Standardized Grass Pollen Extracts are labeled in Bioequivalent Allergy Units (BAU/mL). Standardized Grass Pollen Extracts labeled in BAUM are not interchangeable with Grass Pollen Extracts labeled in AUM. Reference BALU is not standardized for 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.9-12 CBER references which can be diluted 15,000,000 to intradermally elicited a 50 mm of erythema diameter response in highly puncture reactive subjects are assigned 100,000 BAU/mL, whereas references diluted 1,500,000 which elicited the same 50 mm 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 antigen - histamine and other mediators are released. IgE antibodies have been shown to correlate with atopic diseases such as allergic rhinitis and allergic asthma.8,9 In the skin these mediators are responsible for the classic symptoms seen upon antigen specific extract skin testing in persons with the specific allergy.9,11

Puncture test results with eight US reference extracts at 10,000 BAU/mL (15 grasses or antigenic extracts per extract) are shown in Table I. For the eight grass pollens, there was a mean sum of diameter of wheat of 15.2 mm (SD = 1.8) and a mean sum of diameter of erythema of 8.4 mm (SD = 5.8).

### Table I

<table>
<thead>
<tr>
<th>Pollen</th>
<th>Reference</th>
<th>Sum of Wheat (mm)</th>
<th>Puncture</th>
<th>Sum of Erythema (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bermuda</td>
<td>15.7</td>
<td>39.3</td>
<td>43.2</td>
<td>123.0</td>
</tr>
<tr>
<td>Kentucky Blue/Linseed</td>
<td>15.9</td>
<td>7.6 - 28</td>
<td>77.3</td>
<td>47.4 - 107</td>
</tr>
<tr>
<td>Meadow Fescue</td>
<td>15.9</td>
<td>7.6 - 28</td>
<td>81.1</td>
<td>57.0 - 111</td>
</tr>
<tr>
<td>Orach</td>
<td>14.1</td>
<td>9.1 - 19</td>
<td>84.3</td>
<td>57.1 - 111</td>
</tr>
<tr>
<td>Perennial Ry</td>
<td>17.5</td>
<td>9.1 - 19</td>
<td>92.3</td>
<td>73.1 - 123</td>
</tr>
<tr>
<td>Redtop</td>
<td>14.1</td>
<td>9.1 - 19</td>
<td>77.1</td>
<td>42.4 - 98</td>
</tr>
<tr>
<td>Sweet Vernal</td>
<td>15.7</td>
<td>8.3 - 30</td>
<td>81.2</td>
<td>25.0 - 123</td>
</tr>
<tr>
<td>Timothy</td>
<td>16.9</td>
<td>8.3</td>
<td>88.3</td>
<td>51.0 - 109</td>
</tr>
</tbody>
</table>

Intradermal skin tests with eight U.S. reference extracts (Table I) in highly puncture reactive subjects (Table I) 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 dosage was as low as 0.003 BAU/mL, for one grass to 0.002 BAU/mL, for several others. Conversely, dosages of 0.1 to 1.9 BAU/mL were calculated to yield the same reaction in the least-sensitive subjects.

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.10 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 antigens.11 Other changes following immunotherapy have been noted including development of anti-idiotypic antibodies, a decrease in blood basophil sensitivity to allergen, a decrease in lymphocyte proliferation 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.
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. \(^{(10)}\) \(^{(11)}\) Extracts at 10,000 BAU/mL are indicated for use in scratch, prick, or puncture skin text 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 indifferent to scratch, prick, or puncture test 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. \(^{(16)}\) \(^{(17)}\) 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 (extracts indicated if a higher dose is needed). (See DOSAGE AND ADMINISTRATION)

STANDARDIZED GRASS POLLEN EXTRACTS LABELED IN BAU/mL ARE NOT CONSIDERED DILUTABLE. GRASS POLLEN EXTRACTS LABELED IN ALU/mL OR WITH NONSTANDARDIZED GRASS POLLEN EXTRACTS. The above recommendations 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 antigen. (See WARNINGS and PRECAUTIONS).

Allergic 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 disorder. 

General contraindications include:

EXTREME SENSITIVITY TO THE SPECIFIC ALLERGEN - Determined from previous diagnosis 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 systemic reactions including death in extremely sensitive patients. Most reactions occur within 20 minutes after injection, but may occur later. \(^{(18)}\) To minimize the potential for local or systemic reactions, the relative sensitivity of the patient must be assessed from the history, clinical evaluation, and skin test reactivity. 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.

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

- **severe symptoms of rhinitis and/or asthma**
- **infection or fever accompanied by fever**
- **exposure to excessive amounts of clinically relevant allergens prior to a scheduled injection**
- **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/mL 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 mixes may be the same. This reduction in dosage may be necessary: 1) due to the previously used extract having lost potency during storage, 2) to the dose indicated by the APAC test, or 3) due to the different strength or potency of extracts marketed by different companies. The information about nonstandardized extracts shown in Table III 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 the side-by-side comparison with the previously used nonstandardized extract. The availability of 10,000 BAU/mL and 100,000 BAU/mL does is intended to facilitate safe switching by providing the physician access to lower and higher dosages.

Patients receiving beta blocker drugs may not be responsive to beta agonist drugs used to treat anaphylaxis. The risks of anaphylaxis in these patients should be carefully weighed against the benefits of immunotherapy. (See PRECAUTIONS and ADVERSE REACTIONS)

INFORMATION FOR PATIENTS

Most serious reactions following the administration of allergic 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 monitored, for large local reactions may be indicative of subsequent systemic reactions as doses increase. The patient should be instructed not to use the product for another person to use. The patient should not be resuscitated, and should be subsequently observed.

DRUG INTERACTIONS

Skin test diagnosis with Allergenic Extracts may result in false negative responses when used with 5-10 days of its -blockers such as cetirizine, loratadine, and fexofenadine. The negative effect of antihistamine may last up to 60 days. \(^{(19)}\) These products suppress histamine skin test reactions and could mask a positive result. The suppressive action of other drugs should be considered and the emphasis for a histamine positive control test. Patients receiving beta blocker drugs may not be responsive to beta agonist drugs used to treat anaphylaxis. The risks of anaphylaxis in these patients should be carefully weighed against the benefits of immunotherapy.
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 allergic reactions on the fetus. (30) 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 adverse effect of labor and delivery during pregnancy.

Nursing Mothers
It is not known whether allergic 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:
Since allergic extracts have been studied systematically in various age groups, older children and geriatric patients appear to tolerate injections of allergic extracts well. Children less than five years of age on extract therapy may have a more rapid occurrence of a systemic reaction than adults and therefore require more careful observation and management. (30)

PRECAUTIONS
The use of a histamine positive control is especially recommended in patients who have had previous reactions 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 indentation (wheel) and erythema (flare) responses compared to the appropriate controls. The size of the wheel and flare may be recorded by actual measurements. The largest diameter of the wheel and flare may be recorded, or the sum of the diameters of the largest and the orthogonal (right angle) diameter of wheel flare may be used as in the studies in Tables 3 and 4.

Scratch or Prick-Puncture Skin Testing:
For puncture, prick, or scratch skin tests, 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 test at 100,000. At the higher concentration, some nonspecific positives may occur.

Controls for Scratch, Prick-Puncture Testing: As a positive control, glycine buffered histamine phosphate solution 5 mg/mL (0.18 mg/mL histamine base) or aqueous histamine phosphate 0.275 mg/mL (0.1 mg/mL histamine base) may be used as a positive control. A 50% glycerol solution can be used as the negative control.

Intradermal Skin Testing:
Extracts for intradermal testing must be diluted by the concentric 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 II) indicate that a calculated dose of 0.02 BAU/mL should yield an average size of 5 mm in response to 50 mm of 0.02 BAU/mL, as tested in subjects with similar puncture reactions described in Table I to that specific grass pollen extract. However, in the more sensitive subjects, the dose was as low as 0.0005 BAU for one grass to 0.002 BAU for several others. Conversely, doses of 0.1 to 1.8 BAU/mL were calculated to yield the same reaction in the least sensitive subjects.

Controls for Intradermal Testing: As a positive control, glycine buffered histamine phosphate solution 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% glycerol in 0.9% saline.

a. Patients with a negative scratch or prick-puncture test:
Patients who react consistently to prick-puncture test should be tested intradermally, using a 36 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 wheel and flare reactions are obtained. In the event of systemic reaction, the dosing schedule should be carefully reviewed and if necessary adjusted as outlined above under WARNING.

b. Patients tested only by the intradermal method:
Since highly reactive individuals may react intradermally 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 0.01 BAU/mL dilution. A negative test should be followed by repeat tests using progressively stronger concentrations until the maximum calculated strength of 200 BAU/mL is reached. As a negative control use 0.5% to 1% glycerol solution as a positive control, use glycine buffered histamine phosphate solution 0.5 mg/mL (0.18 mg/mL histamine base) or aqueous histamine phosphate 0.275 mg/mL (0.1 mg/mL histamine base).

7. 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 doses in bovine/avulgar 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 III may be helpful in selecting the initial dose for the side-by-side skin test comparison. Patients being converted from nonstandardized extracts to extracts standardized in BAU can be evaluated by diagnostic skin test 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, the new dose can be selected based on a side-by-side comparison.

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 Tables I and II 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 0.025 BAU/mL solution (0.0005 to 0.0025 BAU/mL dilution) or even less for the extremely sensitive patient. Patients with lesser sensitivity may be given 0.05 mL of a 0.3 BAU/mL solution (0.005 to 0.015 BAU/mL).

The amount of allergic 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 preceding injection. Large local reactions which persist for longer than 24 hours are generally considered an indication for repeating the previous injection. The dose may be increased by 3 to 5 times at any one administration. A steady increase in the amount 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. Dosages larger than those suggested in this monograph in 50% glycerin may cause discomfort upon injection.

Dosages of the allergenic extracts do not vary significantly with the allergen base under treatment.

To prepare dilutions starting from a 100,000 BAU/mL concentrate, proceed as shown in Table IV. The 100,000 BAU/mL concentrate can be made up for injection by adding dilutions of sterile water or a 0.05% to 0.025% glycerol solution. A 100 mL solution may be mixed with 100 mL of 0.05% to 0.025% (w/v) glycerol dilution solution uses 0.5 mL of concentrate for 4.5 mL of sterile diluent with additional dilutions made in the same manner.
REFERENCEs


2. EUSA competition assay. Methods of the Allergenic Products Testing Laboratory, Laboratory of Immunobiology, Department of Allergenic Products and Parasitology, Center for Biologic Evaluation and Research, Food and Drug Administration, 401 Rockville Pike, Rockville, MD 20852-1449, 1994.


30. Data on File - Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, MD.


Manufacturer: Greer Laboratories, Inc., Lenor, NC 28645, USA

L-516 Rev. 3/06

13

14

15