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ALLERGENIC EXTRACTS

POLLENS, MOLDS, EPIDERMALS, INSECTS, DUSTS, FOODS, AND MISCELLANEOUS INHALANTS

Suggested Dosage Schedule
and Instructions

Control #:179425

Date of Authorization: October 9, 2015

WARNING

THIS ALLERGENIC PRODUCT IS INTENDED FOR USE BY PHYSICIANS WHO ARE EXPERIENCED IN THE ADMINISTRATION OF ALLERGENIC EXTRACTS AND THE EMERGENCY CARE OF ANAPHYLAXIS, OR FOR USE UNDER THE GUIDANCE OF AN ALLERGY SPECIALIST.

ALLERGENIC EXTRACTS MAY CAUSE SEVERE OR FATAL ANAPHYLAXIS IN EXTREMELY SENSITIVE PATIENTS. THE INITIAL DOSE MUST BE BASED ON SKIN TESTING AS DESCRIBED IN THE DOSAGE AND ADMINISTRATION SECTION OF THIS INSERT. PATIENTS SHOULD BE INSTRUCTED TO RECOGNIZE ADVERSE REACTION SYMPTOMS AND CAUTIONED TO CONTACT THE PHYSICIAN'S OFFICE IF REACTION SYMPTOMS OCCUR. IN CERTAIN INDIVIDUALS, THESE REACTIONS COULD BE FATAL. PATIENTS SHOULD BE OBSERVED FOR AT LEAST 20 MINUTES FOLLOWING TREATMENT.

EMERGENCY MEASURES, AS WELL AS PERSONNEL TRAINED IN THEIR USE, SHOULD BE IMMEDIATELY AVAILABLE IN THE EVENT OF A LIFE-THREATENING REACTION. PATIENTS BEING SWITCHED FROM ONE LOT OF EXTRACT TO ANOTHER FROM THE SAME MANUFACTURER SHOULD HAVE THEIR DOSE REDUCED BY 75%.

THIS PRODUCT SHOULD NOT BE INJECTED INTRAVENOUSLY.

REFER ALSO TO THE WARNINGS, PRECAUTIONS, ADVERSE REACTIONS AND OVERDOSAGE SECTIONS BELOW.

DESCRIPTION

Allergenic Extracts are supplied as a sterile solution for intracutaneous or subcutaneous administration. Concentrates contain the soluble extractants of the source material with 0.5% sodium chloride and 0.54% Sodium bicarbonate at a pH of 6.8 to 8.4 as aqueous extracts in water for injection or in 50% glycerin. Aqueous extracts contain 0.4% phenol as a preservative and 50% glycerinated extracts contain 0.2% phenol. Diluted aqueous extracts contain Buffered Saline with 0.5% sodium chloride, 0.04% potassium phosphate, 0.11% sodium phosphate heptahydrate, and 0.4% phenol in water for injection.

Source materials for these extracts are as follows: Pollens are collected from the respective grasses, weeds, trees, shrubs, cultured plants, and flowers. Mold extracts are produced from pure culture mycelial mats. Rusts and smuts are obtained from natural growths. Epidermal extracts are produced from the hide, hair, or feathers containing the natural dander, or from separated dander. Insects are the whole body insects. House dust is made from various dusts ordinarily found in the home with the extract dialyzed to remove low-molecular weight irritants and concentrated to an extraction ratio of 1:1. Food extracts are prepared from the edible portions of the respective foods, obtained fresh if possible. Certain diagnostic food extracts contain 0.1% sodium formaldehyde sulfoxylate as an antioxidant. Other miscellaneous inhalants involved in respiratory allergy are obtained in the naturally occurring form to which a patient may be exposed.

Extracts are labeled either by weight-to-volume (W/V) based on the weight of the source material to the volume of the extracting fluid, or in protein nitrogen units (PNU) based on assay with one PNU representing 0.00001 mg of protein nitrogen.

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 allergen, histamine and other mediators are released. IgE antibody has been shown to correlate with atopic diseases such as allergic rhinitis and allergic asthma.(1-4) In the skin these mediators are responsible for the characteristic wheal and flare (erythema) reactions upon Allergenic Extract skin testing in persons with the specific allergies.(3-7)

Specific immunotherapy with Allergenic Extracts as employed for over 45 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.(8) 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 antigen.(9) Other changes following immunotherapy have been noted including development of auto-anti-idiotypic antibodies; a decrease in blood basophil sensitivity to allergen; a decrease in lymphokine production and lymphocyte proliferation

by cells exposed to allergen; and development of allergen-specific suppressor cells.(10) The complete mechanisms of immunotherapy are not known and remain the subject of investigation.

INDICATIONS AND USAGE

Allergenic Extracts are indicated for the diagnosis and treatment of patients with immediate hypersensitivity allergy to the respective allergens, inhaled, ingested, or otherwise introduced into contact with sensitive tissues. The diagnosis of IgE-mediated allergy may be established by the allergy history, clinical evaluation, and skin test reactivity.(4,7,11) Immunotherapy with Allergenic 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.(12-14) Food extracts have not been proven effective in immunotherapy.

The use of Allergenic Extracts 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 Allergenic Extracts for immunotherapy. Immunotherapy with specific antigens should not be done in those individuals who do not exhibit skin test or clinical sensitivity to the particular antigens. (See below under WARNINGS and PRECAUTIONS.)

Allergenic 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 disease.

General contraindications include:

EXTREME SENSITIVITY TO THE SPECIFIC ALLERGEN - Determined from previous anaphylaxis 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

Concentrated extracts must be diluted with a sterile diluent prior to first use on a patient for treatment or intradermal testing. Allergenic Extracts are manufactured to assure high potency and have the ability during skin testing and immunotherapy to cause serious local and systemic reactions including death in sensitive patients. Most reactions occur within 20 minutes after injection,(15) but may occur later.(16) To minimize the potential for local or systemic reactions, the relative sensitivity of the patient must be assessed from the allergic history and from clinical observations. Patients should be informed of these risks prior to skin testing and immunotherapy (see PRECAUTIONS and ADVERSE REACTIONS below).

Allergenic Extract immunotherapy doses should be lowered or temporarily withheld from patients if any of the following conditions exist:

- (1) severe symptoms of rhinitis and/or asthma
- (2) infection or flu accompanied by fever
- (3) exposure to excessive amounts of clinically relevant allergen prior to a scheduled injection
- (4) evidence of a local or systemic reaction to the preceding extract injection during a course of immunotherapy.

The dosage must be reduced when modifying dosages or components in a mixture or an individual prescription, or when starting a patient on fresh extract, even though the labeled strength of the old and new vials may be the same. This reduction in dosage may be necessary due to the older vial losing potency during storage, or due to different sensitivities to different components. The amount of new extract given should not exceed 25% of the last dose given from the old vial, assuming both extracts contain comparable amounts of allergen. Any evidence of a local or generalized reaction requires a reduction in dosage during the initial stages of immunotherapy, as well as during maintenance therapy.

PRECAUTIONS

GENERAL:

Not for intravenous use!

Systemic allergic reactions may occur as a result of immunotherapy.

The risk can be minimized by adherence to a careful injection schedule, which starts with a low concentration of extract and is increased slowly. Because of the danger of serious reactions, caution is needed in testing exquisitely sensitive patients, particularly with potent allergens, e.g., peanut, cottonseed, and flaxseed.(8) Such extracts should be appropriately diluted before use.

The physician must be prepared to treat anaphylaxis should it occur and have the necessary drugs and equipment on hand to do so.(17-18) Extracts should not be administered by the patient or other individuals who are not prepared to treat anaphylaxis should it occur.

Patients receiving Allergenic Extracts should be kept under observation a minimum of twenty (20) minutes so that any adverse reaction can be observed and properly handled.(15) This time should be extended for high-risk patients such as those with unstable asthma or those suffering an exacerbation of their symptoms.

Patients receiving beta blockers may not be responsive to beta adrenergic drugs used to treat anaphylaxis. The risks of anaphylaxis in these patients should be carefully weighed against the benefits of immunotherapy.

Check the lot number and dosage schedule of the patient to verify correctness of a prescription number, a vial number, or strength. Only after this verification has been made should an injection be given.

A separate sterile needle and syringe should be used for each patient to prevent transmission of hepatitis or other infectious agents.

INFORMATION FOR PATIENTS:

Most serious reactions following the administration of Allergenic Extracts occur within 20 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 recorded, because increasingly large local reactions may precede a subsequent systemic reaction with increasing dosage. The patient should be instructed to report any unusual reactions. In particular, this includes unusual swelling and/or tenderness at the injection site, or reactions such as rhinorrhea, sneezing, coughing, wheezing, shortness of breath, nausea, dizziness, or faintness. Reactions may occur some time after leaving the physician's office, in which case medical attention should be sought immediately.

DRUG INTERACTIONS: Skin test diagnosis with Allergenic Extracts is contraindicated within 24 hours after the last dose of most antihistamines, within 48 hours after the last dose of terfenadine, and within 3 weeks or longer after the last dose of astemizole. These products suppress histamine skin test reactions and could mask a positive response.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY:

There is no evidence of carcinogenicity, mutagenesis, or impairment of fertility in humans from Allergenic Extracts. No long-term studies in animals have been performed to evaluate carcinogenic potential.

PREGNANCY: PREGNANCY CATEGORY C - Animal reproduction studies have not been conducted with Allergenic Extracts. It is also not known whether Allergenic Extracts can cause fetal harm when administered to a pregnant woman or whether they can affect reproduction capacity. Allergenic Extracts should be given to a pregnant woman only if clearly needed.

There is no evidence of adverse effects of Allergenic Extracts on the fetus.(8) 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 information of adverse effects during labor and delivery.

NURSING MOTHERS: It is not known whether this product is 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: Although most extracts have not been studied systematically in children, children and geriatric patients appear to tolerate injections of Allergenic Extracts well. Studies with pollenosis and asthma have been conducted in children (e.g. Refs. 19-21). Extract usage in children should follow the same precautions as in adults.

ADVERSE REACTIONS

Adverse systemic reactions may occur within minutes upon use of an Allergenic Extract to which a person has specific sensitivity. These reactions consist primarily of allergic symptoms such as generalized skin erythema, urticaria, pruritis angioedema, rhinitis, wheezing, laryngeal edema, and hypotension. Less commonly, nausea, emesis, abdominal cramps, diarrhea and uterine contractions may occur. Severe reactions may cause shock and loss of consciousness. Fatalities have occurred rarely.(8,22,23) These systemic reactions occur with varying frequency in different clinics and are usually less than 1%. To some extent, the reaction rate is related to the type and dose of administered extract and to the sensitivity of the patient. In general, immunotherapy with Allergenic Extracts is considered to be safe.(24) Despite all precautions, occasional reactions are unavoidable.

Adverse systemic reactions should be treated as follows:

A. A tourniquet should be immediately applied to the extremity above the site of the injection. Release the tourniquet every few minutes for a few seconds.

B. Epinephrine 1:1000 should be injected immediately in the opposite arm in amounts of 0.3 to 0.5 mL and 0.2 mL epinephrine should be administered at the site of injection. For children below the age of 6 years, adjust the dosage of epinephrine to 0.005 mL per pound of body weight per dose. Repeat epinephrine dosage in 15 minutes if necessary and if symptoms persist.

C. Adverse reactions not responding to epinephrine therapy may require the use of parenteral bronchodilators, vasopressors, oxygen, or volume replacement therapy.

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 treatment. For marked and prolonged local reactions, steroids may be helpful.

OVERDOSAGE

Systemic reactions are uncommon after injection, but if the patient receives more extract than can be tolerated at that particular time and begins to experience immediate hypersensitivity anaphylaxis, the procedures listed under ADVERSE REACTIONS should be instituted.

Overdosage may occur because of an error in the volume of extract injected, or an incorrect dilution injected, or because the patient may be exposed to airborne or environmental antigens simultaneously with injection of the same antigens. In the event of a systemic reaction occurring, the dosage schedule should be carefully adjusted as outlined above under WARNINGS.

DOSAGE AND ADMINISTRATION

1. DIAGNOSTIC TESTING

For the patient with a suspected diagnosis of allergy to more than one antigen, initial skin testing should include the individual extracts. If a screening skin test with a mixture is used, a positive response should be followed by testing with the individual

extracts to determine the degree of sensitivity to each and to guide in the selection of extracts and their concentration for immunotherapy if indicated. However, because a negative skin test with a mixture may not be indicative of the absence of allergy to one or more of the components due to their dilution, testing with individual extracts is more precise. False negative responses may occur if serum levels of antihistamines remain from prior medication administration (see CONTRAINDICATIONS). The use of a positive control is especially recommended for patients on prior medications which may decrease the histamine skin test response.

Scratch or Prick-Puncture Skin Testing:

Allergenic Extract concentrates may be used for scratch or prick-puncture testing or scratch tests in 50% glycerin 1:20 W/V or strongest available strength in 5 mL vials may be used. Prick-puncture tests with concentrated extracts in patients highly sensitive to the specific antigen should yield distinctive wheals with diameters of greater than 5 mm and with much larger erythema reactions. Glycerinated histamine phosphate 5 mg/mL (1.8 mg/mL histamine base) or aqueous histamine phosphate 2.75 mg/mL (1 mg/mL histamine base; 1:1000W/V) may be used as a positive control.

Intradermal Skin Testing:

Extract for intradermal testing must be prepared by diluting the stock concentrate injection vials with sterile diluent (use normal or buffered saline, or normal saline with human serum albumin) or the appropriate dilutions may be purchased.

a. Patients with a negative scratch or prick-puncture test:

Patients who do not react to a scratch or prick-puncture test should be tested intradermally, using a 26 or 27 gauge 1/4 inch needle, with 0.02 to 0.05 mL of an appropriate extract dilution from 1/100 to 1/1000 of the concentrate. A negative test should be followed by a repeat test using a higher concentration until significant wheal and flare reaction sizes are attained or until the responses remain negative. As a negative control use the diluent or, in the case of extracts in 50% glycerin, use 0.5% to 1% glycerosaline solution. As a positive control use glycerinated histamine phosphate diluted to 0.5 mg/mL (0.18 mg/mL histamine base) or aqueous histamine phosphate 0.275 mg/mL (0.1 mg/mL histamine base).

b. Patients tested only by the intradermal method:

Since highly reactive individuals may react intracutaneously at 1:1 million or even 1:10 million dilutions, any intradermal injection should be preceded by a puncture test and the dose adjusted accordingly. Other patients suspected of being moderately allergic should be tested with 0.02 to 0.05 mL of an appropriate extract dilution on the order of 1/10,000 to 1/100,000 of the concentrate. A negative test should be followed by repeat tests using progressively stronger ten-fold concentrations until significant wheal and flare reaction sizes are attained, or until skin test responses with the higher concentrations remain negative. As a negative control, use the diluent or, in the case of extracts in 50% glycerin, use 0.5% to 1% glycerosaline solution. As a positive control, use glycerinated histamine phosphate diluted to 0.5 mg/mL (0.18 mg/mL histamine base) or aqueous histamine phosphate 0.275 mg/mL (0.1 mg/mL histamine base).

Skin tests are graded in terms of the wheal and erythema response noted at 15 to 20 minutes, and compared to the appropriate controls. Wheal and erythema sizes may be recorded by actual measurement.

2. IMMUNOTHERAPY

Immunotherapy is administered by subcutaneous injection. Dosage of Allergenic Extracts is individualized according to the patient's sensitivity, the clinical response, and tolerance to the extract administered during the phases of an injection regimen. The initial dose of the extract should be determined based on the puncture test reactivity. In patients who appear to be exquisitely sensitive by history and skin test, the initial dose of the extract should be 0.05 to 0.1 mL of a low concentration, such as dilution number 5 or 6 in TABLE 1 below. Patients with lesser sensitivity may be started with 0.05 to 0.1 mL of the next higher concentration. The amount of Allergenic 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 last injection. Large local reactions which persist for longer than 24 hours are generally considered an indication for repeating the previous dose or reducing the dose at the next administration. Any evidence of systemic reaction is an indication for a reduction of 75% in the subsequent dose. The upper limits of dosage have not been established; however, doses larger than 0.2 mL of an extract in 50% glycerin may cause discomfort upon injection. The dosage of Allergenic Extract does not vary significantly with the allergic disease under treatment.

To prepare dilutions starting from a concentrate such as 1:10 W/V, 1:20 W/V OR 20,000 PNU/mL, proceed as in TABLE 1 below. (Note: Add 0.5 mL of concentrate to 4.5 mL of sterile diluent and make additional dilutions in the same manner.)

TABLE 1

Dilution	Extract	Ten-Fold Dilution Series *			PNU/mL
		Diluent	W/V	W/V	
0	Concentrate		1:10	1:20	20,000
1	0.5 mL concentrate	4.5 mL	1:100	1:200	2,000
2	0.5 mL dilution 1	4.5 mL	1:1,000	1:2,000	200
3	0.5 mL dilution 2	4.5 mL	1:10,000	1:20,000	20
4	0.5 mL dilution 3	4.5 mL	1:100,000	1:200,000	2
5	0.5 mL dilution 4	4.5 mL	1:1,000,000	1:2,000,000	0.2
6	0.5 mL dilution 5	4.5 mL	1:10,000,000	1:20,000,000	0.02

*There is no direct potency correlation across the table between PNUs and W/V.

The optimal interval between doses of Allergenic Extract has not been established. Injections usually are given 1 or 2 times per week until the maintenance dose is reached. The injection interval then is increased to 2 weeks, then to 3 weeks, and finally to 4 weeks. If the patient does not return for 6 to 8 weeks, the dose should be reduced to 25% of the last dose. If longer than 8 weeks, a dose reduction of one, two, or three dilutions may be made considering the components and the patient's sensitivity. The dosage and the interval between injections may need to be modified

according to the clinical response of the patient. When switching patients to fresh extract, the initial dose should be reduced to 25% of the previous dose.

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.

HOW SUPPLIED

Stock concentrate extracts containing up to 40,000 PNU/mL, or 1:10 W/V or other dilutions as requested by the physician are supplied in 5, 10, 30, and 50 mL in aqueous or 50% glycerin buffered saline. House dust extract is supplied in a 1:1 W/V concentrate, or a maximum of 10,000 PNU/mL. Extracts are also supplied in dropper vials for scratch or prick testing.

STORAGE

Allergenic Extracts should be stored at 2-8° C and kept at this temperature range during office use. Refer to vial labels for expiration dates. Diluted extracts are inherently less stable than concentrates. Dilutions of glycerinated extracts which result in glycerin below 50% are also less stable. The more dilute extracts in aqueous diluents should be replenished daily. Potency of a particular dilution can be checked by skin test in comparison to a fresh dilution of the extract on an individual known to be allergic to the specific antigen.

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