

ALLERGENIC EXTRACTS FOR DIAGNOSTIC USE ONLY

Scratch, Prick, Puncture
or Intradermal Testing

U.S. Government License No. 308
Canadian License No. 547



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WARNING

THIS ALLERGENIC PRODUCT IS INTENDED FOR DIAGNOSTIC USE ONLY. THIS 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. THIS PRODUCT SHOULD NOT BE INJECTED INTRAVENOUSLY. REFER ALSO TO THE WARNINGS, PRECAUTIONS, ADVERSE REACTIONS AND OVERDOSAGE SECTION BELOW.

DESCRIPTION

Allergenic Extracts intended for diagnostic skin testing are for scratch, prick, puncture or intradermal use only. The extracts are supplied as sterile solutions which contain the soluble extractants of the allergen source material in a buffered saline solution with or without glycerin (50% v/v) added as a stabilizer. Concentrated aqueous extracts 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 in water for injection. Dilutions of aqueous extracts are made with buffered saline (0.5% sodium chloride, 0.04% potassium phosphate, 0.11% sodium phosphate heptahydrate, and 0.4% phenol in water for injection). Glycerinated extracts are concentrated aqueous extracts diluted to 50% v/v with USP Glycerin. Aqueous extracts contain 0.4% phenol as a preservative (0.2% phenol if glycerinated). Certain food extracts contain 0.1% sodium formaldehyde sulfoxylate as an antioxidant. Extracted source material substances are obtained as near as possible in the naturally occurring form to which a patient may be exposed.

Extracts labeled for diagnostic use only include the following foods: Barley, Coffee, Oat, Pineapple, Rye, Spinach, and Wheat. Other extracts for diagnostic only are Flea, House Fly, Mosquito, Moth, Cottonseed, and Flax Seed.

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 10 micrograms of protein nitrogen. (See separate package inserts for standardized extracts such as cat hair, mite, or ragweed.)

CLINICAL PHARMACOLOGY

Allergen specific skin test reactions are mediated by specific immunoglobulin E (IgE) antibodies on the surface of mast cells. Interaction of allergens with cell-bound IgE induces cross linking of the IgE receptor which triggers the release of inflammatory mediators, particularly histamine. The characteristic mediator-induced induration (wheal) and erythema (flare) reaction observed upon diagnostic skin testing is an indication of specific allergy.¹ Allergen pharmacokinetics have not been characterized.

INDICATIONS AND USAGE

FOR DIAGNOSTIC USE ONLY - Allergenic Extracts are indicated for skin test assessment of the allergic state in patients with suspected IgE-mediated, immediate hypersensitivity allergy to the respective allergens when inhaled, ingested, or otherwise introduced into contact with sensitive tissues. The diagnosis of allergy may be established by the allergy history, clinical evaluation, and skin test reactivity. There are no reported limitations such as age group or progression of disease.

Extracts labeled FOR DIAGNOSTIC USE ONLY have not been shown by adequate data to be safe and effective for therapeutic use.

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 skin test diagnosis.

Use of diagnostic extracts may be contraindicated in individuals with bleeding disorders or skin disease.

Skin test reactions can be suppressed when patients have received antihistamine medications within 24 hours, within 48 hours for terfenadine, or within 21 days or longer for astemizole. See DRUG INTERACTIONS.

WARNINGS

Concentrated extracts must be diluted with a sterile diluent (such as normal saline, buffered saline, saline with human serum albumin, or saline with 10% glycerin) prior to use in a patient for intradermal testing. Concentrates of Allergenic Extracts are manufactured to assure high potency and have the ability to cause serious local and systemic reactions including death in sensitive patients. Most reactions occur within 20 minutes after injection, but may occur later. 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 the possibility of these reactions and the precautions should be discussed prior to testing (see PRECAUTIONS and ADVERSE REACTIONS below).

PRECAUTIONS

GENERAL

Not for intravenous or intramuscular use!

Systemic allergic reactions may occur as a result of the use of Allergenic Extracts. The physician must be prepared to treat anaphylaxis should it occur and have the necessary drugs, such as epinephrine, and equipment on hand to do so. Extracts should not be administered by individuals who are not prepared to treat anaphylaxis should it occur.²

A separate, sterile testing device, or needle and syringe, must be used to prevent the transmission of hepatitis or other infectious agents from person to person. Needles should not be recapped and should be disposed of properly.

INFORMATION FOR PATIENTS

The patient should be adequately informed of typical reactions to be expected as a result of diagnostic testing. Because 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 to 30 minutes or longer if instructed by the physician, such as for high-risk patients with unstable asthma, those with a history of reactions on injection, or patients suffering an exacerbation of their symptoms.² The patient should be instructed to report any unusual reactions. In particular, this includes unusual swelling and/or tenderness at the test 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 may result in false negative responses if used 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. The suppressive action of other drugs should be considered and emphasizes the need for a histamine positive-control test.¹

Patients receiving beta blocker drugs may not be responsive to beta adrenergic drugs used to treat anaphylaxis. The risks of anaphylaxis in these patients should be weighed against the benefits of diagnostic skin testing.

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

TERATOGENIC EFFECTS

PREGNANCY CATEGORY C - Animal reproduction studies have not been conducted with Allergenic Extracts for Diagnostic Use Only. 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.

LABOR AND DELIVERY

There is no known information of adverse effects during labor and delivery. Caution should be exercised in testing pregnant females because a systemic reaction may cause an abortion as a result of uterine muscle contractions.

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 Allergenic Extracts have not been studied systematically in children, children and geriatric patients appear to tolerate injections of Allergenic Extracts well. Extract usage in children should follow the same precautions as in adults.

ADVERSE REACTIONS

Adverse systemic reactions usually occur within minutes and consist primarily of allergic symptoms such as generalized skin erythema, urticaria, pruritus, 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. The reaction rate is related to the type and dose of administered extract and to the degree of sensitivity of the patient; severe systemic reactions are not common with skin test diagnosis, but do occur. Despite all precautions occasional reactions are unavoidable.

Adverse systemic reactions should be treated as follows:

- A. If the testing site was an extremity a tourniquet should be immediately applied above the site. 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 (0.01 mL/kg) 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 other measures such as the use of parenteral bronchodilators, vasopressors, oxygen, or volume replacement therapy. Proper equipment and trained personnel should be available.²

Local reactions consisting of erythema, itching, swelling, tenderness and sometimes pain may occur as a result of testing. 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 testing, 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 used, or an incorrect dilution, or because the patient may be exposed to antigens simultaneously to testing with the same antigens.

DOSAGE AND ADMINISTRATION

TECHNIQUES

The most frequently used test sites are the back and the volar surface of the forearms. The skin should be cleansed with alcohol and allowed to dry. A minimum of at least 1 inch should be allowed between test sites, and preferably 2 inches between sites for pollens. A marking pencil may be used to indicate the site locations.

A sterile puncture device, needle, scalpel blade, or scarifier is used. A separate sterile device must be used for each patient to prevent transmission of infectious agents. If the device contacts extracts, use a separate device for each antigen to prevent cross-contamination.

The skin is abraded only enough to enter the dermis without drawing blood. Follow the directions for the device being used. The antigen may be applied directly with a puncture device or is introduced by applying a drop of extract to the scratch or prick site, taking care not to touch the skin with the dropper tip.

The number of tests that can be performed at one sitting depends upon the sensitivity of the patient and other clinical aspects. Normally, 30 to 40 tests administered at one time should be sufficient. For patients of extreme sensitivity, it is advisable to limit the number of tests to not more than 10, and use the forearm only so that a tourniquet can be applied in the event of a severe reaction.

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. 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 DRUG INTERACTIONS). The use of a positive control is especially recommended for patients on prior medications which may decrease the histamine skin test response.

Initial testing may be conducted with the concentrate by means of a puncture test employing a multiple puncture device or other appropriate instrument. Prick testing through a drop of extract or scratch testing with a drop of extract applied to the scratch may also be employed to determine the degree of sensitivity. If a large whealing reaction occurs prior to the 20-minute period, wipe the area free of extract with an alcohol sponge. After final readings, all antigens should be removed by gently wiping with an alcohol sponge or sterile cotton swab. If the response is negative, this initial test may be followed by intradermal testing which should be correlated with the clinical history.

1. Scratch or Prick-puncture Skin Testing:

Scratch and Prick-puncture testing normally is performed with 1:20 w/v extracts in 50% glycerin or the strongest available strength in 5 mL vials for diagnostic use. 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 erythma 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; 1:1,000 w/v) may be used as a positive control.

2. Intradermal Skin Testing:

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

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 the table 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
Ten-Fold Dilution Series*

Dilution	Extract	Diluent	w/v	w/v	PNU/mL
0	Concentrate		1:10	1:20	20,000
1	0.5mL concentrate	4.5 mL	1:10	1:200	2,000
2	0.5mL dilution 1	4.5 mL	1:1,000	1:2,000	200
3	0.5mL dilution 2	4.5 mL	1:10,000	1:20,000	20
4	0.5mL dilution 3	4.5 mL	1:100,000	1:200,000	2
5	0.5mL dilution 4	4.5 mL	1:1,000,000	1:2,000,000	0.2
6	0.5mL 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 PNU and w/v.

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

Patients with a negative scratch or prick-puncture test should be tested intradermally, using a 26 or 27 gauge 1/4 inch needle, with 0.02 to 0.05mL of an appropriate extract dilution of 1/100 to 1/1000 of the concentrate.

B. Patients tested only by the intradermal method:

Since highly reactive individuals may react intracutaneously at high dilutions, it is normally recommended that any intradermal injection should be preceded by and the dose adjusted according to puncture test reactivity. Patients suspected of being highly 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 or higher dilution of the concentrate.

C. Skin test titration:

A negative test should be followed by repeat skin test titration dosages 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.

D. Controls:

As a negative control use the diluent or, in case of extracts in 50% glycerin, use 0.5% to 1% glycerol saline 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).

RESPONSES

Tests should be read 15 to 20 minutes after application of the test antigens.

One means for reporting test results is the “plus” system:

- no reaction or reaction not greater than control
- 1+ erythema smaller than 21 mm
- 2+ erythema larger than 21 mm with no wheal
- 3+ erythema and wheal
- 4+ erythema and wheal with pseudopods

Other systems for reporting positive results include measuring the largest erythema or wheal diameter, or the sum of the orthogonal diameters of the erythema or wheal. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Some concentrated extracts naturally develop a cloudy appearance over time under refrigeration, the material settling to the bottom on standing.

HOW SUPPLIED

Scratch tests in 50% glycerin (v/v) are supplied at 1:20 w/v (or lesser strengths for selected extracts) in 5 mL vials only. Concentrates (which must be diluted for intradermal testing) are supplied in aqueous or 50% v/v glycerin solutions containing 10,000, 20,000, or 40,000 PNU/mL and 1:10, 1:20, 1:40, or 1:100 w/v, in 10, 30, and 50 mL vials. Dilutions for intradermal testing are available in 5 mL vials at 1,000 PNU/mL or 1:1000 w/v. (See separate package inserts for standardized extracts such as cat hair, mite, or ragweed.)

STORAGE AND EXPIRATION DATING: Allergenic Extracts should be stored at 2-8 degrees C and kept at this range during office use. Refer to the vial label for the expiration date of the extract. Diluted extracts are inherently less stable than the concentrates. Dilutions of glycerinated extracts which result in a glycerin content of less than 50% are also less stable. Highly-diluted aqueous extracts 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.

REFERENCES

- ¹ Bousquet, J., Michel, F.B.: In vivo methods for study of allergy. *“Allergy Principles & Practice,”* 4th ed., Eds: Middleton, E., Reed, C.E., Ellis, E.F., et al., Mosby, St. Louis, 1993, 573 ff.
- ² Board of Directors: American Academy of Allergy and Immunology. Guidelines to minimize the risk from systemic reactions caused by immunotherapy with allergenic extracts. (Position statement). *J. Allergy and Clin. Immunol.* 1994; 93:811-12.