

ALLERGENIC EXTRACT
INSTRUCTIONS FOR USE
AND DOSAGE SCHEDULE
ALLERMED LABORATORIES, INC.
7203 Convoy Ct., San Diego, CA 92111-1020
(800) 221-2748 U.S. License 467

WARNINGS

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.

This allergenic extract is not directly interchangeable with other allergenic extracts. The initial dose must be based on skin testing as described in the dosage and administration section of this insert. Patients being switched from other types of extracts, such as alum precipitated extracts, should be started as though they were coming under treatment for the first time. Patients should be instructed to recognize adverse reaction symptoms and cautioned to contact the physician's office if reaction symptoms occur. As with all allergenic extracts, severe systemic reactions may occur. In certain individuals these reactions may be life threatening. Patients should be observed for at least 20 minutes following treatment, and 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 not be injected intravenously (see Dosage and Administration). Refer also to the Warnings, Precautions, Adverse Reactions and Overdosage 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 contains the aqueous extractables from allergenic source material in extracting solution containing 0.25% sodium chloride, 0.125% sodium bicarbonate, and 50% glycerol. 0.4% phenol is added as a preservative. The weight by volume value shown on the label is a measurement of extract concentration, rather than extract potency.

CLINICAL PHARMACOLOGY

Positive skin tests with allergenic extract are the result of histamine release from mast cells sensitized with allergen specific IgE. The exact mechanisms by which immunotherapy relieves symptoms of allergy are still under investigation. Elevations in allergen-specific IgG antibodies and an increase in the activity of T suppressor lymphocytes appear to be some of the immunologic changes that occur from hyposensitization. (1, 2, 3)

INDICATIONS AND USAGE

Allergenic extract may be used as a diagnostic skin test reagent in persons suspected of being sensitive to the allergenic source material from which the extract is made. Skin tests should be used in conjunction with a thorough allergic history to establish the relevance of a given allergen in the etiology of allergic disease. (4, 5, 6)

Immunotherapy with allergenic extract is indicated in persons suffering from allergic rhinitis, bronchitis, conjunctivitis, urticaria and asthma. The therapeutic efficacy of allergenic extract has been proven in ragweed, grass, and mountain cedar pollinosis, cat-induced asthma and hypersensitivity to hymenoptera venoms. (7-12)

Immunotherapy may be used along with or exclusive of antihistamines and other medications used to control allergic symptoms.

CONTRAINDICATIONS

Allergenic extract should not be administered to a non-allergic person. However, there are no absolute contraindications to the use of allergenic extract for treatment in appropriate individuals. Relative contraindications include: **EXTREME SENSITIVITY TO AN ALLERGEN** — Determined from the allergic history, or from previous anaphylaxis following skin testing or subcutaneous injection; **AUTO-IMMUNE DISEASE** — Individuals with autoimmune disease may be at risk, due to the possibility of routine immunizations exacerbating symptoms of the underlying disease; **PREGNANCY** — In limited controlled studies of women receiving allergenic extract during conception and throughout all trimesters of pregnancy, no evidence was found that extract is harmful to the fetus or mother. However, because of the known pharmacologic action of histamine on uterine muscle, any treatment that might result in the release of significant amounts of this mediator should be avoided if possible (13). See *Precaution #4*: **MYOCARDIAL INFARCTION** — Patients who have experienced a recent myocardial infarction may not be able to tolerate immunotherapy. As in all of the above circumstances, the benefit to risk ratio must be carefully evaluated; **BLEEDING DIATHESIS** — Patients with a bleeding tendency should not be tested or treated with allergenic extract, unless the physician responsible believes that such procedures are safe to perform.

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 allergens prior to skin testing or immunotherapy.

WARNINGS

The only approved method for determining hypersensitivity to Allermed Laboratories Allergenic Extracts is by diagnostic skin testing (See **DOSAGE AND ADMINISTRATION — DIAGNOSIS**).

Physicians who administer allergenic extract should have emergency medication and equipment available to treat anaphylaxis (14). See **Precautions, Adverse Reactions and Overdosage** below.

To reduce the risk of anaphylaxis, the following measures must be observed:

1. Concentrated extract must be diluted before use for intradermal skin testing and for beginning immunotherapy. It should never be injected intravenously during testing or treatment procedures.
2. Patients who are highly sensitive, determined from clinical findings and test results, may require that treatment start with a very weak concentration of extract, such as 1:10,000,000 v/v.
3. The dosage of fresh (new) extract given to a patient receiving maintenance injections must be reduced to one-fourth the amount given from the previous (old) lot (See **Immunotherapy**, last paragraph).
4. Patients who are transferred to standardized extract after previous treatment with unstandardized extract must be skin tested with serial dilutions, starting with a 1:100,000 v/v dilution of the standardized extract, to determine a safe, non-reacting starting dose.
5. Patients who are transferred to this extract after treatment with alum precipitated or other modified extract must re-start injections with the beginning recommended dose of this extract.

PRECAUTIONS

1. Extract should be stored at 2°C to 8°C since higher temperatures may adversely affect the stability of the product. Do not freeze.
2. After the needle is inserted subcutaneously, the plunger should be withdrawn slightly to check for the presence of blood in the syringe. If blood is observed, a new injection should be prepared and given at another site, observing the same precautions.
3. 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 allergic reaction.
4. **PREGNANCY CATEGORY C**. Allergenic extract. Animal reproduction studies have not been conducted with allergenic extract. It is also not known whether allergenic extract can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Allergenic extract should be given to a pregnant woman only if clearly needed.
5. **PATIENT INSTRUCTIONS**: Patients should be instructed to remain in the physician's office for at least 20 minutes after skin testing and after each treatment injection, and immediately notify the physician if symptoms of a generalized reaction or shock occur.
6. **CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY**: Long term studies have not been conducted with allergenic extracts to determine their potential for carcinogenesis, mutagenesis, and impairment of fertility.
7. **NURSING MOTHERS**: Data are not available on the secretion of allergenic extract in human milk and it is not known what affect this might have on the nursing infant.
8. **PEDIATRIC USE**: The dose of allergenic extract recommended for children is the same as that used for adults, except in the injection of large doses of extract for treatment. In this case, the amount of extract given to a child may be modified so that the discomfort of the injection is minimized.

ADVERSE REACTIONS

Local Reactions: The occurrence of a hive 5 to 15 minutes after the subcutaneous injection of extract does not require a reduction in dosage. However, a local reaction with edema larger than 2 cm in diameter or swelling and redness that persist for several hours or longer indicates that too much extract has been given. Treatment should be altered as follows:

1. Additional injections should not be given until all evidence of the reaction has disappeared.
2. The next injection administered should be 50% of the last non-reacting dose or less, depending upon the size and severity of the local reaction.
3. Subsequent injections should be continued at the reduced dose-age unless the physician responsible for treatment believes that it is safe to increase the dose, and that possible clinical improvement would result from the administration of a larger dose of extract.

Systemic Reactions: Systemic (generalized) reactions may range from a mild exacerbation of the patient's allergic symptoms to hives, anaphylactic shock, or even death from anaphylaxis. The reaction usually occurs 5 to 20 minutes after injection. As a rule, the more quickly a reaction develops, the more serious it is likely to become. Symptoms may include sneezing, coughing, itching, shortness of breath, abdominal cramps, vomiting, diarrhea, tachycardia, hypotension and respiratory failure in severe cases. The reaction is usually stopped by the subcutaneous injection of Epinephrine HCl 1:1,000 (See **Overdosage** below). The oral administration of antihistamines and the placement of a tourniquet proximal to the injection site are helpful adjuncts. In the event that additional measures are required, it may be necessary to treat the patient for **BRONCHOSPASM** with intravenous aminophylline, intravenous fluids and corticosteroids; for **HYPOTENSION**

with vasopressors, volume repletion, isoproterenol and corticosteroids; for LARYNGEAL OBSTRUCTION with oxygen and tracheostomy and for CARDIAC ARREST with cardiopulmonary resuscitation and other appropriate measures.

Immunotherapy after anaphylaxis should only be continued if the cause of the reaction can be identified and appropriate precautions taken to insure that a subsequent reaction does not occur.

OVERDOSAGE

A strong local reaction to the injection of extract may be treated with oral antihistamines and the local application of a cold compress. The dosage must be reduced and additional extract must not be given until all evidence of the reaction has disappeared.

A systemic reaction following the injection of extract must be treated immediately as follows (Ref. #4, vol. 2, p. 888):

- 0.01 mL/kg up to 0.2 mL of aqueous epinephrine HCl 1:1000 subcutaneously at the injection site of antigen.
- 0.01 mL/kg up to 0.3 mL of aqueous epinephrine HCl 1:1000 subcutaneously at another site.
- Diphenhydramine intravenously or intramuscularly, 1.25 mg/kg up to 50 mg.
- Tourniquet above the injection site of antigen.
- Specific reactions:
 - Bronchospasm: intravenous aminophylline 4 mg/kg up to 500 mg given over 10 to 15 minutes, aqueous hydrocortisone 5 mg/kg up to 200 mg, oxygen.
 - Laryngeal edema: oxygen, intubation, tracheostomy.
 - Hypotension: vasopressors, fluids, corticosteroids.
 - Cardiac arrest: resuscitation, sodium bicarbonate, defibrillation, antiarrhythmia medications.

DOSAGE AND ADMINISTRATION

Diagnosis: Concentrated extract may be used for scratch or prick testing. Provided that the patient is not extremely sensitive, concentrated extract may be used for scratch or prick testing. In the case of extreme sensitivity, the extract should be diluted 10 fold before a scratch or prick test is performed. Extract for intradermal testing must be used as follows:

- Patients with positive scratch or prick tests:* It is not advisable to perform an intradermal skin test if the patient has a positive scratch or prick test.
- Patients with a negative scratch or prick test:* Patients who do not react to a valid scratch or prick test should be tested intradermally with 0.05 mL of a 1:1000 v/v dilution of the concentrate. If the test is negative, a second test should be performed with 0.05 mL of a 1:100 v/v dilution of concentrate.
- Patients tested only by the intradermal method:* Patients suspected of being highly allergic should be tested with 0.05 mL of a 1:100,000 v/v dilution of the concentrate. A negative test should be followed by repeat tests using 10 fold stronger concentrations until the maximum dose of 0.05 mL of a 1:100 v/v dilution is reached.

Interpretation of Results

Scratch and Prick Test

A negative test shows only a slight red area at the site of scarification or prick penetration. Positive tests are scored as follows:

- 1+ Erythema with a 5 mm wheal
- 2+ Erythema with a 5-10 mm wheal
- 3+ Erythema with a 10-15 mm wheal
- 4+ Erythema with a wheal 15 mm (or larger) with pseudopodia

Intradermal Test

A negative test shows no change in the appearance and size of the 5 mm wheal created by the I.D. injection of 0.05 mL of extract. Positive tests are scored as follows:

- 1+ Erythema 10-20 mm with a 5-10 mm wheal
- 2+ Erythema 20-30 mm with a 5-10 mm wheal
- 3+ Erythema 30-40 mm with a 10-15 mm wheal
- 4+ Erythema greater than 40 mm with a 15 mm wheal (or larger) with pseudopodia

Immunotherapy

Allergenic extract should be administered subcutaneously in the outer aspect of the upper arm using a sterile tuberculin syringe and needle. The skin should be cleaned with 70% alcohol and aseptic technique should be observed in removing the extract from the vial. Care must be taken to avoid injecting the extract into a blood vessel because of the risk of anaphylaxis.

Concentrated extract must be diluted before administration to new patients. A 1:100,000 v/v dilution of concentrate is usually satisfactory to start treatment. However, as a precaution against overdose, a skin test with the intended starting dose should be done to help evaluate the patient's sensitivity to the product. If the skin response is larger than 5 mm edema/15 mm erythema, the extract is too strong and must be diluted before it is given subcutaneously. The doses shown in the Suggested Dosage Schedule below are recommended unless the patient's skin test response and allergic history indicates that more dilute extract should be used.

Little is known about the required accumulated dosage of allergen that is needed to relieve symptoms. However, studies have shown that high dose immunotherapy is efficacious in the treatment of allergic rhinitis and asthma. For this reason, treatment with extract from Vial #5 is

recommended, providing the patient can tolerate the extract without experiencing local or systemic reactions. Treatment with Vial #6 may be used for patients who have not had adverse reactions to extract in Vial #5 and who require more concentrated extract to control or relieve symptoms.

Patients who have received allergenic extract for maintenance therapy SHOULD NOT be given the same dose from a fresh vial of extract. IT IS ADVISABLE TO REDUCE THE DOSAGE OF FRESH EXTRACT TO ONE-FOURTH THE AMOUNT GIVEN FROM A PREVIOUS LOT OF EXTRACT MADE AT THE SAME CONCENTRATION AND BY THE SAME FORMULA.

Suggested Dosage Schedule

	Vial #1 1:100,000 v/v frequency twice weekly	Vial #2 1:10,000 v/v frequency twice weekly	Vial #3 1:1,000 v/v frequency once weekly	Vial #4 1:100 v/v frequency once weekly	Vial #5 1:10 v/v frequency every two-four weeks	Vial #6 Concentra te frequency every two-four weeks
No	mL	mL	mL	mL	mL	mL
1	0.025	0.025	0.025	0.025	0.025	0.025
2	0.05	0.05	0.05	0.05	0.05	0.05
3	0.10	0.10	0.10	0.10	0.10	0.10
4	0.15	0.15	0.15	0.15	0.15	0.15
5	0.20	0.20	0.20	0.20	0.20	0.20
6	0.25	0.25	0.25	0.25	0.25	-
7	0.30	0.30	0.30	0.30	0.30	-

HOW SUPPLIED

Allergenic extract is supplied in 5 mL dropper vials for scratch or prick testing and in 10, 30, and 50 mL vials for bulk use.

Storage and Handling

Extract should be stored at 2-8°C since higher temperatures may adversely affect stability. Do not freeze.

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