ALLERGENIC EXTRACT
for
Diagnostic Skin Testing

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WARNINGS

This product is intended for use by physicians who are experienced in the administration of allergenic extracts or for use under the guidance of an allergy specialist. Skin tests should be performed after the patient's physical well being and allergic history have been evaluated. Patients should be instructed to recognize adverse reaction symptoms and cautioned to contact the physician if symptoms occur. As with all allergenic extracts, severe systemic reactions may occur, and in certain individuals these reactions may cause death. Patients should be observed for at least 20 minutes after skin tests have been completed. Emergency measures as well as personnel trained in their use should be immediately available in the event of a life threatening reaction.

This product should never be injected intravenously (see DOSAGE AND ADMINISTRATION). Also, see WARNINGS, PRECAUTIONS, ADVERSE REACTIONS and OVERDOSE Sections below.

Serious adverse reactions to this product should be reported to MEDWATCH, Food and Drug Administration, 5600 Fishers Lane, MD 20852-9787. Telephone 1-800-822-7967 or www.vaers.hhs.gov.

DESCRIPTION

Allergenic extract for diagnostic skin testing is a sterile solution that is prepared by extracting allergenic source material with an aqueous solution of 0.25% sodium chloride, 0.125% sodium bicarbonate and 50% glycerol v/v. Phenol is added at 0.4% w/v as a preservative. Extract for intradermal administration is diluted with the above solution without glycerol. The strength of allergenic extract (Table 1) is expressed in the following labeled designations:

WEIGHT BY VOLUME (W/V) Weight by volume refers to the weight of raw product added to a measured volume of extraction solution. A 1:10 w/v extract is manufactured by extracting 1 gram of source material in 10 mL of extraction solution. The w/v designation refers to concentration rather than potency. Extract labeled w/v has No U.S. Standard of Potency.

Amb a1 (Antigen E) Amb a1 is considered to be the most important allergen of short ragweed pollen extract and is used to measure the potency of the extract. The Amb a1 content of short ragweed pollen extract is assayed by radial immunodiffusion using standardized reagents supplied by the Center for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration. Most concentrates of short ragweed pollen extract contain 200 - 600 units per mL of Amb a1. The minimum allowable values are 135 units per mL for a 1:10 w/v concentrate and 67.5 units per mL for a 1:20 w/v concentrate. The Amb a1 concentration of diluted or mixed extracts containing short ragweed can be determined by calculation, starting with the Amb a1 content of the concentrated product.

ALLERGY UNITS (AU/mL) Allergy units are used to designate the potency of standardized extracts of house dust mites *Dermatophagoides farinae* and *D. pteronyssinus*. The biological strength of these extracts is determined by ELISA competition using standardized reagents supplied by CBER. The CBER reference extract has a designated potency of 10,000 AU/mL based on quantitative skin testing (1).

BIOEQUIVALENT ALLERGY UNITS (BAU/mL) Bioequivalent Allergy Units are used to designate the potency of standardized cat hair extract. The biological strength of cat hair extract is based on Fel d 1 content, measured by radial immunodiffusion using CBER reference standards. Cat hair extract containing 10 to 20 Fel d 1 units per mL has a designated potency of 10,000 BAU/mL based on quantitative skin testing (1).

The potency of standardized grass pollen extract is expressed in Bioequivalent Allergy Units per mL (BAU/mL). Potency is determined by an *in vitro* ELISA Competition Assay using a U.S. reference grass pollen extract available from CBER. Bioequivalent Allergy Units per mL (BAU/mL) have been assigned to the reference extract based on quantitative skin testing. CBER reference extract labeled 100,000 BAU/mL can be diluted 1:5 million and yield a 50 mm sum of erythema diameter response intradermally in highly puncture reactive subjects. CBER reference extract labeled 10,000 BAU/mL can be diluted 1:500,000 for the same response (1).

Table 1. Labeled strength of Diagnostic Allergenic Extract administered by the prick-puncture and intradermal skin test methods.*

EXTRACT	PRICK-PUNCTURE	INTRADERMAL
Pollens	1:10 & 1:20 w/v	1:1,000 w/v
Environmentals	1:10 w/v	1:500 w/v
Fungi	1:10 w/v	1:500 w/v
Mite	10,000 AU/mL	100 AU/mL
Cat Hair	10,000 BAU/mL	100 BAU/mL
Grass Pollen	10,000 BAU/mL	100 BAU/mL

* The extract concentrations shown in the table have not been studied in well-controlled clinical trials.

CLINICAL PHARMACOLOGY

In sensitive persons, allergenic extract elicits immediate-type skin reactions consisting of erythema and edema at the test site. This allergic inflammatory response is thought to begin with the reaction of allergen with immunoglobulin E (IgE) on the surface of the mast cell. This antigen-antibody reaction initiates a series of biochemical events that result in the release of histamine and other mediators from the mast cell. These mediators are responsible for the characteristic wheal and flare response associated with a positive skin test. The initial antigen-antibody reaction appears to be a specific response that is dependent upon the presence of allergen-specific IgE attached to the mast cell (2,3).

INDICATIONS AND USAGE

Allergenic extract for diagnostic skin testing is indicated for use in patients with immediate hypersensitivity to allergenic environmental substances. Positive skin tests have been shown to correlate with bronchial provocation tests in patients with asthma (4) and the prevalence of allergic rhinitis and asthma has been shown to increase with a corresponding increase in allergen skin test reactivity (5).

To maximize the informational value of allergen skin tests, the procedure should be performed after the allergic history and physical examination have been completed. A positive wheal and flare response 15 to 20 minutes after administration of the test indicates the presence of IgE mediated sensitivity to the substance. However, the clinical relevance of a positive skin test must be assessed in conjunction with the patient's allergic history and physical findings.

The size and intensity of the wheal-flare response depends upon the potency of the extract and the sensitivity of the patient. A negative response by the prick-puncture method does not conclusively rule out sensitivity to an allergen. As with all percutaneous methods, the prick-puncture test may not elicit a wheal-flare response in persons with mild sensitivity to an allergenic substance. In these individuals, intradermal skin tests may be required to detect the presence of IgE to the allergen. Although the intradermal procedure is more sensitive than the prick-puncture method, it is less safe to perform and may give non-specific positive reactions in some individuals.

CONTRAINDICATIONS

Conditions under which the administration of allergenic extract may be contraindicated, depending upon individual circumstances, include: EXTREME SENSITIVITY TO AN ALLERGEN — Determined from the allergic history, or from previous anaphylaxis following skin testing or subcutaneous injection; MYOCARDIAL INFARCTION — Patients who have experienced a recent myocardial infarction may be less able to tolerate the life-threatening effects of a serious adverse reaction. ASTHMA — Patients with highly unstable asthma are at greater risk of fatal reactions from skin tests than are patients without asthma, especially during seasonal exacerbations of the disease. Also, the combination of unstable asthma and treatment with B-adrenergic blockers appears to increase this risk (6). Allergenic extract should be temporarily withheld from patients if any of the following conditions exist: 1) severe symptoms of hay fever and/or asthma; 2) infection or flu accompanied by fever; and 3) exposure to excessive amounts of clinically relevant allergen(s) prior to skin testing.

WARNINGS

Physicians who use allergenic extracts should have a knowledge and practical understanding of allergy skin testing as described in the published literature (7,8,9).

Allergenic extracts are manufactured to assure high potency and therefore have the ability to cause serious local and systemic reactions, including death in highly sensitive patients (6). Patients should be informed of the risks of skin testing and instructed in the recognition of symptoms of an adverse allergic reaction (see PRECAUTIONS and ADVERSE REACTIONS below).

Excessively large local reactions or systemic reactions are more likely to occur if the patient is skin tested shortly after exposure to allergens to which he or she is sensitive.

PRECAUTIONS

GENERAL It is recommended that the device used to perform skin tests be disposable to prevent the possibility of accidental transfer of serum hepatitis, HIV and other infectious agents from one person to another. Injectable epinephrine should be available when skin tests are administered (see ADVERSE REACTIONS).

PATIENT INFORMATION Skin tests with allergenic extracts are usually safe and effective in the diagnosis of allergic diseases when used properly and when interpreted in conjunction with the allergic history and clinical findings. Patients should be observed in the office for 20 minutes after skin tests have been completed (10) and instructed to return to the office or emergency room if symptoms of an allergic reaction or shock occur. The risk of a serious adverse reaction is always present. However, it is minimized by the use of the prick-puncture procedure as the initial method of testing. In a study of 16,204 persons in the United States between 6 and 74 years of age, no anaphylactic reactions were observed after prick-puncture skin testing with eight different allergenic extracts. The authors concluded that the risk of adverse reactions to prick-puncture skin tests is low and similar to other routine medical procedures, such as venipuncture (11).

Since drugs may affect the reactivity of the skin, patients should be instructed to avoid medications, particularly antihistamines and sympathomimetic drugs prior to skin testing (see DRUG INTERACTION below).

DRUG INTERACTION Treatment with beta-blocking drugs may make patients refractory to the usual dose of epinephrine, in the event epinephrine is required to control an adverse reaction (12).

Since drugs may affect the reactivity of the skin, patients should be instructed to avoid medications, particularly antihistamines and sympathomimetic drugs for at least 24 hours prior to skin testing. Non-sedating antihistamine suppresses the erythema/edema response for longer periods and should be withheld according to information included in the package insert. Adrenal corticosteroids and ACTH do not alter the immediate hypersensitivity reaction of the skin. Adrenal corticosteroids are often helpful in controlling the patient's symptoms while other drugs are withdrawn prior to skin testing.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY Long-term studies in animals have not been conducted with allergenic extracts to determine their potential for carcinogenicity, mutagenicity or impairment of fertility.

PREGNANCY CATEGORY C Allergenic Extracts. 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 can affect reproduction capacity. Allergenic extracts should be given to a pregnant woman only if clearly needed. Since studies indicate no increased risk to the fetus or to the mother who is treated cautiously with immunotherapy during a normal pregnancy, it is unlikely that extract administered by skin test will be harmful. However, on the basis of histamine's known ability to contract uterine muscle, extensive testing with its possibility of histamine release should be avoided during pregnancy. Also, immunologic suppressive action can occur during pregnancy and for this reason it is possible that the results of allergy skin tests may not accurately reflect the allergic state of the pregnant patient (13).

NURSING MOTHERS It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when allergenic extract is administered to a nursing woman.

PEDIATRIC USE The procedures and precautions that are observed in skin testing adults should be observed with children (14).

ADVERSE REACTIONS

LOCAL REACTIONS Large, persistent local reactions or minor exacerbations of the patient's allergic symptoms may be treated by local cold applications and/or the use of oral anti-histamines.

SYSTEMIC REACTIONS Allergenic extracts are highly potent and in highly sensitive individuals can cause systemic symptoms, including anaphylaxis. It cannot be overemphasized that anaphylactic shock is always a possibility under certain unpredictable combinations of circumstances. Other possible systemic reaction symptoms may include fainting, pallor, bradycardia, hypotension, angioedema, cough, wheezing, conjunctivitis, rhinitis and urticaria. Therefore, it is imperative that physicians administering skin tests understand and be prepared to treat severe allergic reactions.

If a systemic or anaphylactic reaction occurs during or following skin testing, the patient should be treated with 1:1000 epinephrine hydrochloride. The recommended dose: infants to 2 years of age 0.05 to 0.1 mL, children 2 to 6 years, 0.15 mL, children 6 to 12 years, 0.2 mL, adults 0.3 - 0.5 mL. If necessary, treatment may be repeated up to three times every 10 - 15 minutes.

After administration of epinephrine, profound shock or vasomotor collapse should be treated with intravenous fluids and possibly vasoactive drugs. Oxygen should be given by mask. Intravenous antihistamine, aminophylline, inhaled bronchodilators 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 should be available immediately. The physician should be prepared in advance for all contingencies. Promptness in beginning emergency treatment is of utmost importance (15).

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OVERDOSAGE

The signs and symptoms of overdosage are the same as those listed under ADVERSE REACTIONS, paragraphs 1 and 2.

The treatment of a systemic allergic reaction resulting from skin tests should include the following:

- The patient should be placed in the recumbent position to maintain blood flow to the head.
- Aqueous epinephrine 1:1,000 should be administered subcutaneously. See ADVERSE REACTIONS for dose and other supportive measures.
- Reassurance should be provided.

The above steps should be performed nearly simultaneously and as soon as possible after the reaction begins. Persistent wheezing may necessitate treatment with intravenous aminophylline and inhaled bronchodilators. For profound shock and hypotension, intravenous fluids, vasopressors and oxygen also may be needed. Maintenance of an open airway is critical if upper airway obstruction is present. Corticosteroids may provide benefit if symptoms are prolonged or recurrent.

DOSAGE AND ADMINISTRATION

Prior to administering skin tests, the skin should be cleaned with alcohol and allowed to dry completely. The tests should be placed on the volar surface of the forearms or on the back. Test sites should be approximately 1 - 1 ½ inches apart. Two rows may be placed on each arm and four rows may be placed on the back.

PRICK-PUNCTURE TEST The prick-puncture test is performed by placing a drop of extract on the skin and passing the sharp end of the testing device through the drop, penetrating the skin, but without drawing blood. After applying the tests, the skin may be blotted, so that the drops do not run or spread on the skin. The test sites should be examined after 15 - 20 minutes and the results recorded.

The skin response to the glycerol-saline control should be negative. The response to the histamine control should be positive for edema and erythema. The degree of reactivity to allergens is determined by comparison to the negative control response. Test sites that are similar in appearance to the negative control should be reported as negative (Ø). Test sites that show a wheal and flare response should be measured and reported in mm of edema and erythema or scored as 1+ to 4+ based on a mm reference scale.

INTRADERMAL TEST The intradermal test is performed by administering 0.05 mL of extract intracutaneously. The injection should be given as superficially as possible creating a distinct bleb approximately 5 mm in diameter. A positive histamine control and a negative saline control should be administered concurrently with the test extracts. All tests should be examined after 15 - 20 minutes and read as negative or positive compared to the controls (see paragraph 2 under PRICK-PUNCTURE TEST). Induration after 24 - 48 hours may occur with some fungus extracts. However, this reaction is not related to Type I immediate hypersensitivity.

HOW SUPPLIED

Extract for prick-puncture skin testing is supplied in dropper vials. Extract for intradermal skin testing is supplied in sealed multidose vials. Refer to Table 1 in DESCRIPTION section for available strengths.

STORAGE

Extract should be stored at 2°C to 8°C, since higher temperatures may adversely affect the stability of allergens. Do not freeze.

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