliliter of concentrate added to 4 milliliters of sterile 50% glycerin diluent. Subsequent dilutions are made in a similar manner.

To prepare 5-fold dilutions for intradermal testing and immunotherapy, start with a 10,000 BAU/milliliter or 100,000 BAU/milliliter stock concentrate. Proceed as shown in [Table 2](#). The 5-fold dilution series uses 1 milliliter of concentrate added to 4 milliliters of sterile diluent

(glycerin-free diluents for intradermal testing, glycerin-free or 10% glycerin-saline diluents for immunotherapy). Subsequent dilutions are made in a similar manner.

**Table 2: 5-fold Dilution Series**

<b>Dilution</b>	<b>Extract</b>	<b>Milliliters of Diluent</b>	<b>Dilution Strength (BAU/mL)</b>	<b>Dilution Strength (BAU/mL)</b>
0	Concentrate		100,000	10,000
1	1 mL Concentrate	4	20,000	2,000
2	1 mL Dilution 1	4	4,000	400
3	1 mL Dilution 2	4	800	80
4	1 mL Dilution 3	4	160	16
5	1 mL Dilution 4	4	32	3.2
6	1 mL Dilution 5	4	6.4	0.64

## **2.2 Diagnostic Testing**

Diagnostic testing can be performed via percutaneous or intradermal administration of the Standardized Grass Pollen Allergenic Extracts. A positive skin test reaction should be interpreted in relation to the patient’s history and known exposure to the allergen.

If a skin test with a grass pollen extract mixture elicits a positive reaction, then the single-species grass pollen extracts can be used to determine the degree of sensitivity to each individual grass species and to guide in the selection of extracts and their concentration for immunotherapy, if indicated.

### **Percutaneous Skin Testing**

Determine the patient’s sensitivity to the grass pollen allergens.

#### ***Preparation and Dose***

For percutaneous testing (prick or puncture), use 10,000 or 100,000 BAU/milliliter stock concentrates. If a lower concentration is desired in patients suspected to be at greater risk for a systemic allergic reaction, 10-fold or 5-fold dilutions of the concentrate can be tested.

Prick test: Place one drop of extract with appropriate controls on the skin and, with a skin test device, pierce through the drop into the skin with a slight lifting motion. Alternatively, use skin test devices loaded with the extract from the storage trays in a similar manner or in accordance with the device manufacturer’s recommendations.

Puncture test: Place one drop of extract or control on the skin and pierce the skin through the drop with a skin test device perpendicular to the skin. Alternatively, use skin test devices loaded with the extract from the storage trays in a similar manner, or in accordance with the device manufacturer’s recommendations.

#### ***Interpreting Results***

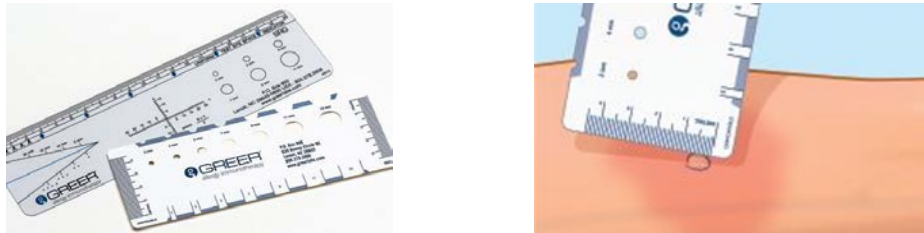
When using percutaneous skin test devices, follow the directions provided with the test devices. A glycerinated histamine control solution (6 milligrams/milliliter or 1 milligram/milliliter

histamine base) may be used as the positive control. A 50% glycerin-saline solution may be used as the negative control.

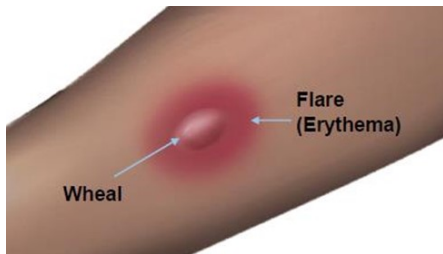
Read and record skin test responses 15 to 20 minutes after exposure. Individual patient reactivity can vary with time, allergen potency, and/or immunotherapy, as well as testing technique. The most reliable method of recording a skin test reaction is to measure the largest diameter of both wheal and erythema. While some correlation exists between the size of the skin test reaction and the degree of sensitivity, other factors should be considered in the diagnosis of allergy to specific allergens (see [Figure 1](#) below).

### Figure 1: Measurement of Wheal and Flare

Use a paper or plastic millimeter skin reaction guide as shown below.



Fifteen minutes after application of the skin test, measure the length and midpoint orthogonal width of each flare and wheal from the inner edge of the reaction.

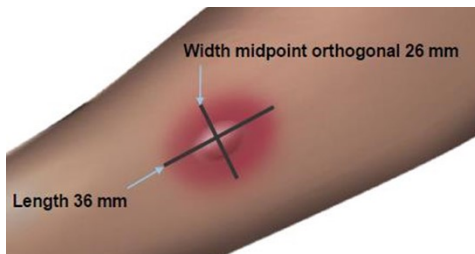


The wheal is a smooth, slightly elevated area which is redder or paler than the surrounding skin.

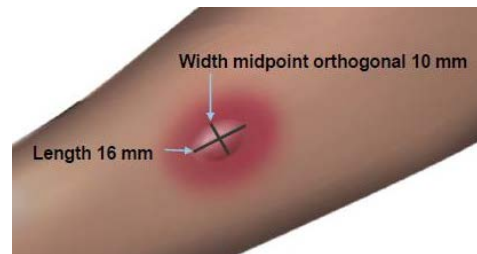
The flare is the red outermost zone of a wheal reaction.

The length of the skin test is defined as the largest diameter and the width of the skin test is defined as the diameter perpendicular to the length at its midpoint. Consider the wheal and flare as separate entities. First, measure the flare and then independently measure the wheal.

#### Measuring the Flare



#### Measuring the Wheal



The average diameter measurement in the example above of the flare is  $(26 \text{ mm} + 36 \text{ mm})/2 = 31 \text{ mm}$  and the average diameter of the wheal is  $(10 \text{ mm} + 16 \text{ mm})/2 = 13 \text{ mm}$ .

Responses to positive controls should be at least 3 millimeters larger than responses to the negative controls.

Negative controls should elicit no reaction or only reactions of small diameters (less than 2 millimeters wheal, less than 5 millimeters erythema).

If either the positive or negative control response does not meet the above criteria, results for the allergenic extracts tested at the same time should be considered invalid and be repeated.

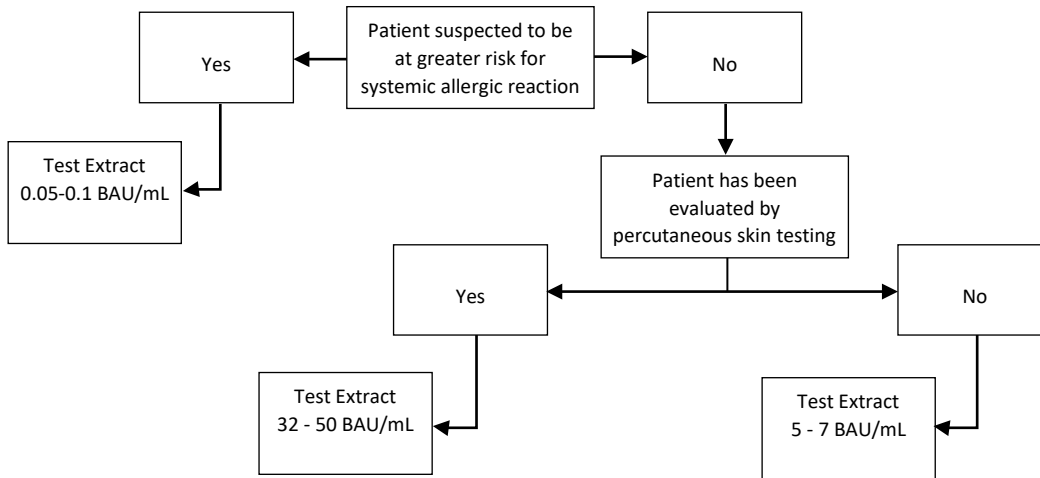
### **Intradermal Skin Testing**

#### ***Preparation and Dose***

For intradermal testing, use 10,000 BAU/milliliter or 100,000 BAU/milliliter of Standardized Grass Pollen Allergenic Extracts stock concentrate solution. Dilute the stock concentrate solution with sterile diluent [see *Dosage and Administration (2.1)*]. Use normal or buffered saline or normal saline with human serum albumin (HSA) diluent. If the result from the initial test dose is negative, subsequent intradermal tests using increasingly stronger doses may be performed up to the maximum recommended strength of 200 BAU/milliliters dilution of the extract concentrate solution.

Inject 0.02 milliliters of the extract solution intradermally according to the algorithm shown in [Figure 2](#):

**Figure 2: Algorithm for Dilution of Stock Concentration Solution of Standardized Grass Pollen Allergenic Extracts for Intradermal Skin Testing**



Note: For each skin test application as outlined in the algorithm, a Positive Control (0.10 mg/mL Histamine Base) and a Negative Control (Normal Saline or 1% Glycerin Saline) should also be applied.

## **2.3 Immunotherapy**

**For subcutaneous administration only.**

#### ***Preparation and Dose***

Stock concentrates of Greer Standardized Grass Pollen Allergenic Extracts are available at 10,000 BAU/milliliter or 100,000 BAU/milliliter in 50% glycerin-saline for immunotherapy. Stock concentrates are diluted in normal saline, buffered saline, HSA-saline, or 10% glycerin-saline,

depending on the patient's reactivity to the diluent. See [Table 1](#) and [Table 2](#) for dilution preparation.

### ***Administration of Immunotherapy***

Administer immunotherapy by subcutaneous injection in the lateral aspect of the upper arm or thigh. Avoid injection directly into any blood vessel.

The optimal interval between doses of allergenic extract varies among individuals. Injections are usually given 1 to 2 times per week until the maintenance dose is reached, at which time the injection interval is increased to 2, then 3, and finally 4 weeks. Dosages vary by mode of administration, and by clinical response and tolerance. The minimum course of treatment may be three to five years, depending on the clinical response.

### ***Guidelines for Immunotherapy***

The initial dose of the extract should be based on the skin test reactivity. In patients suspected to be at greater risk for systemic allergic reaction by history and skin test, the initial dose of the extract should be 0.05 to 0.1 milliliter of a 0.1 to 0.64 BAU/milliliter extract dilution. Patients not suspected to be at greater risk for systemic allergic reaction may be started at a 0.1 milliliter of a 10 to 16 BAU/milliliter extract dilution.

The dose of allergenic extract is increased at each injection by no more than 50% of the previous dose, and the next increment is governed by the response to the last injection.

Select the maximum tolerated maintenance dose based on the patient's clinical response and tolerance. Doses larger than 0.2 milliliter of the stock concentrate are rarely administered because an extract mixed in 50% glycerin diluent can cause discomfort upon injection.

### ***Dosage Modification Guidelines for Immunotherapy***

The following conditions may indicate a need to withhold or reduce the dosage of immunotherapy.

- Symptoms of rhinitis and/or asthma
- Infection accompanied by fever
- Exposure to excessive amounts of clinically relevant environmental allergen prior to a scheduled injection
- Large local reactions that persist for longer than 24 hours can be an indication for repeating the previous dose or reducing the dose at the next administration

Any evidence of a systemic adverse reaction is an indication for a significant reduction (at least 75%) in the subsequent dose. Repeated systemic adverse reactions are sufficient reason for the cessation of further attempts to increase the dose.

Local adverse reactions require a decrease in the next dose by at least 50%. Proceed cautiously in subsequent dosing. In situations prompting dose reduction, once the reduced dose is tolerated, a cautious increase in dosage can be attempted.

**Changing extract to a different lot or from a different manufacturer:** When switching to a different lot of extract, or from another manufacturer's extract, decrease the starting dose. Because manufacturing processes and sources of raw materials differ among manufacturers, the interchangeability of extracts from different manufacturers cannot be assured. In general, a dose

reduction of 50 to 75% of the previous dose should be adequate, but each situation must be evaluated separately, considering the patient's history of sensitivity, tolerance of previous injections, and other factors. Dose intervals should not exceed one week when rebuilding the dose.

**Unscheduled gaps between treatments:** Patients can lose tolerance to allergen injections during prolonged periods between doses which increases their risk for an adverse reaction. The duration of tolerance between injections varies from patient to patient.

During the build-up phase, when patients receive injections 1 to 2 times per week, repeat or reduce the extract dosage if there has been a substantial time interval between injections. This depends on: 1) the concentration of allergen immunotherapy extract that is to be administered; 2) a previous history of systemic reactions; and 3) the degree of variation from the prescribed interval of time, with longer intervals since the last injection leading to greater reductions in the dose to be administered.

This suggested approach to dose modification, due to unscheduled gaps between treatments during the build-up phase, is not based on published evidence. The individual physician should use this or a similar protocol for the specific clinical setting.

Similarly, if unscheduled gaps occur during maintenance therapy, it may be necessary to reduce the dosage and bring the patient up to maintenance dosing using an established build-up protocol.

**Changing from non-stabilized to human serum albumin (HSA) stabilized diluents:** Allergenic extracts prepared with diluents containing HSA and 0.4% phenol are more stable than those prepared with diluents that do not contain stabilizers. When switching from a non-stabilized to an HSA-stabilized diluent, consider lowering the dose for immunotherapy.

### **3 DOSAGE FORMS AND STRENGTHS**

Standardized Bermuda Grass Pollen Allergenic Extract solution is available only at 10,000 Bioequivalent Allergy Units (BAU)/milliliter.

Other Standardized Grass Pollen Allergenic Extract solutions are available as stock concentrates at 10,000 and 100,000 BAU/milliliter.

### **4 CONTRAINDICATIONS**

Standardized Grass Pollen Allergenic Extracts are contraindicated in patients with:

- Severe, unstable or uncontrolled asthma
- History of any severe systemic allergic reaction or any severe local reaction to subcutaneous allergen immunotherapy



## 5 WARNINGS AND PRECAUTIONS

### 5.1 Serious Systemic Adverse Reactions

Serious systemic adverse reactions have occurred following the administration of other allergenic extracts and may occur in individuals following the administration of Standardized Grass Pollen Allergenic Extracts in the following situations:

- Extreme sensitivity to grass pollen allergenic extracts
- Receipt of an accelerated immunotherapy build-up schedule (e.g., “rush” immunotherapy)
- Receipt of high doses of grass pollen allergenic extracts or concomitant exposure to similar environmental allergens
- Change from one allergenic lot to another allergenic lot

High-risk patients have had fatal reactions. Consider using more dilute preparations in patients suspected to be at greater risk of systemic allergic reaction [see *Dosage and Administration (2.1)*].

Administer Standardized Grass Pollen Allergenic Extracts in a healthcare setting under the supervision of a physician prepared to manage a severe systemic or a severe local allergic reaction. Observe patients in the office for at least 30 minutes following administration.<sup>1</sup>

### 5.2 Epinephrine

Standardized Grass Pollen Allergenic Extracts 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.

These products 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 Cross-Reactions and Dose Sensitivity**

Since many grass species tend to cross-react, the total allergen content should be considered in determining the maximum maintenance dose of the mixture.

Determine the initial dilution of allergenic extract, starting dose, and progression of dosage based on the patient's history and results of skin tests [see *Dosage and Administration (2.2)*].<sup>2</sup> Strongly positive skin tests can be indicators for potential systemic reactions.

## **6 ADVERSE REACTIONS**

The most common adverse reactions, occurring in 26 to 82% of all patients who receive subcutaneous immunotherapy are local adverse reactions at the injection site (e.g., erythema, itching, swelling, tenderness, pain).<sup>1</sup> Systemic adverse reactions, occurring in 7% of patients who receive subcutaneous immunotherapy,<sup>3</sup> include generalized skin erythema, urticaria, pruritus, angioedema, rhinitis, wheezing, laryngeal edema, and hypotension. These adverse reactions can be fatal.<sup>1</sup>

## **7 DRUG INTERACTIONS**

### **7.1 Antihistamines**

Do not perform skin testing with allergenic extracts within 3 to 10 days of use of first-generation H<sub>1</sub>-histamine receptor blockers (e.g., clemastine, diphenhydramine) and second-generation antihistamines (e.g., loratadine, cetirizine). These products suppress histamine skin test reactions and could mask a positive response.<sup>2</sup>

### **7.2 Topical Corticosteroids and Topical Anesthetics**

Topical corticosteroids can suppress skin reactivity; therefore, discontinue use at the skin test site for 2 to 3 weeks before skin testing. Avoid use of topical local anesthetics at skin test sites as they can suppress flare responses.<sup>2</sup>

### **7.3 Tricyclic Antidepressants**

Tricyclic antidepressants can have potent antihistamine effects that can affect skin testing. If tricyclic medication has been recently discontinued, allow 7 to 14 days before initiating skin testing.<sup>2</sup>

## **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. There are no human or animal

data to establish the presence or absence of Standardized Grass Pollen Allergenic Extracts-associated risks during pregnancy.

## **8.2 Lactation**

### *Risk Summary*

It is not known whether Standardized Grass Pollen Allergenic Extracts are present in human milk. Data are not available to assess the effects of these extracts 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 Standardized Grass Pollen Allergenic Extracts and any potential adverse effects on the breastfed child from the extracts or from the underlying maternal condition.

## **8.4 Pediatric Use**

For use of these products in children younger than 5 years of age, consideration should be given to the patients' ability to comply and cooperate with allergen immunotherapy and the potential for difficulty in communicating with the child regarding systemic reactions.<sup>1</sup>

## **8.5 Geriatric Use**

Data are not available to determine if subjects 65 years of age and older respond differently to allergen immunotherapy than younger subjects.

# **11 DESCRIPTION**

Standardized Grass Pollen Allergenic Extracts include Standardized Bermuda Grass Pollen (*Cynodon dactylon*) at 10,000 BAU/milliliter, 50% glycerin volume/volume, and 0.4% phenol (preservative); and the following grasses at both 10,000 BAU/milliliter and 100,000 BAU/milliliter, 50% glycerin volume/volume, and 0.4% phenol: Standardized Kentucky Blue (June) Grass Pollen (*Poa pratensis*), Standardized Meadow Fescue Grass Pollen (*Festuca elatior*), Standardized Orchard Grass Pollen (*Dactylis glomerata*), Standardized Perennial Rye Grass Pollen (*Lolium perenne*), Standardized Redtop Grass Pollen (*Agrostis alba*), Standardized Sweet Vernal Grass Pollen (*Anthoxanthum odoratum*), and Standardized Timothy Grass Pollen (*Phleum pratense*). Inactive ingredients include 0.25% sodium chloride for isotonicity and 0.25% sodium bicarbonate as a buffer.

Standardized Grass Pollen Allergenic Extracts should be clear light yellow to brownish solutions that are free of particulate matter.

Standardized Grass Pollen Allergenic Extracts are labeled in BAU/milliliter. 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.<sup>4,5,6,7</sup> CBER references which can be diluted 1:5,000,000 to intradermally elicit a 50 millimeter sum of erythema diameter response in highly puncture reactive subjects are assigned 100,000 BAU/milliliter; whereas references diluted 1:500,000 which elicit the same 50 millimeter sum of erythema diameter response are assigned 10,000 BAU/milliliter.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The skin test reaction results from interaction of the introduced allergen and allergen-specific IgE antibodies bound to mast cells, leading to mast cell degranulation and release of histamine, tryptase and other mediators, which results in the formation of the wheal and flare.

The precise mechanisms of action of allergen immunotherapy are not known. Immunologic responses to immunotherapy include changes in allergen-specific IgE levels, allergen-specific IgG levels, and regulatory T cell responses.<sup>1</sup>

## 14 CLINICAL STUDIES

Specific immunotherapy with pollen extracts 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.<sup>8</sup>

## 15 REFERENCES

1. Cox L, Nelson H, Lockey R. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol.* 2011:S1-S55.
2. Bernstein IL, Li JT, Bernstein DI, et al. Allergy diagnostic testing: an updated practice parameter. *Ann Allergy Asthma Immunol.* 2008;100:S1-148.
3. Greenberg MA, Kaufman CR, Gonzalez GE, et al. Late and immediate systemic-allergic reactions to inhalant allergen immunotherapy. *J Allergy Clin Immunol.* 1986;77:865-870.
4. Turkeltaub PC, Rastogi SC, Baer H, et al. 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.
5. ELISA competition assay. Methods of the Allergenic Products Testing Laboratory. Rockville, MD: Laboratory of Immunobiochemistry, Division of Allergenic Products and Parasitology, Center for Biologics Evaluation and Research, Food and Drug Administration; October 1993. (On file)
6. Turkeltaub PC, Rastogi SC. Quantitative intradermal procedure for evaluation of subject sensitivity to standardized allergenic extracts and for assignment of bioequivalent allergy units to reference preparations using the ID<sub>50</sub>EAL method. Rockville, MD: Laboratory of Immunobiochemistry, Division of Allergenic Products and Parasitology, Center for Biologics Evaluation and Research, Food and Drug Administration; November 1994. (On file)
7. Turkeltaub PC. Assignment of bioequivalent allergy units based on biological standardization methods. *Arb Paul Ehrlich Inst Bundesamt Sera Impfstoffe Frankf A M.* 1988;(82):19-40.
8. Implementation of Efficacy Review, Allergenic Extracts, Federal Register 1985; 50: 3082-3288.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

### 16.1 How Supplied

Greer Standardized Grass Pollen Allergenic Extracts and mixes are supplied as stock concentrates at 10,000 BAU/milliliter and 100,000 BAU/milliliter in 50% glycerin for use in percutaneous skin testing, intradermal testing, and subcutaneous immunotherapy. Standardized Grass Pollen Allergenic Extracts are labeled in BAU/milliliter and are provided in 5, 10, and 50 milliliter vials. Note, the total potency of mixes containing standardized grasses may be cumulative.

Standardized Bermuda Grass Pollen Allergenic Extract solution is available only at 10,000 BAU/milliliter.

Greer Standardized Grass Pollen Allergenic Extracts and mixes are supplied as follows:

<b>Standardized Bermuda Grass Pollen (<i>Cynodon dactylon</i>)</b>	
<b>NDC Number</b>	<b>Strength/Container</b>
22840-0200-5	10,000 BAU/mL, 5 mL dropper vial for prick (skin) testing
22840-0200-2	10,000 BAU/mL, 10 mL multiple-dose vials
22840-0200-4	10,000 BAU/mL, 50 mL multiple-dose vials
<b>Standardized Bluegrass, Kentucky (June) Grass Pollen (<i>Poa pratensis</i>)</b>	
<b>NDC Number</b>	<b>Strength/Container</b>
22840-0201-5	10,000 BAU/mL, 5 mL dropper vial for prick (skin) testing
22840-0201-2	10,000 BAU/mL, 10 mL multiple-dose vials
22840-0201-4	10,000 BAU/mL, 50 mL multiple-dose vials
22840-0202-5	100,000 BAU/mL, 5 mL dropper vial for prick (skin) testing
22840-0202-2	100,000 BAU/mL, 10 mL multiple-dose vials
22840-0202-4	100,000 BAU/mL, 50 mL multiple-dose vials
<b>Standardized Meadow Fescue Grass Pollen (<i>Festuca elatior</i>)</b>	
<b>NDC Number</b>	<b>Strength/Container</b>
22840-0203-5	10,000 BAU/mL, 5 mL dropper vial for prick (skin) testing
22840-0203-2	10,000 BAU/mL, 10 mL multiple-dose vials
22840-0203-4	10,000 BAU/mL, 50 mL multiple-dose vials
22840-0204-5	100,000 BAU/mL, 5 mL dropper vial for prick (skin) testing
22840-0204-2	100,000 BAU/mL, 10 mL multiple-dose vials
22840-0204-4	100,000 BAU/mL, 50 mL multiple-dose vials
<b>Standardized Orchard Grass Pollen (<i>Dactylis glomerata</i>)</b>	
<b>NDC Number</b>	<b>Strength/Container</b>

22840-0205-5	10,000 BAU/mL, 5 mL dropper vial for prick (skin) testing
22840-0205-2	10,000 BAU/mL, 10 mL multiple-dose vials
22840-0205-4	10,000 BAU/mL, 50 mL multiple-dose vials
22840-0206-5	100,000 BAU/mL, 5 mL dropper vial for prick (skin) testing
22840-0206-2	100,000 BAU/mL, 10 mL multiple-dose vials
22840-0206-4	100,000 BAU/mL, 50 mL multiple-dose vials
<b>Standardized Perennial Rye Grass Pollen (<i>Lolium perenne</i>)</b>	
<b>NDC Number</b>	<b>Strength/Container</b>
22840-0209-5	10,000 BAU/mL, 5 mL dropper vial for prick (skin) testing
22840-0209-2	10,000 BAU/mL, 10 mL multiple-dose vials
22840-0209-4	10,000 BAU/mL, 50 mL multiple-dose vials
22840-0210-5	100,000 BAU/mL, 5 mL dropper vial for prick (skin) testing
22840-0210-2	100,000 BAU/mL, 10 mL multiple-dose vials
22840-0210-4	100,000 BAU/mL, 50 mL multiple-dose vials
<b>Standardized Redtop Grass Pollen (<i>Agrostis alba</i>)</b>	
<b>NDC Number</b>	<b>Strength/Container</b>
22840-0207-5	10,000 BAU/mL, 5 mL dropper vial for prick (skin) testing
22840-0207-2	10,000 BAU/mL, 10 mL multiple-dose vials
22840-0207-4	10,000 BAU/mL, 50 mL multiple-dose vials
22840-0208-5	100,000 BAU/mL, 5 mL dropper vial for prick (skin) testing
22840-0208-2	100,000 BAU/mL, 10 mL multiple-dose vials
22840-0208-4	100,000 BAU/mL, 50 mL multiple-dose vials
<b>Standardized Sweet Vernal Grass Pollen (<i>Anthoxanthum odoratum</i>)</b>	
<b>NDC Number</b>	<b>Strength/Container</b>
22840-0211-5	10,000 BAU/mL, 5 mL dropper vial for prick (skin) testing
22840-0211-2	10,000 BAU/mL, 10 mL multiple-dose vials
22840-0211-4	10,000 BAU/mL, 50 mL multiple-dose vials
22840-0212-5	100,000 BAU/mL, 5 mL dropper vial for prick (skin) testing
22840-0212-2	100,000 BAU/mL, 10 mL multiple-dose vials
22840-0212-4	100,000 BAU/mL, 50 mL multiple-dose vials
<b>Standardized Timothy Grass Pollen (<i>Phelum pratense</i>)</b>	
<b>NDC Number</b>	<b>Strength/Container</b>
22840-0213-5	10,000 BAU/mL, 5 mL dropper vial for prick (skin) testing

22840-0213-2	10,000 BAU/mL, 10 mL multiple-dose vials
22840-0213-4	10,000 BAU/mL, 50 mL multiple-dose vials
22840-0214-5	100,000 BAU/mL, 5 mL dropper vial for prick (skin) testing
22840-0214-2	100,000 BAU/mL, 10 mL multiple-dose vials
22840-0214-4	100,000 BAU/mL, 50 mL multiple-dose vials
<b>Standardized Timothy - Orchard Grass Pollen Mix (equal parts mix)</b>	
<b>NDC Number</b>	<b>Strength/Container</b>
22840-0226-2	10,000 BAU/mL, 10 mL multiple-dose vials
22840-0215-5	100,000 BAU/mL, 5 mL dropper vial for prick (skin) testing
22840-0215-2	100,000 BAU/mL, 10 mL multiple-dose vials
22840-0215-4	100,000 BAU/mL, 50 mL multiple-dose vials
<b>Standardized K-O-T Grass Pollen Mix (equal parts mix of Kentucky, Orchard, and Timothy pollens)</b>	
<b>NDC Number</b>	<b>Strength/Container</b>
22840-0216-5	10,000 BAU/mL, 5 mL dropper vial for prick (skin) testing
22840-0216-2	10,000 BAU/mL, 10 mL multiple-dose vials
22840-0216-4	10,000 BAU/mL, 50 mL multiple-dose vials
22840-0217-5	100,000 BAU/mL, 5 mL dropper vial for prick (skin) testing
22840-0217-2	100,000 BAU/mL, 10 mL multiple-dose vials
22840-0217-4	100,000 BAU/mL, 50 mL multiple-dose vials
<b>Standardized K-O-R-T Grass Pollen Mix (equal parts mix of Kentucky, Orchard, Redtop, and Timothy pollens)</b>	
<b>NDC Number</b>	<b>Strength/Container</b>
22840-0218-5	10,000 BAU/mL, 5 mL dropper vial for prick (skin) testing
22840-0218-2	10,000 BAU/mL, 10 mL multiple-dose vials
22840-0218-4	10,000 BAU/mL, 50 mL multiple-dose vials
22840-0219-5	100,000 BAU/mL, 5 mL dropper vial for prick (skin) testing
22840-0219-2	100,000 BAU/mL, 10 mL multiple-dose vials
22840-0219-4	100,000 BAU/mL, 50 mL multiple-dose vials
<b>Standardized K-O-R-T &amp; Sweet Vernal Grass Pollen Mix (equal parts mix of Kentucky, Orchard, Redtop, Timothy and Sweet Vernal pollens)</b>	
<b>NDC Number</b>	<b>Strength/Container</b>
22840-0220-5	10,000 BAU/mL, 5 mL dropper vial for prick (skin) testing
22840-0220-2	10,000 BAU/mL, 10 mL multiple-dose vials

22840-0220-4	10,000 BAU/mL, 50 mL multiple-dose vials
22840-0221-5	100,000 BAU/mL, 5 mL dropper vial for prick (skin) testing
22840-0221-2	100,000 BAU/mL, 10 mL multiple-dose vials
22840-0221-4	100,000 BAU/mL, 50 mL multiple-dose vials
<b>Standardized 7 Grass Pollen Mix (equal parts mix of Kentucky, Meadow Fescue, Orchard, Perennial Ryegrass, Redtop, Sweet Vernal and Timothy pollens)</b>	
<b>NDC Number</b>	<b>Strength/Container</b>
22840-0222-5	10,000 BAU/mL, 5 mL dropper vial for prick (skin) testing
22840-0222-2	10,000 BAU/mL, 10 mL multiple-dose vials
22840-0222-4	10,000 BAU/mL, 50 mL multiple-dose vials
22840-0223-5	100,000 BAU/mL, 5 mL dropper vial for prick (skin) testing
22840-0223-2	100,000 BAU/mL, 10 mL multiple-dose vials
22840-0223-4	100,000 BAU/mL, 50 mL multiple-dose vials
<b>Standardized T-O-S Grass Pollen Mix (equal parts mix of Timothy, Orchard and Sweet Vernal pollens)</b>	
<b>NDC Number</b>	<b>Strength/Container</b>
22840-0224-5	10,000 BAU/mL, 5 mL dropper vial for prick (skin) testing
22840-0227-5	100,000 BAU/mL, 5 mL dropper vial for prick (skin) testing
22840-0227-2	100,000 BAU/mL, 10 mL multiple-dose vials
22840-0227-4	100,000 BAU/mL, 50 mL multiple-dose vials
<b>9 Southern Grass Pollen Mix [equal parts mix of 10,000 BAU/mL Bermuda and 100,000 BAU/mL each Kentucky, Meadow Fescue, Orchard, Perennial Rye, Redtop, Sweet Vernal, Timothy pollens and non-standardized Johnson Grass (<i>Sorghum halpense</i>) pollen extract]</b>	
<b>NDC Number</b>	<b>Strength/Container</b>
22840-0225-5	Concentrate, 5 mL dropper vial for prick (skin) testing
22840-0225-2	Concentrate, 10 mL multiple-dose vials
22840-0225-4	Concentrate, 50 mL multiple-dose vials

## 16.2 Storage and Handling

Maintain at 2 to 8°C (36 to 46°F) during storage and use.

Dilutions of concentrated extract result in a glycerin content of less than 50%, which can result in reduced stability. Extract dilutions at 1:100 volume/volume of the 10,000 BAU/milliliter or 100,000 BAU/milliliter should be kept no longer than a month, and more dilute solutions no more than a week. The potency of a dilution can be checked by skin test comparison to a fresh dilution of the extract on a known grass-allergic patient.



## **17 PATIENT COUNSELING INFORMATION**

Instruct patient to remain under observation in the office for 30 minutes or longer after an injection.

Caution patient that reactions can occur more than 30 minutes after skin testing or an injection.

Instruct patient to recognize the following symptoms as adverse reactions and to immediately return to the office or immediately seek other medical attention if any of these symptoms occur following skin testing or an injection:

- Unusual swelling and/or tenderness at the injection site
- Hives or itching of the skin
- Swelling of face and/or mouth
- Sneezing, coughing or wheezing
- Shortness of breath
- Nausea
- Dizziness or faintness

Manufacturer:

U.S. License No. 308

GREER Laboratories, Inc.

Lenoir, NC 28645 U.S.A