

INSTRUCTIONS

ALLERGENIC EXTRACTS FOR INTRADERMAL TESTING



HollisterStier

A Jubilant Organosys Company

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WARNINGS

This product is intended for use only by physicians who are experienced in the use of allergenic extracts, or for use under the guidance of an allergist.

Allergenic extracts may potentially elicit a severe life-threatening systemic reaction, rarely resulting in death.⁷ Therefore, emergency measures and personnel trained in their use should be available immediately in the event of such a reaction. Patients should be instructed to recognize adverse reaction symptoms and cautioned to contact the physician's office if symptoms occur.

Scratch, prick or puncture test first. Test intradermally only to those antigens giving negative or questionable reactions on scratch, prick or puncture testing.

This product should never be injected intravenously.

Patients on non-selective beta blockers may be more reactive to allergens given for testing or treatment and may be unresponsive to the usual doses of epinephrine used to treat allergic reactions.⁶

Refer also to the WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS Sections below for further discussion.

DESCRIPTION

Extracts for intradermal testing are supplied in sterile multi-dose vials containing, in addition to the extract allergens and antigens, 0.5% sodium chloride, 0.275% sodium bicarbonate, up to 2% glycerin, 2.5% glycerin for APTM products; and, as preservative, 0.4% phenol. The strength of these extracts may be expressed in terms of

1. Weight to Volume (w/v)
2. Protein Nitrogen Units/mL (PNU/mL)
3. Allergy Units/mL (AU/mL)
4. Bioequivalent Allergy Units/mL (BAU/mL)
5. Concentrate

1. **Weight to volume (w/v).** For regular extracts this describes the extraction ratio, i.e., the amount of crude allergen added to the extracting fluid. A 1:10 extract, therefore, indicates that the solution contains the extracted material from one gram of raw material added to each 10 mL of extracting fluid. The amount and composition of extracted material will vary with the kind of antigen, the extracting fluid, duration of extraction, pH, temperature, and other variables.

In contrast to this, APTM (acetone precipitated) extracts, if present, are prepared by reconstituting dry allergenically active concentrates produced by a precipitation process from extracts of raw materials. For those APTM extracts labeled on a weight per volume (w/v) basis, the strength designation indicates the dry weight of finished (acetone) precipitate per volume of reconstituting fluid. For example, 1:50 (w/v) means that each gram of dry precipitate obtained from the original extract is reconstituted in 50 mL of solution.

2. **Protein Nitrogen Units per mL (PNU/mL).** One protein nitrogen unit represents 0.0001 mg phosphotungstic 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, PNU contents of extracts from different manufacturers are not comparable unless the PNU method is known to be the same and 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.

- Allergy Units per mL (AU/mL).** The potency of standardized APTM and regular extracts labeled in Allergy Units (AU)/mL is determined by *in vitro* comparison to the reference standard established by the Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration.
- Bioequivalent Allergy Units per mL (BAU/mL).** When originally licensed, the Reference Preparations for standardized extracts were arbitrarily assigned 100,000 Allergy Units (AU)/mL. Subsequently, quantitative skin testing by the ID₅₀EAL method¹⁴ was used to determine that some Reference Preparations should be assigned 10,000 AU/mL, and others 100,000 AU/mL. To avoid possible confusion about this change in the method of allergy unit assignment, the nomenclature changed for standardized extracts whose allergy units are assigned based on quantitative skin testing, and are labeled in Bioequivalent Allergy Units (BAU)/mL. References labeled 10,000 BAU/mL can be diluted one to a half million fold, and references labeled 100,000 BAU/mL can be diluted one to 5 million fold and produce a sum of erythema diameter of 50 mm when Intradermal testing highly reactive subjects.
- Concentrate.** “Concentrate” label terminology applies to allergenic extract mixtures, where the individual allergens being combined vary in strength or the designation of strength.

CLINICAL PHARMACOLOGY

Allergenic extracts for intradermal testing used according to the DOSAGE AND ADMINISTRATION Section, produce erythema or erythema and wheal reactions in patients with significant IgE-mediated sensitivity to the relevant allergen. This allergic inflammatory response, although not completely understood, is thought to begin with the reaction of antigen with IgE on the surface of basophils, or mast cells, which initiates a series of biochemical events resulting in the production of histamine, slow-reacting substance of anaphylaxis and other mediators. These, in turn, produce the immediate-type “wheal and flare” skin reaction.

INDICATIONS AND USAGE

Certain diagnostics carry labeling which states **Allergenic Extract for Diagnostic Use Only**. Data to support the therapeutic use of products labeled with this statement have not been established.¹⁵

In addition to a carefully taken history, the use of intradermal testing extracts is an accepted method in the diagnosis of allergenic conditions.^{1, 2, 3} When scratch, prick or puncture reactions are small, or if the patient gives a history of allergic symptoms to a substance but scratch, prick or puncture tests are inconclusive, intradermal tests may be indicated. However, ANTI-GENS PRODUCING LARGE 3 TO 4+ SCRATCH, PRICK OR PUNCTURE TESTS SHOULD NOT BE TESTED INTRADERMALLY.

Extracts of all allergens do not produce equivalent results in intradermal testing. The intensity of the skin reaction produced will be determined by two factors: the degree of sensitivity of the patient and the nature of the antigenic extract applied. In general, pollen extracts produce whealing reactions, whereas other inhalants produce erythematous reactions with wheals less often. Skin tests to foods seldom produce whealing reactions except for infrequent instances of severe sensitivity to fish, nuts or spices, and rarely other foods.

CONTRAINDICATIONS

There are no known absolute contraindications to allergy skin testing. Patients with cardiovascular diseases or pulmonary diseases such as symptomatic asthma, and/or 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 anaphylaxis treatment regime.

WARNINGS

Scratch, prick or puncture test first. Test intradermally only to those antigens giving negative or questionable reactions on scratch, prick or puncture testing. Excessively large local reactions or systemic reactions are more likely to occur if the patient is skin tested shortly after exposure to large amounts of antigen to which he or she is sensitive. Therefore, use caution when applying pollen tests to patients during their active pollen season, or after an exposure to inhalant allergens that produce symptoms. Refer to boxed WARNINGS Section.

PRECAUTIONS

1. General

It is recommended that disposable syringes and needles are used for intradermal tests to prevent the possibility of accidental transfer of serum hepatitis and other infectious agents from one person to another.

Always have injectable epinephrine and a tourniquet available when tests

are being made. (See ADVERSE REACTION Section.)

Patients should be observed in the office for 30 to 45 minutes after each set of intradermal tests and instructed to return to the office promptly if symptoms of an allergic reaction or shock occur.

In order to avoid darkening and possible precipitation, do not dilute the following extracts with solutions containing phenol: Privet pollen and food extracts of White Potato, Corn, Oat, Rye, and Wheat. Injections of such extracts discolored by reaction with phenol may produce lasting tattoo-like discoloration of the skin.

2. **Information for Patients**

Patients should be instructed in the recognition of adverse reactions to diagnostic testing. Patients should be made to understand the importance of a 30 to 45 minute observation period and be warned to return to the office promptly if symptoms occur after leaving.

3. **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.

4. **Pregnancy** ^{4,5}

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 can affect reproduction capacity. Allergenic extracts should be given to a pregnant woman only if clearly needed.

5. **Nursing Mothers**

There are no current studies on secretion of the allergenic extract components in human milk or 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.

6. **Drug Interactions**

Patients on non-selective beta blockers may be more reactive to allergens given for testing or treatment and may be unresponsive to the usual doses of epinephrine used to treat allergic reactions.⁶

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.¹⁰ Topical steroids should be discontinued at the skin test site for at least 2-3 weeks before skin testing.^{10, 11}

Tricyclic antidepressants such as Doxepin should be withheld for at least 7 days before skin testing.¹² Topical local anesthetics may suppress the flare responses and should be avoided in skin test sites.¹³

7. **Geriatric Use**

Skin test wheal size decreases with age. The decrease in allergen-induced skin test reaction parallels that to histamine; therefore, appropriate positive skin test controls should always be performed.¹

8. **Pediatric Use**

Wheal sizes in response to allergen skin testing can be smaller in infants than in adults. The skin response to histamine parallels that for allergens; therefore, appropriate positive control skin tests should always be performed.¹

ADVERSE REACTIONS

1. **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 antihistamines, but they should be considered a warning of possible severe systemic reactions.

2. **Systemic Reactions**

With careful attention to dosage and administration, such reactions occur infrequently, but it must be remembered that allergenic extracts are highly potent in sensitive individuals and OVERDOSE could result in anaphylactic symptoms. Therefore, it is imperative that physicians administering allergenic extracts understand and be prepared for the treatment of severe reactions.

Adverse reaction frequency data for allergenic extract administration for testing and treatment show that risk is low.^{7,8}

It cannot be overemphasized that, under certain unpredictable combinations of circumstances, anaphylactic shock is a possibility. Other possible systemic reaction symptoms, in varying degrees of severity, are fainting, pallor, bradycardia, hypotension, angioedema, cough, wheezing, conjunctivitis, rhinitis and urticaria.

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

EPINEPHRINE:

ADULT DOSAGE: 0.3 to 0.5 mL should be injected. Repeat in 5 to 10 minutes if necessary.

PEDIATRIC DOSAGE: 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 0.05 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. Oxygen should be given by mask. Intravenous antihistamine, theophylline 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 in the event of a serious systemic or anaphylactic reaction not responsive to the above measures. [Ref. J. Allergy Clin. Immunol. 77 (2): 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.

OVERDOSAGE

See ADVERSE REACTIONS Section.

DOSAGE AND ADMINISTRATION

1. General

Parenteral Drug Products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

2. Intradermal Testing Methods

Cleanse the rubber stopper of the vial with liquid antiseptic before withdrawing extract. A sterile tuberculin syringe with 26-gauge, short-bevel needle should be used for the injection. The anterior surface of the upper and lower arm is preferable for testing. Cleanse the skin with soap

and water or wash with alcohol or other antiseptic. Introduce the needle between the superficial layers of the skin and inject 0.02 mL of the extract.

Test sites should be at least 2.5 cm apart, and no more than 10 to 20 antigens should be introduced at one time. This group can be followed with additional groups of 10, providing the reactions are not numerous or strong. The same amount of extract should be injected in each site for proper comparison. It is advisable to avoid testing with more than one allergen in the same group in each series, i.e., nuts, fish, epidermals, etc.

A site should be injected with 0.02 mL of the control solution. All skin tests should be validated by appropriate positive control tests (e.g., histamine) and negative control tests [e.g., Glycerin, Albumin Saline with Phenol (0.4%), or Buffered Saline with Phenol (0.4%)]. The negative control test should be the same material as is used as a diluting fluid in the tested extracts. Diluting fluid is used in the same way as an active test extract. False positive reactions are sometimes encountered in intradermal testing, and the possibility of irritation reactions should always be taken into consideration.

In cases where the patient is known to be quite sensitive, screen testing by scratch, prick or puncture method is recommended, and intradermal testing should be done with caution.

The intradermal strength supplied is usually safe for testing patients presenting negative scratch, prick or puncture test reactions. It is recommended that a 1:10 dilution of the stock intradermal strength be used in preliminary testing of patients not previously screened by scratch, prick or puncture tests.

3. Use of Antigen Mixes

The use of complicated mixes of unrelated pollens for testing is not recommended since in the case of a positive reaction it does not indicate which pollen(s) are responsible, and in the case of a negative reaction, it fails to indicate whether the individual pollens at full concentration would give a positive reaction.

4. Reading Skin Test Reactions

A positive reaction consists of an urticarial wheal with surrounding erythema (resembling somewhat a mosquito bite reaction) larger than the control site. The smallest reaction considered positive is erythema with a central papule at least 5 mm in diameter. In some instances with no reaction at the control site, erythema may be considered an indication of

sensitivity. In general, the size of wheal and erythema response correlates directly with the patient's sensitivity to that allergen.

Standardized Products

(a) **Mites:** The skin test concentrations of 30 AU/mL and 300 AU/mL in multiple dose vials are used for intradermal testing.

Intradermal skin test results in selected highly sensitive subjects are presented for reference purposes:

<u>Allergen</u>	<u>Number of Persons</u>	<u>AU/mL that Elicited $\Sigma E=50$ mm</u>	
		<u>Mean</u>	<u>2 Std. Dev. Range</u>
D. farinae	12	0.0609	0.0015-2.6016
D. pteronyssinus	12	0.0333	0.0003-4.0077

Intradermal extracts should be used as follows:

- (1) **Patients with a negative scratch, prick or puncture test:** Patients who do not react to a valid scratch, prick or puncture test should be tested intradermally with 0.02 to 0.05 mL of a 30 AU/mL extract solution. If this test is negative, a second intradermal test may be performed using a 300 AU/mL extract solution. The negative control used with this latter dilution should contain 0.5% glycerin.
 - (2) **Patients tested only by the intradermal method:** Patients suspected of being highly allergic should be tested with 0.02 to 0.05 mL of a solution containing 0.03 AU/mL. A negative test should be followed by repeat tests using progressively stronger concentrations until the maximum recommended strength of 300 AU/mL is reached. The negative control used with this latter dilution should contain 0.5% glycerin.
- (b) **Cat Hair and Cat Pelt:** Intradermal endpoint titration (IET) tests were completed with Cat Pelt extract using 15 subjects to determine the mean concentration required to produce a ΣE of 50 mm (D_{50}). That concentration contained 0.042 BAU/mL (range 0.002 to 0.890 BAU/mL).
IET tests were completed with Cat Hair extract using 15 subjects to determine the mean concentration required to produce a ΣE of 50 mm (D_{50}). That concentration contained 0.049 BAU/mL (range 0.006 to 0.661 BAU/mL).

Intradermal extract should be used as follows:

Intradermal Tests should be done only on patients with a negative prick or puncture test. Patients who do not react to a valid prick or puncture test should be tested intradermally with 0.02 to 0.05 mL of a 100 BAU/mL extract solution. If this test is negative, a second intradermal test may be performed using a 1,000 BAU/mL extract solution. If the intradermal dilutions were prepared from glycerinated concentrate, the negative control used with this latter dilution should contain 5% glycerin.

Standardized Cat Hair and Cat Pelt products are not interchangeable with each other or any other cat products including those labeled AU/mL.

- (c) **Ragweed pollen (Short Ragweed or Giant and Short Ragweed Mixture) Amb a 1 (formerly known as Antigen E) Assayed:** The intradermal strength for Short Ragweed extract is usually 500 PNU, which by calculation contains approximately 0.7 to 3 units of Amb a 1/mL. For Giant and Short Ragweed mix the suggested intradermal strength is 500 PNU, which by calculation contains 0.4 to 1.5 units of Amb a 1/mL. These strengths are usually safe for testing patients previously having negative scratch, prick or puncture test reactions. A 1:10 dilution of the stock intradermal strength should be used in preliminary testing of patients not previously screened by scratch, prick, or puncture tests.

A study of ragweed sensitive patients⁹ indicates that intradermal tests, using 0.05 mL of extract, produce positive reactions (1+ to 2+) at Amb a 1 concentrations of from 2.7×10^{-1} to 2.7×10^{-6} units per mL. The equivalent PNU range was 100 to 0.001 PNU per mL.

Skin tests are graded in terms of the wheal and erythema response noted at 15 minutes. Wheal and erythema size may be recorded by actual measurement of the extent of both responses.

5. Geriatric Use

The dose is the same in patients of all age groups. Because the wheal size in response to allergen skin testing decreases with age, appropriate histamine positive control skin tests must be performed.¹

6. Pediatric Use

The dose is the same in patients of all age groups. Wheal size in response to allergen skin testing can be smaller in infants than in adults. Appropriate histamine positive control skin tests must be performed.¹

Refer to the following table to determine the skin test sensitivity grade. The corresponding ΣE (sum of the longest diameter and the mid-point orthogonal diameters of erythema) is also presented.

Grade	Erythema mm	Papule or Wheal mm	Corresponding mm \pm SE
0	<5	<5	<10
\pm	5-10	5-10	10-20
1+	11-20	5-10	20-40
2+	21-30	5-10	40-60
3+	31-40	10-15 ^a	60-80
4+	>40	>15 ^b	> 80

^a or with pseudopods ^b or with many pseudopods
A positive skin reaction to any allergen must be interpreted in light of the patient's history of symptoms, time of year, known exposures, and eating habits.

THE SKIN TESTS ARE IN NO WAY A SUBSTITUTE FOR A CAREFUL ALLERGENIC HISTORY; RATHER, THEY SERVE AS ADDITIONAL INFORMATION TO AID IN IDENTIFYING CAUSATIVE ALLERGENS IN PATIENTS WITH ALLERGIC DISORDERS.

HOW SUPPLIED

Most allergens are available in multiple dose 5 mL vials at PNU, w/v, some mixes as Concentrate, Standardized Mite products at AU/mL (30 AU/mL and 300 AU/mL each species), or Standardized Grass products at BAU/mL [100 BAU/mL and 1,000 BAU/mL (Bermuda 100 BAU/mL only)]. Product labels state vials are for intradermal testing and list strengths.

STORAGE

The expiration date of the diagnostic extracts is listed on the container label. The extract should be stored at 2° to 8°C, and kept at this temperature range during office use.

LIMITED WARRANTY

A number of factors beyond our control could reduce the efficacy of this product or even result in an ill effect following its use. These include storage and handling of the product after it leaves our hands, diagnosis, dosage, method of administration and biological differences in individual patients. Because of these factors, it is important that this product be stored properly, and that the directions be followed carefully during use.

No warranty, express or implied, including any warranty of merchantability or fitness, is made. Representatives of the Company are not authorized to vary the terms or the contents of any printed labeling, including the package insert, for this product except by printed notice from the Company's headquarters. The prescriber and user of this product must accept the terms hereof.

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