INSTRUCTIONS AND DOSAGE SCHEDULE

ALLERGENIC EXTRACT OF RAGWEED POLLEN
(Short Ragweed or Giant and Short Ragweed Mixture)
Amb a 1 Assayed

DESCRIPTION: The sterile Short Ragweed or Giant and Short Ragweed Mix Allergenic Extract in this vial may be supplied for scratch, prick or puncture testing; intradermal testing; treatment; or as a "bulk" extract which is designed primarily for the physician equipped to prepare dilutions and mixtures as required.

Each concentrated lot of Short Ragweed and Giant and Short Ragweed Mix is assayed for Amb a 1 \(^\text{1}\text{a}\) (also known as Antigen E) and submitted to the Center for Biologics Evaluation and Research for official release. The Amb a 1 concentrations for dilutions of extracts greater than 1:20 w/v have been obtained by calculation from the assayed value. The following is a brief description of the three expressions of concentration applied to these extracts.

1. Weight to volume (w:v). The amount of allergenic source material added to the extract. The PNU content of extracts of the same antigen may vary according to the method of measuring the PNU. Thus, the PNU content of extracts from different manufacturers is not comparable unless the PNU method is known to be the same and is reproducible from lot to lot. Also, the amount of protein nitrogen extracted from an antigen is influenced by the same variables as the weight to volume extract. Allergenic materials make up a variable proportion of the total protein of an extract.

2. Protein Nitrogen Units (PNU). One protein nitrogen unit represents 0.00001 mg phosphophatase acid precipitable protein nitrogen dissolved in one ml of antigen extract. The PNU content of extracts of the same antigen may vary according to the method of measuring the PNU. Thus, the PNU content of extracts from different manufacturers is not comparable unless the PNU method is known to be the same and is reproducible from lot to lot. Also, the amount of protein nitrogen extracted from an antigen is influenced by the same variables as the weight to volume extract. Allergenic materials make up a variable proportion of the total protein of an extract.

3. Of the many allergens from Short Ragweed which have been purified and char-

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terized (Amb a 1, Amb a 2\(^\text{1}\text{a}\) also known as Antigen K), Ra-3\(^\text{1}\text{a}\), Ra-4 (BPA-Ra\(^\text{1}\text{a}\)), Ra-5, Ra6, Ra7 and Ra8, and cytochrome C), Amb a 1 is considered the most important and has been selected as the basis for standardization. Extracts of Short Ragweed containing Amb a 1 are diffused in agar against standard anti-serum to Amb a 1, and compared to the diffusion of standard Amb a 1 solutions. The amount of Amb a 1 is expressed as units of Amb a 1 per ml of extract. Amb a 1 units are approximately equal to micrograms previously used to measure Amb a 1 concentration. The Amb a 1 assay therefore provides an absolute measure of extract potency related to the Amb a 1 antigen in Short Ragweed, rather than only an expression of extract strength.

Ingredients: Active ingredients are the allergen(s) noted on the vial label. Preservative is 50% (w/v) glycerin or 0.4% phenol, as indicated on the vial label. Glycerinated extracts contain 0.5% sodium chloride, 0.275% sodium bicarbonate and 50% glycerin (w/v) as a preservative. Non-glycerinated extracts contain 0.5% sodium chloride, 0.275% sodium bicarbonate and 0.4% phenol (w/v) as a preservative.

CLINICAL PHARMACOLOGY: The mechanism by which hypo-sensitization is achieved is not known completely. It has been shown that repeated injections of appropriate allergenic extracts will ameliorate the intensity of allergic symptoms upon contact with the allergens in non-clinical studies which address the efficacy of immunotherapy. The allergens which have been studied are cat, mite, venoms, and some pollen extracts. 8, 15, 16, 17, 18 IgE antibodies bound to receptors on mast cell membranes are required for the allergen, and their level is probably related to serum IgE concentrations. Immunotherapy has been associated with decreased levels of IgE, and allergens in vivo and in vitro reduce IgE levels. The Histamine release response of circulating basophils to a specific allergen is reduced in some patients by hypo-sensitization, but the mechanism of this change is not clear. Further study and clarification of the relationships among changes in blocking antibody, reaginic antibody, and mediator-releasing cells, and between these three factors and successful immunotherapy, is needed.

INDICATIONS AND USAGE: 20, 21, 22, 23 Allergenic extracts are indicated for use in diagnosis and immunotherapy of patients presenting symptoms of allergy (hay fever, rhinitis, etc.) to specific environmental allergens. The selection of allergenic extracts to be used should be based on a thorough and carefully taken history of hypersensitivity, and confirmed by skin testing. 24, 25 The use of mixes of unrelated antigens for skin testing is not recommended, since in the case of a positive reaction, it does not indicate which component of the mix is responsible for the reaction; while, in the case of a negative reaction, it fails to indicate whether the individual antigen would give a positive reaction. Utilization of such mixes for compounding a treatment may result, in the former case, in administering nonallergic antigens and, in the latter case, in the omission of a needed antigen.

Statistically controlled blind studies have demonstrated the effectiveness of therapy with Amb a 1. 24, 25 Double blind studies have demonstrated a greater effectiveness for whole Short Ragweed extract when compared to Amb a 1 alone. 26 Short Ragweed Extracts, standardized on the basis of Amb a 1 extract, would seem to be a logical choice for immunotherapy.

Allergens to which a patient is extremely sensitive should not be included in treatment regimens, the greater dose reduction required. If the patient is intolerant to the injection, the frequency over time, and a fresh extract could have an effective potency that is substantially greater than that of the old extract. Even though it is the same formula and concentration, the first dose from the new vial should not exceed 50% of the previous dose.

IF THE PREVIOUSLY PREPARED WAS FROM ANOTHER MANUFACTURER: Since manufacturing processes and sources of raw materials differ among manufacturers, the interchangeability of extracts from different manufacturers cannot be insured. The starting dose of the extract should therefore be greatly decreased even though the extract is the same formula and dilution. In general, a dose reduction of 50% of the previous product dose should be adequate, but each situation must be evaluated separately according to the patient’s tolerance of sensitivity, tolerance of previous injections, and other factors. If the patient tolerates a 50% decrease, the next dose could be raised to the previous dose amount. If the decrease is greater than 50%, the next dose would need to be determined by the allergist, depending on the situation. Dose levels should not exceed 50% of the previous immunizing dose. See DOSAGE AND ADMINISTRATION.

IF A PROLONGED PERIOD OF TIME HAS ELAPSED SINCE THE LAST INJECTION: Patients may lose tolerance for allergen injections during prolonged periods between doses. The duration of tolerance is an individual characteristic and varies from patient to patient. In general, the longer the lapse in the injection schedule, the greater the re-establishment of sensitivity required. If the interval since last dose is over four weeks, perform skin tests to determine starting dose. See DOSAGE AND ADMINISTRATION.

IF THE PREVIOUS EXTRACT WAS OUTDATED: The dating period for allergenic extracts indicates the time that they can be expected to remain potent under refrigerated storage conditions (2° - 8°C). During a storage period of extracts, even under ideal conditions, some loss of potency occurs. For this reason, extracts should not be used beyond their expiration date. If a patient has been receiving injections of an outdated extract, s/he may experience excessive local or systemic reactions when changed to a new and possibly more potent extract. In general, the longer the material has been outdated, the greater the dose reduction necessary for the fresh extract.

IF CHANGING TO A DIFFERENT LOT OF EXTRACT: All extracts lose potency over time, and a fresh extract could have an effective potency that is substantially greater than that of the old extract. Even though it is the same formula and concentration, the first dose from the new vial should not exceed 50% of the previous dose.

WARNINGS: See WARNINGS box at the beginning of this package insert. See also PRECAUTIONS.

Allergic extracts must be temporarily withheld from patients or the dose adjusted downward if any of the following conditions exist: (1) severe symptoms of rhinitis and/or asthma; (2) infection or flu accompanied by fever; (3) any evidence of an excessively large local or generalized reaction during the initial stages of immunotherapy or during maintenance therapy, and/or (4) exposure to excessive amounts of clinically relevant allergen prior to a scheduled injection.

Do not administer immunotherapy during a period of symptoms due to exposure. Since the individual components of the extract are those to which the patient is allergic, and to which s/he will be exposed, typical allergic symptoms may follow shortly after the injection, particularly while the antigen load from exposure plus the injected antigen exceeds the patient’s antigen tolerance.

THE CONCENTRATE MUST NOT BE INJECTED AT ANY TIME UNLESS TOLERANCE HAS BEEN ESTABLISHED. DILUTE CONCENTRATED EXTRACTS WITH STERILE DILUENT FOR INTRADERMAL TESTING AND IMMUNOTHERAPY.

INJECTIONS MUST NEVER BE GIVEN INTRAVENOUSLY. Subcutaneous injection is recommended in those intravenous or intramuscular injection may produce large local reactions or be excessively painful. AFTER INSERTING NEEDLE SUBCUTANEOUSLY, BUT BEFORE INJECTING, ALWAYS WITHDRAW THE PLUNGER SLIGHTLY. IF BLOOD APPEARS IN THE SYRINGE, CHANGE NEEDLE AND GIVE THE INJECTION IN ANOTHER SITE.

REACTANTS: When the patient previously has been receiving alum-adsorbed or alum-precipitated extract, the safest course is to start over as though the patient had not been receiving immunotherapy. See DOSAGE AND ADMINISTRATION.
ADVERSE REACTIONS

2. Drug Interactions

Patients with cardiovascular diseases and/or pulmonary diseases such as symptomatic unstable, steroid-dependent asthma, and/or those who are receiving cardiovascular drugs such as beta-blockers, may be at higher risk for severe adverse reactions. These patients may also be more refractory to the normal allergy treatment regimen. Patients should be treated only if the benefit of treatment outweighs the risks.\(^2\)

Patients on beta blockers may be more reactive to allergens given for testing or treatment and may be unresponsive to the usual doses of ephedrine used to treat allergic reactions.\(^3\) (See WARNINGS.)

Certain medications may lessen the skin test wheal and erythema responses elicited by allergens and histamine for varying time periods. Conventional antihistamines should be discontinued at least 5 days before skin testing. Long-acting antihistamines should be discontinued for at least 3 weeks prior to skin testing.\(^2\) Topical steroids should be discontinued at the skin test site for at least 2-3 weeks before skin testing.\(^2\) Tricyclic antidepressants such as Doxepin should be withheld for at least 7 days before skin testing.\(^2\) Topical local anesthetics may suppress flare responses and should be avoided in skin test sites.\(^9\)

When using other drugs in patients receiving allergen extracts, always consult the product labeling of the other drugs to determine any possible interaction with use of allergen extracts.

4. Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been conducted with allergen extracts to determine their potential for carcinogenicity, mutagenicity, or impairment of fertility.\(^2\)

5. Pregnancy\(^b\)

Animal reproduction studies have not been conducted with allergen extracts. It is not known whether allergen extracts can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Allergen extracts should be given to a pregnant woman only if clearly needed. The physician must carefully consider the benefit-risk ratio to both patient and fetus, of performing skin testing or continuing immunotherapy during pregnancy. The recommended precautions (See WARNINGS AND PRECAUTIONS) for preventing adverse reactions are especially important in the pregnant patient. Based on the physician’s discretion, immunotherapy maintenance doses may be continued during pregnancy if the patient has not experienced adverse side effects. Immunotherapy is generally not initiated during pregnancy due to the risks associated with systemic reactions and their treatment.\(^2\)

6. Nursing Mothers

There are no current studies on the secretion of allergenic extract components in human milk or their effect on the nursing infant. Because many drugs are excreted in human milk, caution should be exercised when allergenic extracts are administered to a nursing woman.\(^2\)

7. Pediatric Use

Since dosage for children is the same as for adults,\(^2,\)^\(^19,\)^\(^20\) larger volumes of solution may produce excessive discomfort. Therefore, in order to achieve the total dose required, the volume of the dose may need to be divided into more than one injection per visit.

8. Geriatric Use

The reactions from immunotherapy can be expected to be the same in elderly patients as in younger ones. Elderly patients may be more likely to be on medication that could block the effects of immunotherapy or that might be used to treat serious reactions, or they could be more sensitive to the cardiovascular side effect of epinephrine because of pre-existing cardiovascular disease.\(^2\)

ADVERSE REACTIONS

Physicians administering allergen extract testing or treatment materials should be experienced in the treatment of severe systemic reactions. See WARNINGS box at the beginning of this package insert.

1. Local Reactions

Some erythema, swelling, or pruritus at the site of injection are common, the extent varying with the patient. Such reactions should not be considered significant unless they persist for at least 24 hours.

Local reactions (erythema or swelling) which exceed 4-5 cm in diameter are not only uncomfortable, but also indicate the possibility of a systemic reaction if dosage is increased. In such cases the dosage should be reduced to the last level not causing the reaction and maintained at this level for two or three treatments before cautiously increasing again.

Large, persistent local reactions may be treated by local cold, wet dressings and/or the use of oral antihistamines. They should be considered a warning of possible severe systemic reactions and the need for temporarily reduced doses.

A mild burning immediately after the injection is to be expected; this usually subsides in 10 to 20 seconds.

2. Systemic Reactions

With careful attention to dosage and administration, systemic reactions occur infrequently, but it cannot be overemphasized that in sensitive individuals any injection could result in anaphylactic shock. Therefore, it is imperative that physicians administering allergen extracts understand and be prepared for the treatment of severe reactions.

Most severe systemic reactions will begin within a 30 minute time period, but systemic reactions may occur at any time after skin tests or immunotherapy. Symptoms may range from mild to life-threatening (due to anaphylaxis) as described below.

Other possible systemic reaction symptoms which may occur in varying degrees of severity are laryngeal edema, fainting, pallor, bradycardia, hypotension, anaphylactic shock, hypokalemia, convulsions, cyanosis, and urticaria. Adverse reaction frequency data for allergenic extract administration for testing and treatment show that risk is low.\(^2,\)^\(^3\)

If a systemic or anaphylactic reaction does occur, apply a tourniquet above the site of injection and inject 1:1000 epinephrine-hydrochloride intramuscularly into the opposite arm. Leave the tourniquet at least every 10 minutes. Do not obstruct arterial blood flow with the tourniquet.

EPIEPINEPHROLE DOSAGE

ADULT: 0.3 to 0.5 mL should be injected. Repeat in 5 to 10 minutes if necessary. PEDICATRIC: The usual initial dose is 0.01 mg (mL) per kg body weight or 0.3 mg (mL) per square meter of body surface area. Suggested dosage for infants to 2 years of age is 0.1 mL to 0.1 mL; for children 2 to 6 years, 0.15 mL; and children 6 to 12 years, 0.2 mL. Single pediatric doses should not exceed 0.3 mg (mL). Doses may be repeated as frequently as every 20 minutes, depending on the severity of the condition and the response of the patient.

After administration of epinephrine, profound shock or vasomotor collapse should be treated with intravenous fluids, and possibly vasoactive drugs. Airway patency should be insured. Oxygen should be given by mask. Intravenous antihistamine, inhaled bronchodilators, theophylline, and/or adrenal corticosteroids may be used if necessary after adequate epinephrine and circulatory support have been given.

Emergency resuscitation measures and personnel trained in their use must be available immediately in the event of a serious systemic or anaphylactic reaction not responsive to the above measures [Ref. J. Allergy and Clinical Immunology 77(2): p. 271-273, 1986].

Rarely are all of the above measures necessary; the tourniquet and epinephrine usually produce prompt responses. However, the physician should be prepared in advance for all contingencies. Promptness in beginning emergency treatment measures is of utmost importance.

Severe systemic reactions mandate a decrease of at least 50% in the next dose, followed by cautious increases. Repeated systemic reactions, even of a mild nature, are sufficient reason for the cessation of further attempts to increase the reaction-causing dose.

3. Adverse Event Reporting

Report all adverse events to Jubilant HollisterStier LLC, Customer Technical Services Department at 1 (800) 992-1120. A voluntary adverse event reporting system for health professionals is available through the FDA MEDWATCH program. Preprinted forms (FDA Form 3500) are available from the FDA by calling 1 (800) FDA-1088. Completed forms should be mailed to MEDWATCH, 5600 Fisher Lane, Rockville, MD 20852-9787 or Fax to: 1 (800) FDA-0178.
2. OVERDOSAGE: See ADVERSE REACTIONS.

DOSEAGE AND ADMINISTRATION: 25, 26, 27

1. General

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Sterile aqueous diluent containing human serum albumin (Albumin Salyne with Phenol (0.4%) or diluent of 50% glycerin may be used when preparing dilutions of the concentrate for immunotherapy. For intradermal testing dilutions, Albumin Salyne with Phenol (0.4%) is recommended.

Dilutions should be made accurately and aseptically, using sterile diluent, vials, syringes, etc. Mix thoroughly and gently by rocking or swirling. Maintain stock solutions and dilutions constantly at 2° to 8°C.

2. Pediatric Use

The dose for the pediatric population is the same as for adults. (See PRECAUTIONS.)

3. Geriatric Use

a. General

The dose for the elderly patients is the same as for adult patients under 65. 40

b. Immunodiagnosis

Immunotherapy

Doseage of allergenic extracts is a highly individualized matter and varies according to the degree of sensitivity of the patient, his or her clinical response, and tolerance to the extract administered during the early phases of an injection regimen. Allergens extracts should be administered using a sterile syringe with 0.01 mL graduated and a 25-27 gauge × 1/2 to 5/8” needle. The injections are given subcutaneously. The most common sites of injection are the lateral aspect of the upper arm or thigh. Intracutaneous or intramuscular injections may produce large local reactions which may be very painful.

To prepare dilutions for intradermal and therapeutic use, make a 1:10 dilution by adding 1.0 mL of the concentrate to 9.0 mL of the sterile aqueous diluent. Subsequent serial dilutions are made in a similar manner.

Following is a suggested schedule for average patients that will be satisfactory in most cases. However, the degree of sensitivity varies in many patients. The size of the dose should be adjusted and should be regulated by the patient’s tolerance and reaction. Decrease the size of the dose if the previous injection resulted in marked local or the slightest general reaction. Another dose should never be given until all local reactions resulting from the previous dose have disappeared.

The starting dose should be based on skin tests of the extract to be used for immunotherapy. To determine the starting dose, begin intradermal testing with the most dilute extract, test preparation. Inject 0.02 mL and read the reaction at 15 minutes. Intradermal testing is continued with increasing concentrations of the extract until a reaction of 10-20 mm erythema (SE 20–40 mm) and/or a 5 mm wheal occurs. This concentration at a dose of 0.03 mL then can serve as a starting dose for immunotherapy and be increased by 0.03 mL as high as 0.12 mL increments each time until 0.3 mL is reached, at which time a dilution 10 times as strong can be used, starting with 0.03 mL. Proceed in this way until a tolerance dose is reached or symptoms are controlled. Suggested maintenance dose is 0.2 mL of the concentrate. Occasionally, higher doses are necessary to relieve symptoms. Special caution is required in administering doses greater than 0.2 mL. The interval between doses is normally 3 to 7 days during dose building regimen.

In some patients, the dosage may be increased more rapidly than called for in the schedule. In seasonal allergies, treatment should be started and the interval between doses regulated so that at least the first 20 doses will have been administered by the time symptoms are expected. Thus, the shorter the interval between the start of immunotherapy and the expected onset of symptoms, the shorter the interval between each dose. Some patients may even tolerate daily doses. Should symptoms develop before the next injection is scheduled, the interval between doses should be decreased. Should allergic symptoms or local reactions develop shortly after the dose is administered, the size of the dose should be decreased. In seasonal allergies, it is often advisable to decrease the dose to one-half or one-quarter of the maximum dose previously attained if the patient has any seasonal symptoms.

A maintenance dose, the largest dose tolerated by the patient that relieves symptoms without producing undesirable local or general reactions, is recommended for most patients. The upper limits of dosage have not been established; however, doses larger than 0.2 mL of the glycerinated concentrate may be painful due to the glycerin content. The dosage of allergenic extract does not vary significantly with the respiratory allergic disease under treatment. The size of this dose and the interval between doses will vary and can be adjusted as necessary.

The interval between maintenance doses can be increased gradually from one week to 10 days, to two weeks, to three weeks, or even to four weeks, if tolerated. Repeat the maintenance dose at four times to check for untoward reactions before further increasing the interval. Protection is lost rapidly if the interval between doses is more than four weeks. (See WARNINGS Section.)

The usual duration of treatment has not been established. A period of two or three years of injection therapy constitutes an average minimum course of treatment. In two hyposensitization studies using Amb a 1, 27, 43 the amount administered over a preessional course of injections varied from 4 to 2,000 units of Amb a 1. The maximum individual dose attained ranged up to 170 units in one series.

Short Ragweed pollen extracted at 1:20 (w/v) usually assays within a range of 50,000 to 70,000 PNU/mL and 100 to 300 units Amb a 1/mL. Most treatment programs use a w/v concentrate of 1:10 to 1:20 or a PNU/mL concentrate of 20,000 to 40,000. This would approximate a 100 units Amb a 1/mL average concentration of Short Ragweed extract (Giant and Short Ragweed mix would be one-half this value). The following suggested dose schedule is based on this average concentration of 100 Units/mL.

UNITED STATES BUREAU OF INDUSTRY

SUDDEN Doseage Schedule BASED ON Amb a 1 Concentration

<table>
<thead>
<tr>
<th>Units</th>
<th>Amb a 1/mL</th>
<th>Short Ragweed Pollen Extract</th>
<th>Giant and Short Ragweed Mix Contains 1/2 These Amounts</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>1.0 0.05</td>
<td>0.1 0.05</td>
<td>0.1 0.05</td>
</tr>
<tr>
<td>0.02</td>
<td>1.0 0.05</td>
<td>0.2 0.05</td>
<td>0.2 0.05</td>
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<td>0.03</td>
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<td>0.3 0.05</td>
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<tr>
<td>0.04</td>
<td>1.0 0.05</td>
<td>0.4 0.05</td>
<td>0.4 0.05</td>
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</tbody>
</table>

(A = Short Ragweed Only  B = Giant and Short Ragweed Mix)

The Amb a 1 content of different batches of Short Ragweed extract will vary so it will be necessary to dilute extract concentrate to the same Amb a 1 concentration when using a new lot of antigen.

Formula for calculating dilutions:

\[ A = C \times (A / C) \]

\[ A = \text{Amount of extract you wish to prepare.} \]

\[ C = \text{Concentration you wish to prepare.} \]

\[ A = \text{Amount of extract you will need for dilution.} \]

\[ C = \text{Concentration of extract you will use.} \]

Formula for determining diluent required:

\[ A / C \]

\[ A = \text{Amount of diluent required.} \]

HOW SUPPLIED

Scratch, Prick or Puncture Test extracts are supplied in 5 mL dropper bottles at 1:20 w/v and are preserved with glycerin. Intradermal extracts are supplied in multiple doses 5 mL vials at a concentration of 500 PNU/mL, and are preserved with phenol. Treatment sets are supplied as ordered by the physician. “Bulk” extracts are preserved with glycerin and are supplied in 10, 30 and 50 mL multidose vials at the w/v or PNU/mL ordered by the physician. Please see the current catalog or professional price list.
REFERENCES


