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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U.S. Lic. 467

Printed in U.S.A. January, 1982

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 capable of 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 been shown to be comparably effective to whole short ragweed pollen extract in reducing symptoms related to ragweed pollen exposure (3).

The weight by volume value 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 — Expirating dating is based on the antigen E content of the extract. Extracts containing 50% 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 comparable antigen E content.

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 short ragweed pollen (9, 10, 11), 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 IgE 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 accepted principles of skin testing 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 allergenic extracts 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 relative sensitivity of the patient must be assessed 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 given should not exceed one-half the last dose given from the old vial, assuming 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 hyposensitization as well as during maintenance therapy.

PRECAUTIONS

1. Extract must be stored at 2°C to 8°C to retain potency. Storage at this temperature 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 homologous 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 testing or immunotherapy, and to return immediately to the office if any signs of a generalized allergic reaction occur, including hives, symptoms of hay fever, 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 hive 5 to 15 minutes after injection is usually due to leakage of extract into the skin along the needle tract. 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 disppeared.
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 has not been heeded, 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, and 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 tourniquet proximal to the injection site are helpful adjuncts. In the event that additional measures are required, it may be necessary to treat the patient for *bronchospasm* with intravenous aminophylline, intravenous fluids and corticosteroids; for *hypotension* with vasopressors, volume repletion, isoproterenol and corticosteroids; for *laryngeal obstruction* 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 concentrated 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 pronounced 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 antihistamine within 24 hours prior to testing.*

PROCEDURES

Scratch Test: 1 drop of extract concentrate applied to a small scratch or scarification on the volar 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 pricking the skin under the drop.

Intradermal Test: 0.05 ml of extract containing 0.25 antigen E units per ml given intradermally on the volar 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.* A final intradermal test using 0.05 ml of extract containing 2.5 antigen E units per ml may be used to rule out skin sensitivity to ragweed allergen.

INTERPRETATION OF RESULTS

Scratch and Prick Test

A negative test shows only a slight red area at the site of scarification or prick penetration. Positive tests are scored as follows:

1+ Erythema with a 5 mm wheal
2+ Erythema with a 5-10 mm wheal
3+ Erythema with a 10-15 mm wheal
4+ Erythema with a wheal 15 mm (or larger) with pseudopodia

Intradermal Test

A negative test shows no change in the appearance and size of the 5 mm wheal created by the I.D. injection of 0.05 ml of extract. Positive tests are scored as follows:

1+ Erythema 10-20 mm with a 5-10 mm wheal
2+ Erythema 20-30 mm with a 5-10 mm wheal
3+ Erythema 30-40 mm with a 10-15 mm wheal
4+ Erythema greater than 40 mm with a 15 mm wheal (or larger) with pseudopodia

IMMUNOTHERAPY

Concentrated ragweed extract must be diluted before administration to new patients. As a rule, extract containing 0.01 to 0.05 units of antigen E per ml are safe to initiate immunotherapy. An intradermal skin test with the intended starting dose may be done as an additional precaution in evaluating the patient's sensitivity.

Injections should be given subcutaneously in the outer aspect of the upper arm. Care must be taken to avoid injecting the extract into a blood vessel, because of the potential hazard of anaphylaxis. Concentrated extract is usually administered once every two to four weeks at a maximum dose of 0.2 ml. A mild burning sensation immediately following the injection of concentrated extract is due to the glycerol in the extract. It should not be interpreted as an adverse allergic response. A suggested dosage schedule is shown in the Table below.

Patients who have received allergenic extract for maintenance therapy should not be given the same dose from a fresh vial of extract. The antigen E content of ragweed pollen extract varies from lot to lot. Although the potency of fresh extract can be compared with that of previously administered product and adjusted accordingly, it is advisable to reduce the dosage of fresh extract to one-half the amount given from a previous lot. The antigen E content of ragweed pollen extract diminishes during storage and use in the physician's office and, therefore, may be less than that specified on the vial label. In addition, ragweed pollen extract contains other components which may contribute to the overall allergenicity of the product (18).

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

Concentrated extracts (w/v 1:20) of short ragweed pollen usually contain between 100 and 300 units antigen E per ml. Mixed short-giant ragweed pollen extracts contain approximately one-half these values.

AgE Units 0.01/ml frequency twice weekly		AgE Units 0.1/ml frequency twice weekly		AgE Units 1.0/ml frequency once weekly		AgE Units 10/ml frequency once weekly		AgE Units 100/ml frequency every 2-4 weeks	
No.	Ml.	No.	Ml.	No.	Ml.	No.	Ml.	No.	Ml.
1	0.025	1	0.025	1	0.025	1	0.025	1	0.025
2	0.05	2	0.05	2	0.05	2	0.05	2	0.05
3	0.10	3	0.10	3	0.10	3	0.10	3	0.10
4	0.15	4	0.15	4	0.15	4	0.15	4	0.15
5	0.20	5	0.20	5	0.20	5	0.20	5	0.20
6	0.25	6	0.25	6	0.25	6	0.25	6	0.25
7	0.30	7	0.30	7	0.30	7	0.30	7	0.30

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-giant 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 interval between maintenance injections should not exceed 4 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 also may be necessary during the ragweed season, due to the overdosing effects of inhaled allergen combined 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 symptoms. 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 should 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 hours or longer, or a recurrence of allergic symptoms following an injection requires that the dosage be reduced. Additional extract should not be given until all evidence of a previous reaction has disappeared.

Severe generalized symptoms or anaphylaxis following an injection must be treated immediately with epinephrine HCL 1:1000 as follows: *Usual 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 antihistamines and hydrocortisone also may 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-giant 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. Dilutions 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 extract is used, or the purposes intended, neither a good nor bad effect following its administration is warranted.

The users of this product should be aware of the potential dangers involved in the injection of allergenic extract and accept the risk of any consequences resulting from such injections.

No representatives of the Laboratories may change this warranty whether written, oral or implied. The buyer or user must assume full responsibility for the product after it leaves the premises of the Laboratories.

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