ALLEGRENIC EXTRACT
Standardized Grass Pollen Extract
ALLERMED LABORATORIES, INC.
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U.S. License 467

DESCRIPTION
Standardized grass pollen extract is a sterile solution containing the extractables of grass pollen in 0.25% 135 sodium bicarbonate, 0.125% sodium chloride, 50% glycerol and 0.4% phenol w/v. Standardized grass pollen extracts include Bermuda Grass (Cynodon dactylon), June Grass (Poа pratensis), Meadow Fescue Grass (Festuca elatior), Orchard Grass (Dactylis glomerata), Perennial Rye Grass (Lolium perenne), Redtop Grass (Agrostis alba), Sweet Vernal (Anthoxanthum odoratum) and Timothy Grass (Phleum pratense). The extract may be administered by the scratch, prick, puncture, or intradermal methods of skin testing for diagnostic purposes and subcutaneously for therapeutic purposes as directed under DOSAGE AND ADMINISTRATION.

The potency of standardized grass pollen extracts is expressed in Bioequivalent Allergen Units per mL (BAU/mL) and is determined by an in vitro ELISA Competition Assay comparing the extract to a U.S. reference grass pollen extract, which has been accepted as the standard of reference. Physicians not familiar with the U.S. Reference may refer to Table 3 as a guide (see CLINICAL PHARMACOLOGY). Extracts labeled in BAU/mL are not directly interchangeable with any other grass pollen preparations.

Patients receiving beta-blocking drugs may be refractory to the usual dose of epinephrine, in the event that epinephrine is required to control an adverse allergic reaction to this product. Caution must be exercised in testing and treating patients with steroid-dependent or labe allergy. This product should never be injected intravenously. See also WARNINGS and ADVERSE REACTIONS below. Serious adverse reactions to this product should be reported to VAERS at 1-800-822-7967 or www.vaers.hhs.gov.

Table 2. Calculated intradermal dose of CBER reference grass pollen extracts to elicit 50 mm sum of erythema.*

<table>
<thead>
<tr>
<th>RECIPIENT POLLEN</th>
<th>FDA LOT</th>
<th>BAU/mL</th>
<th>MEAN†</th>
<th>RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bermuda</td>
<td>E4-Ber</td>
<td>0.02</td>
<td>0.4</td>
<td>0.003</td>
</tr>
<tr>
<td>June E3-JkB</td>
<td>0.02</td>
<td>0.1</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Meadow Fescue E4-MF</td>
<td>0.02</td>
<td>0.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orchard</td>
<td>E4-Or</td>
<td>0.02</td>
<td>0.19</td>
<td>0.002</td>
</tr>
<tr>
<td>Perennial Rye E10-Rye</td>
<td>0.02</td>
<td>0.7</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Redtop E4-RE</td>
<td>0.02</td>
<td>0.8</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>Sweet Vernal E4-SV</td>
<td>0.02</td>
<td>1.0</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Timothy</td>
<td>E5-Ti</td>
<td>0.02</td>
<td>0.6</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Sum of the largest and orthogonal diameters.
†0.02 BAU/mL = 1:500,000 v/v dilution of 10,000 BAU/mL extract and 1:5,000,000 v/v dilution of 100,000 BAU/mL extract.

Table 3 includes potency data for two lots each of non-standardized 1:10 w/v glycerinated extract manufactured and distributed by Allermed. The data show two lots of Bermuda Grass Pollen Extract were more potent than the CBER 10,000 BAU/mL Bermuda Grass Pollen reference extract; two lots of Meadow Fescue Grass Pollen Extract, two lots of Perennial Rye Grass Pollen Extract, one lot of Redtop Grass Pollen Extract and one lot of Timothy Grass Pollen Extract were more potent than the respective 100,000 BAU/mL CBER reference extracts; and two lots of June Grass Pollen Extract, two lots of Orchard Grass Pollen Extract, two lots of Sweet Vernal Grass Pollen Extract and one lot of Redtop Grass Pollen Extract were equivalent to the CBER 100,000 BAU/mL reference extracts.

Table 3. Estimated BAU/mL of non-standardized 1:10 w/v glycerinated grass pollen extracts manufactured and distributed by Allermed.

<table>
<thead>
<tr>
<th>EXTRACT</th>
<th>BAU/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bermuda</td>
<td>21,400 - 22,300</td>
</tr>
<tr>
<td>Perennial Rye</td>
<td>183,000 - 205,000</td>
</tr>
<tr>
<td>Meadow Fescue E4-MF</td>
<td>136,000 - 234,000</td>
</tr>
<tr>
<td>Orchard E4-Or</td>
<td>153,000 - 244,000</td>
</tr>
<tr>
<td>Sweet Vernal</td>
<td>76,000 - 76,000</td>
</tr>
<tr>
<td>Timothy E5-Ti</td>
<td>111,000 - 148,000</td>
</tr>
</tbody>
</table>

Note: Relative potency compared to the U.S. Reference with a potency of 1.0. The U.S. Reference for Bermuda Grass is 10,000 BAU/mL (range: 6,900 – 14,310 BAU/mL). The U.S. References for other grasses are 100,000 BAU/mL (range: 69,000 – 143,000 BAU/mL).

INDICATIONS AND USAGE
Standardized grass pollen extract is indicated for use in the diagnosis of grass allergy in patients with a history of allergic symptoms that occur during grass pollination. Skin tests with standardized grass pollen extract should be done first by the puncture method using 10,000 BAU/mL extract. If these tests are negative, they may be repeated by the puncture method with 100,000 BAU/mL extract, or by the intradermal method using an appropriate dilution (see DOSAGE AND ADMINISTRATION). The extract also is indicated for use in the treatment of allergic symptoms by immunotherapy in patients with a history of grass pollen allergy and established sensitivity to grass pollen extract by skin testing. The availability of 10,000 and 100,000 BAU/mL extract facilitates safe switching to standardized grass pollen extracts. Previously untreated patients should be initially treated with appropriately diluted 10,000 BAU/mL. If tolerated, higher doses may be indicated. The use of grass pollen extract for the above purposes should be made only by physicians with special familiarity and knowledge of allergy as described in a standard allergy textbook (13).

Allermed's standardized grass pollen extracts labeled in BAU/mL are not interchangeable with alumn-precipitated grass pollen extracts, grass pollen extracts labeled in ALU/mL, or non-standardized grass pollen extracts.

CONTRAINDICATIONS
Immunotherapy should not be started in patients until a specific diagnosis of Type I allergy to the specific lot of standardized grass pollen has been made from the patient's history and from a positive skin test to grass pollen extract. Other contraindications include:

EXTREME SENSITIVITY TO GRASS POLLEN: Patients who experience serious adverse reactions to a specific lot of standardized grass pollen extract should be protected from further exposure to the product.

AUTOIMMUNE DISEASE: Individuals with autoimmune disease may be at risk, due to the possibility of routine immunizations exacerbating symptoms of the underlying disease.

MYOCARDIAL INFARCTION: Patients who have experienced a recent myocardial infarction may not be able to tolerate adverse reactions resulting from skin testing or immunotherapy. The benefit-to-risk ratio must be carefully evaluated in these patients.

CHILDREN WITH NEPHROTIC SYNDROME: Children with nephrotic syndrome require careful consideration of the benefits and risks of immunotherapy due to a variety of seemingly unrelated events that may cause an exacerbation of nephrotic disease.

BLEEDING DIATHESIS: Injections of grass pollen extract should not be administered in the presence of diseases characterized by a bleeding diathesis.

WARNINGS
Standardized grass pollen extract must be diluted prior to first use on a patient for immunotherapy or intradermal testing (see DOSAGE AND ADMINISTRATION). Grass pollen extract is manufactured to assure high potency and has the ability to cause serious local and systemic reactions, including death, in allergic patients (14). Patients should be informed of this risk and precautions should be discussed prior to initiating skin testing and immunotherapy (see PRECAUTIONS).

The use of grass pollen extract should be temporarily withheld from a patient if any of the following conditions exist: (a) severe symptoms of rhinitis and/or asthma; (b) infection or flu conditions exist; (a) exposure to excessive amounts of grass pollen allergen prior to a medical procedure; (b) fever; (c) exposure to excessive amounts of grass pollen allergen prior to a procedure; (d) elevation of blocking IgA/IgG antibodies in secretions, (d) reduced basophil cell responsiveness to allergens (8). There is evidence that symptoms are effectively altered only by the administration of the relevant allergen (9,10,11).

The results shown in Table 1 were observed with 10,000 BAU/mL reference extract administered to 15 high sensitive grass allergic persons by the puncture method (data on file at FDA). The intradermal doses (BAU/mL) of grass pollen extracts required to elicit 50 mm sum of erythema are shown in Table 2 (12).

Table 1. Puncture data (bicurated needle) with 10,000 BAU/mL reference grass pollen extracts.

<table>
<thead>
<tr>
<th>REFERENCE POLLEN</th>
<th>FDA LOT</th>
<th>N</th>
<th>PEE (mm)</th>
<th>MEAN</th>
<th>RANGE</th>
<th>PESW (mm)</th>
<th>MEAN</th>
<th>RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bermuda</td>
<td>E4-Ber</td>
<td>15</td>
<td>90.3</td>
<td>43 - 123</td>
<td>15.7</td>
<td>7 - 31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>June E3-JkB</td>
<td>15</td>
<td>77.3</td>
<td>47 - 107</td>
<td>15.9</td>
<td>6 - 28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meadow Fescue E4-MF</td>
<td>15</td>
<td>81.1</td>
<td>57 - 111</td>
<td>15.9</td>
<td>6 - 28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orchard</td>
<td>E4-Or</td>
<td>15</td>
<td>84.3</td>
<td>57 - 111</td>
<td>14.1</td>
<td>9 - 19</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perennial Rye E10-Rye</td>
<td>15</td>
<td>92.3</td>
<td>73 - 135</td>
<td>17.5</td>
<td>6 - 36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Redtop E4-RE</td>
<td>15</td>
<td>77.7</td>
<td>42 - 91</td>
<td>14.9</td>
<td>8 - 19</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweet Vernal E4-SV</td>
<td>15</td>
<td>81.2</td>
<td>28 - 123</td>
<td>15.7</td>
<td>8 - 30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timothy</td>
<td>E5-Ti</td>
<td>15</td>
<td>88.3</td>
<td>51 - 109</td>
<td>16.9</td>
<td>8 - 40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PEE = Sum of erythema of the longest and orthogonal diameters. PESW = Sum of edema (wheat) of the longest and orthogonal diameters.

Table 2. Calculated intradermal dose of CBER reference grass pollen extracts to elicit 50 mm sum of erythema.*
When switching from alun precipitated grass pollen extract to standardized grass pollen extract, the patient should be managed as a new patient coming under treatment for the first time.

PRECAUTIONS
GENERAL: The risk of a severe allergic reaction usually can be reduced by eliciting the patient's allergy history and by percutaneous testing by the scratch, prick or puncture method. If a scratch, prick or puncture test is not performed, the patient should be observed for at least 20 minutes. The patient also should be instructed to report any unusual reactions to the physician, such as swelling and/or tenderness at the injection site or rhinorrhea, sneezing, coughing, wheezing, shortness of breath, nausea, dizziness or faintness following the injection of allergenic extract.

SYSTEMIC REACTIONS may occur as a result of immunotherapy. The risk can be reduced by adherence to a careful injection schedule, which starts with a low concentration of extract and is increased slowly. The physician must be prepared to treat anaphylaxis should it occur and to have available the necessary drugs and equipment on hand to treat serious adverse reactions. Extracts should not be administered by the patient or by other individuals who are not prepared to treat anaphylaxis, should it occur.

Local reaction may occur with anaphylaxis to grass pollen immunotherapy. It must not be given intravenously. A separate sterile tuberculin syringe graduated in 0.1 mL should be used for each injection.

INFORMATION FOR PATIENTS: Because the most serious reactions occur within 20 minutes after the injection of allergenic extract, the patient should remain on observation for at least this length of time. The patient also should be instructed to report any unusual reactions to the physician, such as swelling and/or tenderness at the injection site or rhinorrhea, sneezing, coughing, wheezing, shortness of breath, nausea, dizziness or faintness following the injection of allergenic extract.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Long term studies in animals have not been conducted with standardized grass pollen extract to determine the potential for carcinogenicity, mutagenicity or impairment of fertility.

PREGNANCY CATEGORY C: Animal reproduction studies have not been conducted with standardized grass pollen extract. It is also not known whether standardized grass pollen extract can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Caution should be exercised in treating pregnant females, because a systemic reaction might conceivably cause uterine muscle contractions leading to abortion. Standardized grass pollen extract should be given to a pregnant woman only if the benefit outweighs the risk.

Standardized grass pollen extract should be given to a pregnant woman only if the benefit outweighs the risk. It is also not known whether standardized grass pollen extract is excreted in human milk. Because many drugs are excreted in human milk, breastfeeding mothers should be informed of the possible effects on the nursing infant.

The dose of allergenic extract recommended for children is the same as for adults. Allergenic extract is not recommended for initial treatment in children. In this case, it may be advisable to modify the dose and frequency of injections, so that the discomfort is minimized.

NURSING MOTHERS: It is not known whether standardized grass pollen extract is excreted in human milk. Because many drugs are excreted in human milk, breastfeeding mothers should be informed of the possible effects on the nursing infant.

DRUG INTERACTION: Antihistamines and hydroxyzine can inhibit the immediate skin test reaction. Patients receiving such therapy may delay skin testing until complete recovery from the antihistamine therapy has occurred. Epinephrine tablets, in the event epinephrine is required to treat an adverse allergic reaction, should be freely available for at least several hours. Beta-blocking drugs may make a patient refractory to the usual dose of epinephrine, in the event epinephrine is required to treat an adverse allergic reaction. Beta-blocking drugs may make a patient refractory to the usual dose of epinephrine.

ADVERSE REACTIONS
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.

Adverse systemic reactions usually occur within minutes and consist primarily of allergic symptoms such as generalized skin erythema, urticaria, pruritus, angioedema, rhinitis, wheezing, laryngeal edema and hypotension. Less common, nausea, emesis, abdominal cramps, diarrhea and uterine contractions may occur.

Severe reactions may cause shock and loss of consciousness to patients with a history of serum sickness. The treatment of systemic allergic reactions is somewhat dependent upon the symptom complex. Epinephrine hydrochloride 1:1000 aqueous, in an adult dose of 0.3 - 0.5 mL (or 0.1 mL per kg for children) administered subcutaneously in the opposite arm is the immediate treatment of choice. A tourniquet should be placed above the site of the injection if the injection was done on the extremities. Antihistamines may offer relief of recurrent urticaria, associated with the use of grass pollen extracts. In patients with marked and prolonged local reactions, steroids may be helpful. Beta-blocking drugs may make a patient refractory to the usual dose of epinephrine, in the event epinephrine is required to treat an adverse allergic reaction.

INTRADERMAL TEST:
An intradermal test should only be performed after a puncture test has been properly administered with a negative result. It is usually safe to initiate intradermal testing with a 1:10,000 v/v dilution of the extract to which a negative puncture test was observed. For example, if a puncture test is done with 10,000 BAU/mL extract and is negative, the initial intradermal test may be performed with 0.05 mL of 10 BAU/mL extract. The dose may be increased to 0.05 mL of 100 BAU/mL extract if the intradermal test with 10 BAU/mL extract is negative.

INJECTIVE USE: The dosage of grass pollen extract administered by subcutaneous injection during immunotherapy is highly individualized and varies according to the patient. In patients who appear to be highly sensitive by history and skin test, the initial dose of the extract should be 0.1 mL of a 0.1% solution. The dose may be increased at each injection, but not more than 50%-100% of the previous amount, and the next increment is governed by the response to the last injection. Local reactions that persist longer than 24 hours are undesirable and any systemic reaction is an indication that the dose should be reduced. If the patient has shown an allergic reaction on previous testing, the dose may not be increased, but doses larger than 0.2 mL of concentrate containing 50% glycerol may be painful due to the glycerol in the extract. The potency of each standardized grass pollen in a final mixture should not exceed the potency of any one of the grass included in the mix. Concentrate containing 100,000 BAU/mL should be diluted to 10,000 BAU/mL before being used to prepare final mixtures, or alternatively, the volume of 100,000 BAU/mL extract added to the mixture should be reduced to 1/10 of the dose.

A period of three to five years of injection therapy constitutes an average course of treatment.

Children and geriatric patients appear to tolerate injections of allergic extract well, and no special recommendations need to be made for these groups (see PRECAUTIONS - PEDIATRIC USE).

PREPARING DILUTIONS
To prepare dilutions for intradermal skin tests and therapeutic use, the stock concentrate may be diluted as shown in Table 1. The mixture should be prepared in a diluter or dilution bottle, agitated for at least 2 minutes, and shaken gently just before use. Dilution B is to be used for dilutions of allergenic extract. Because most serious reactions occur within 20 minutes after the injection of allergenic extract, the patient should be managed as a new patient coming under treatment for the first time.

PREPARATION: The patient should be seated in an upright position, as close as possible, and kept in this temperature range during testing.

The expiration date of standardized grass pollen extract is listed on the container label. The extract should be stored at 2 - 8°C, if possible, and kept in this temperature range during office use. Dilutions of the stock concentrate containing less than 50% glycerol are less stable. Loss of such dilutions should be checked by skin testing with equal units of a freshly prepared diluted extract.

REFERENCES


