INSTRUCTIONS FOR THE USE OF SHORT RAGWEED POLLEN AND MIXED SHORT-GIANT RAGWEED POLLEN EXTRACTS IN THE DIAGNOSIS AND TREATMENT OF RAGWEED ALLERGY

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DESCRIPTION

INGREDIENTS — Allergenic extract of short ragweed pollen is a clear, amber-colored solution prepared from the dry, defatted pollen of Ambrosia elatior. The extract contains the water extractables of the pollen, 0.25% sodium chloride, 0.125% sodium bicarbonate, 0.5% phenol and 50% glycerol by volume. Extract of mixed short-giant ragweed has the same appearance as short ragweed pollen extract and contains the same chemical ingredients. It is prepared from equal gram weights of the pollens of Ambrosia elatior and Ambrosia trifida.

STANDARDIZATION — The potency of ragweed pollen extract is based on antigen E, a protein component which is believed to be the most important allergen of short ragweed pollen. Extracts of short ragweed pollen sold in the U.S. must have a minimum antigen E content of 67.5 units per ml for a 1:20 w/v concentrate. Extracts of mixed short-giant ragweed must have a minimum antigen E content of 33.75 units/ml for a 1:20 w/v concentrate. The importance of antigen E in ragweed allergy is based on the following observations:

1. In vitro studies with antigen E have shown that it is the most antigenic component of ragweed pollen allergens causing histamine release from peripheral leukocytes of ragweed sensitive persons (1).
2. The antigen E content of short ragweed pollen extract has been found to correlate with extract potency when measured by skin test response in persons allergic to short ragweed pollen (2).
3. Immunotherapy with antigen E has shown to be comparable effective to whole short ragweed pollen extract in reducing symptoms related to ragweed pollen exposure (3).

The weight by volume shown on the label is a measurement of extract concentration, rather than extract potency. Weight by volume designations may be used to identify dilutions of extract for skin testing and immunotherapy, and are useful from a practical standpoint in identifying the relative strength of a given extract. However, studies have shown that the antigen E content varies in extracts with the same weight by volume concentration (4).

EXPIRATION DATING — Expiring dating is based on the antigen E content of the extract. Extracts containing 100% glycerol by volume have longer dating periods due to the protective effects of glycerol on antigen E (5, 6). The expiration period of aqueous concentrate and saline dilutions of glycerinated concentrate is approximately one-half that of glycerinated extract containing controls (7).

Ragweed extract should be kept at 2°C to 8°C during use and office storage to retain potency. Higher temperatures have an adverse affect on antigen E.

INDICATIONS

Studies have shown that properly performed and interpreted skin tests with ragweed pollen extract are useful in the diagnosis of allergy to ragweed pollen (7, 8, 20, 21). Immunotherapy with the appropriate dosage of short ragweed pollen extract is effective in reducing symptoms of hay fever and asthma resulting from exposure to ragweed pollen (8, 12, 13), and it is believed to be effective with extract of giant ragweed, although carefully controlled studies are unavailable. However, clinical observations and known cross reactivity between short and giant ragweed pollens have led to the practice of using a mixture of the two species for skin testing and treatment (22, 23, 24, 25, 26, 27).

This form of treatment is recommended for patients who cannot avoid exposure to pollen and who do not obtain satisfactory relief of symptoms from other medications, such as antihistamines. Immunologic changes resulting from treatment with short ragweed pollen extract are believed to include:

1. The induction of specific anti-ragweed IgG antibodies commonly referred to as "blocking antibodies" (12, 13).
2. A decrease in the elevation of ragweed specific IgG during and immediately following the ragweed pollen season (14).
3. A reduction of circulating anti-ragweed IgE after long-term immunotherapy (15).
4. A decrease in skin reactivity to the extract (16) and a decrease in leukocyte sensitivity to histamine release (17) after long-term immunotherapy.

CONTRAINDICATIONS

There are no absolute contraindications to the use of ragweed pollen extract in the diagnosis and treatment of ragweed allergy. When used in accordance with the principles and practice of allergy and immunotherapy, the extract is considered safe and effective. Relative contraindications include (1) extreme sensitivity to the extract as demonstrated by previous anaphylaxis following skin testing or subcutaneous injection (2) recent myocardial infarction, and (3) pregnancy (see Precautions #4). The benefit to risk ratio must be evaluated in each of the above situations. Ragweed pollen extract should not be administered to persons who are not sensitive to ragweed pollen.

WARNING

Physicians who elect to administer ragweed pollen extract should be familiar with the clinical use of all ragweed pollen and have the necessary emergency equipment and medication available to treat systemic allergic reactions.

The injection of ragweed pollen extract may cause severe local and/or systemic anaphylactic reactions in some individuals. To minimize this potential hazard, the dosage of antigen E in the patient's initial skin test should be titrated from the allergic history and from clinical observations. Patients should be informed of this risk prior to skin testing and immunotherapy (see adverse reactions).

The dosage must be reduced when starting a patient on fresh standardized (Antigen E) extract or when transferring a patient from non-standardized to standardized extract, even though the labeled strength of the old and new vials may be the same. This is necessary due to a loss of extract potency during storage in the physician's office. The antigen E content of old and new extract must be compared and adjusted by dosage reduction and/or dilution before new extract is administered. The amount of new extract should not exceed one-half the last dose given of the old vial when both extracts contain comparable amounts of antigen E. Any evidence of a local or generalized reaction requires a reduction in dosage during the initial stages of hypersensitization as well as during maintenance therapy.

PRECAUTIONS

1. Extract must be stored at 2°C to 8°C to retain potency. Local or generalized reactions should be observed as closely as possible, since higher temperatures adversely affect the antigen E content of the product. Extract should not be left at room temperature for the purpose of making dilutions or mixing with other allergenic materials, unless precautions are taken to maintain the recommended temperature using special cooling trays or other suitable methods.
2. Extract should be administered with autoclaved or sterile disposable syringes, needles and testing devices, to prevent the transmission of homosexual serum hepatitis and other infectious agents from person to person.
3. Extract may cause local or generalized reactions. Physicians who administer the product should be familiar with the principles and practice of allergy and should have epinephrine HCL 1:1,000, as well as other emergency medication and equipment available to treat anaphylaxis. Persons receiving extract by skin test or by subcutaneous injection for treatment must be instructed to remain in the physician's office for 20 minutes following treatment, and to return immediately to the office if any signs of a generalized allergic reaction occur, including hives, symptoms of hyperventilation, and/or asthma.
4. PREGNANCY CATEGORY C. Ragweed pollen extract Animal reproduction studies have not been conducted with ragweed pollen extract. It is also not known whether ragweed pollen extract can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Ragweed pollen extract should be given to a pregnant woman only if clearly needed.

ADVERSE REACTIONS

LOCAL REACTIONS. The occurrence of a hives to 15 minutes after injection is usually due to leakage of extract into the skin along the needle track. Firm pressure (not rubbing) at the site of injection immediately after withdrawal of the needle will usually prevent this reaction. It does not require a reduction in dosage. A strong local reaction with erythema and edema which persists at the injection site for several hours indicates that too much extract has been given. Failure to note this response may result in a serious generalized reaction. Treatment should be altered as follows:

1. Additional injections should not be given until all evidence of the reaction has disappeared.
2. The dosage should be reduced three levels, e.g., from 0.4 cc to 0.5 cc or the equivalent, and held at that level for two or three treatments.

A second reaction at or near the dose which caused the first local response indicates that a maximum tolerated amount of extract has been reached and no further increases in dosage should be attempted. Maintenance therapy should be continued thereafter at the highest possible non-reacting dose.

SYSTEMIC REACTIONS. Systemic (generalized) reactions may range from a mild exaggeration of the patient's allergic symptoms to hives, anaphylactic shock, or even death from anaphylaxis. Systemic reactions may occur when a previous local reaction is noted or when the extract is accidentally injected intravenously. The reaction usually occurs 5 to 20 minutes after injection. Symptoms may include sneezing, coughing, itching, shortness of breath, abdominal cramps, vomiting, diarrhea, tachycardia, hypotension, respiratory failure in severe cases. The reaction is usually stopped by the subcutaneous injection of epinephrine HCL 1:1,000 (See Overdosage below). The oral administration of antihistamines and the placement of a bronchial or nasal drip are only helpful in the event that additional measures are required, it may be necessary to treat the patient for bronchospasm with inhaled aminophylline, intravenous fluids and corticosteroids; for hypertension with vasopressors, volume repletion, isoproterenol and dopamine; for hypoglycemia with oxygen and tracheostomy and for cardiac arrest with cardiopulmonary resuscitation and other appropriate measures.

DOSAGE AND ADMINISTRATION

DIAGNOSIS. If the extract supplied in this package is considered product (w/v 1:20), it should not be used for intradermal testing. Concentrated extract may be used for scratch or prick testing providing the patient is not exposed to high levels of ragweed pollen and experiencing prominent symptoms of hay fever or asthma at the time of testing. Extract for intradermal testing must be diluted to a strength of 0.25 units of antigen E per ml (7). Skin tests should not be performed if the patient has taken antihistamines within 24 hours prior to testing.
PROCEDURES
Scratch Test: 1 drop of extract concentrate applied to a small scratch or a scarification on the outer surface of the forearm or the flat aspect of the back.
Prick Test: 1 drop of extract concentrate applied to the unbroken skin of the forearm or the back followed by prickling the skin under the drop.

Intradermal Test: 0.05 ml of extract containing 0.25 antigen E units per ml given intradermally on the outer surface of the forearm or outer aspect of the upper arm. This test should not be performed unless the patient is negative to a properly administered and interpreted scratch or prick test.

SUGGESTED DOSAGE SCHEDULE FOR RAGWEED EXTRACT BASED ON ANTIGEN E CONCENTRATION (parts per ml)

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Note: Do not exceed a dose of 0.2 ml if the extract being administered contains 50% glycerol by volume.

Studies (10, 11) have shown that the accumulated pre-seasonal dose of short ragweed pollen extract should be in the range of 250 to 1000 units of antigen E to effectively reduce ragweed-related symptoms (3, 19). This dosage of antigen E is contained in 2.5 ml to 10.0 ml of extract containing 100 antigen E units/ml. Treatment with a maximum tolerated dose is recommended for both short ragweed pollen extract and mixed short-grit ragweed extract.

The maintenance dose of ragweed pollen extract is defined as the highest tolerated dose that is consistently well tolerated without undue pain or swelling and which provides maximum relief of symptoms. The intradermal tests may not be performed more than four weeks, since tolerance to the extract may be lost at longer intervals. If the interval exceeds 4 weeks, the dosage should be reduced by one-half for every additional two week period. A reduction in the maintenance dose of pollen extract may be necessary during the ragweed season, due to the overpowering effects of inhaled allergen mixed with injected allergen. As a rule, it is advisable to reduce the dosage by one-half during ragweed pollination and to increase the frequency of injections as needed to provide adequate relief of itching, sneezing, and congestion. The dosage of ragweed pollen extract given to children is the same as the adult dose except for slight modifications due to body size and weight. A child’s dose of 0.2 ml is considered comparable to an adult dose of 0.5 ml of the same dilution. Maintenance injection therapy may be continued for a period of two to three years or longer, depending upon patient tolerance and clinical response.

OVERDOSAGE
A local reaction characterized by erythema and edema that persists for several days or longer is a common recurrence of allergic symptoms following an injection requiring that the dose be reduced. Additional extract should not be given until all evidence of a previous reaction has disappeared.

Severe generalized symptoms or anaphylaxis following injection in the skin are treated immediately with epinephrine HCl 1:1000 as follows: Usually Dosage — Children under 12 years 0.1 to 0.2 cc; persons over 12 years 0.3 to 0.5 cc, repeated, as necessary every 10 to 15 minutes. Intravenous anti­histaminics 0.1 to 0.2 mg hydrocortisone may also be used, but only after sufficient epinephrine has been given. (see Adverse Reaction Systemic).

Immunotherapy after anaphylaxis should only be considered if the probable cause of anaphylaxis can be identified, such as accidental intravenous injection or failure to reduce the dosage after a previous local reaction or during periods of high external exposure to ragweed pollen.

SUPPLIED
Short ragweed pollen extract and mixed short-grit ragweed pollen extract in concentrated form (w/v 1:20) are supplied in 1 ml dropper vials for scratch or prick testing and in 10 ml, and 50 ml vials for bulk use. Concentrations other than 1:20 w/v may be custom ordered.

WARRANTY
Allermed Laboratories, Inc. certifies that allergenic extract prepared within the Laboratories meet the safety and sterility standards of the F.D.A. Because the Laboratories have no control over the conditions under which allergenic extracts are used, the patient is responsible for all results. Should an unexpected reaction occur, such as accidental intravenous injection or failure to reduce the dosage after a previous local reaction or during periods of high external exposure to ragweed pollen, no representation is made concerning the effectiveness of this product. However, the Laboratories will work with the medical practitioner to ensure the patient’s safety.

REFERENCES