



P.O. Box 800
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U.S. Government License No. 308

ALLERGENIC EXTRACTS

STANDARDIZED CAT HAIR EXTRACT

Suggested Dosage Schedule
and Instructions

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.

STANDARDIZED CAT HAIR EXTRACT WITH POTENCY LABELING IN BIOEQUIVALENT ALLERGY UNITS per mL (BAU/mL) IS NOT INTERCHANGEABLE WITH OTHER CAT EXTRACTS. STANDARDIZED CAT HAIR EXTRACT IS NOT INTERCHANGEABLE WITH STANDARDIZED CAT PELT EXTRACTS LABELED IN BIOEQUIVALENT ALLERGY UNITS OR WITH OTHER CAT EXTRACTS LABELED IN ALLERGY UNITS (AU).

THE INITIAL DOSE OF STANDARDIZED CAT HAIR EXTRACT 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 TO STANDARDIZED CAT HAIR EXTRACT 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 IMMUNOTHERAPY. PATIENTS WITH LABILE OR STEROID-DEPENDENT ASTHMA ARE "HIGH RISK PATIENTS" WHO REQUIRE SPECIAL CAUTION IN DOSE ADMINISTRATION AND SHOULD REMAIN IN THE OFFICE FOR AT LEAST 30 MINUTES. AIRWAY OBSTRUCTION IN HIGH RISK PATIENTS CAN BE MONITORED BY PEAK FLOW MEASUREMENTS BEFORE AND AFTER ADMINISTRATION OF ALLERGENS. 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%.

RISK OF ANAPHYLAXIS SHOULD BE WEIGHED AGAINST BENEFITS IN IMMUNOTHERAPY: IN PATIENTS RECEIVING BETA BLOCKERS AS THEY MAY NOT BE RESPONSIVE TO BETA ADRENERGIC DRUGS SHOULD ANAPHYLAXIS OCCUR; IN PATIENTS WITH UNSTABLE OR STEROID-DEPENDENT ASTHMA; OR IN PATIENTS WITH CARDIOVASCULAR DISEASE.

THIS PRODUCT SHOULD NOT BE INJECTED INTRAVENOUSLY.

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

DESCRIPTION

Each vial contains a sterile extract of cat (*Felis domesticus*) pelt and cat dander, 0.50% sodium chloride, 0.25% sodium bicarbonate, 50% glycerin by volume, and 0.4% phenol as a preservative. Source materials for the extract are dry cat dander and dry defatted cat pelt.

Standardized Cat Hair Extract is a sterile solution for intracutaneous or subcutaneous administration. The extract is standardized by comparing potency in cat allergen 1 (*Fel d 1*) units measured by radial immunodiffusion against a reference

standard from the Center for Biologics Evaluation and Research of the U.S. Food and Drug Administration (FDA).⁽¹⁻³⁾ An extract with 10 to 19.9 *Fel d I* units per mL is designated as 10,000 Bioequivalent Allergy Units/mL (BAU/mL) by the FDA based on quantitative skin testing.⁽²⁾ Greer Standardized Cat Hair Extract concentrate is 10,000 BAU/mL.

Cat albumin is considered to be a minor allergen, but may be significant for certain patients.⁽⁴⁾ *Fel d I* is a relatively stable component while albumin is more labile and more easily destroyed by heat.⁽⁵⁻⁶⁾ For lot release, Standardized Cat Hair Extract is compared to FDA reference by isoelectric focusing (IEF) to differentiate it from Cat Pelt Extract.

CLINICAL PHARMACOLOGY

The allergic reaction is dependent upon the presence of antigen-specific IgE antibodies that are bound to specific receptors on mast cells and basophils and has been demonstrated for cat-allergic individuals.⁽⁷⁾ 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.⁽⁸⁾ In the skin these mediators are responsible for the characteristic wheal and flare reaction.⁽⁹⁾

An increase in cat antigen-specific IgG antibodies has been demonstrated as a result of immunotherapy.⁽¹⁰⁻¹¹⁾ The complete mechanisms of immunotherapy are not known and are still under investigation.

Immunotherapy with cat extract has been studied by several investigators. It is generally believed that hyposensitization with this product is helpful in reducing allergic symptoms associated with exposure to cat allergens in homes or the environment.⁽¹²⁻¹⁶⁾

INDICATIONS AND USAGE

Standardized Cat Hair Extract is indicated for the diagnosis and treatment (immunotherapy) of patients with a history of allergy to cats. The diagnosis of cat allergy is established by the allergy history, clinical evaluation, and skin test reactivity. Cat emanations are common causes of allergy and occur not only upon direct exposure to cats, but also occur in high levels in house dust and other environmental dusts.⁽¹⁷⁾ Persons suspected of having allergy to house dust should be tested for sensitivity to cat allergens. Immunotherapy is indicated when cat allergy is established and the patient cannot avoid exposure to cat allergens.

The use of cat extract for the above purposes should be made only by physicians with special familiarity with 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 cat antigens is contraindicated in those individuals who do not exhibit skin test or clinical sensitivity to cat antigens. (See below under WARNINGS AND PRECAUTIONS)

Cat 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.

Other contraindications include:

EXTREME SENSITIVITY TO CAT - Determined from previous anaphylaxis following skin testing.

AUTOIMMUNE DISEASE - Individuals with autoimmune disease may be at risk, due to the possibility of routine immunizations exacerbating symptoms of the underlying disease.

WARNINGS

Please also refer to warning box at beginning of package insert.

Concentrated extracts must be diluted with sterile diluent prior to first use on a patient for immunotherapy or intradermal testing. All concentrates of allergenic extracts are manufactured to assure high potency and therefore 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,⁽¹⁸⁾ but may occur later.⁽¹⁹⁾ 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 this and the precautions should be discussed prior to immunotherapy (see PRECAUTIONS below).

Standardized Cat Hair Extract labeled in Bioequivalent Allergy Units is not interchangeable with Standardized Cat Pelt Extract or with cat extracts labeled in Allergy Units. Patient doses stated or calculated in Allergy Units should not be confused with Bioequivalent Allergy Units because the BAU is ten times as potent as the Allergy Unit used for cat extracts before September 1992.

The dosage must be reduced when starting a patient on fresh Standardized Cat Hair Extract or when transferring a patient from any other cat extract product to Standardized Cat Hair 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 a loss of extract potency during storage in the physician's office. **The cat allergen content of old and new extracts must be compared and adjusted by dosage reduction and/or dilution before the new extract is administered.** 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 cat allergens. 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.

Allergenic extracts should be temporarily withheld from patients or the dose adjusted downward 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.

Risk of anaphylaxis should be weighed against benefits of immunotherapy: in patients receiving beta blockers as they may not be responsive to beta adrenergic drugs should anaphylaxis occur; in patients with unstable or steroid-dependent asthma; or in patients with cardiovascular disease.

Not for intravenous use!

PRECAUTIONS

GENERAL:

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. The physician must be prepared to treat anaphylaxis should it occur and have the necessary drugs and equipment on hand to do so.⁽²⁰⁾ 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 20 minutes so that any adverse reaction can be observed and properly handled. This time should be extended to at least 30 minutes for high-risk patients such as those with labile or steroid-dependent asthma or those suffering an exacerbation of their symptoms.⁽²⁴⁾ Airway obstruction in high risk patients can be monitored by peak flow measurements before and after administration of allergens.

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

A separate, sterile syringe and needle or sterile disposable unit must be used for each patient 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.

Do not use the same syringe for different extracts, nor for the diluent after using it for an extract.

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.⁽¹⁸⁾ The size of the local reaction should be recorded, because increasingly large local reactions may precede a subsequent systemic reaction with increasing dosage. In particular, this includes unusual swelling and/or tenderness at the injection site or reactions such as shortness of breath, rhinorrhea, sneezing, coughing, wheezing, nausea, dizziness or faintness. Reactions may occur some time after leaving the physician's office, in which case medical attention should be sought immediately.

The patient should be instructed to report any unusual reactions to the physician.

DRUG INTERACTIONS:

Skin test diagnosis with Allergenic Extracts may result in false negative responses when used within 3-10 days of H₁ -Blockers such as cetrizine, loratadine, and terfenadine. The inhibitory effect of astemizole may last up to 60 days.⁽²⁵⁾ These products suppress histamine skin test reactions and could mask a positive response.

The suppressive action of other drugs such as tricyclic antidepressants or topical steroids should be considered and emphasizes the need for a histamine positive-control test.

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 carefully weighed against the benefits of immunotherapy.

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 cat extract. It is also not known whether cat extract can cause fetal harm when administered to a pregnant woman or whether it can affect reproduction capacity. Cat extract should be given to a pregnant woman only if clearly needed.

There is no evidence of adverse effects of allergenic extract on the fetus. Studies have not been performed in animals to determine whether this extract affects fertility in males or females, has teratogenic potential, or has 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 standardized cat extract has not been well-studied in children, children and geriatric patients appear to tolerate injections of allergenic extract well. Use in children under six years of age is not recommended. Cat extracts have been administered to children with adverse systemic responses occurring only when given in doses sufficiently high to induce an immediate hypersensitivity reaction.⁽¹⁴⁻¹⁵⁾

ADVERSE REACTIONS

SYSTEMIC REACTIONS

Adverse systemic reactions may occur within minutes with any allergenic extract, including cat. These reactions 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 with allergenic extracts have occurred rarely.⁽²¹⁾ Anaphylaxis and deaths following the subcutaneous injection of extracts have also been

reported by the British Committee on Safety of Medicine.⁽²²⁾ 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 degree of sensitivity of the patient. In general, immunotherapy with allergenic extracts is considered to be safe.⁽²³⁾ Despite all precautions, occasional reactions are unavoidable.

Adverse reactions should be treated as follows:

A. A tourniquet should be immediately applied to the extremity above the site of 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

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 immunotherapy. 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, 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 reviewed and if necessary adjusted as outlined above under WARNINGS.

DOSAGE AND ADMINISTRATION

GENERAL

Concentrated standardized cat hair extracts should be diluted prior to intradermal testing or first use in immunotherapy.

Normal or buffered saline or normal saline with human serum albumin may be used to prepare appropriate dilutions. Vials should be visually inspected to ensure particulate free prior to use.

DIAGNOSTIC TESTING

For the patient with a suspected diagnosis of cat allergy, 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 the response is negative, this initial test may be followed by intradermal testing where the clinical history is strongly indicative of allergy to cats. Use of a positive and negative control is recommended.

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. A marking pencil may be used to indicate the site locations.

Skin tests read after 15 to 20 minutes are graded in terms of the induration (wheal) and erythema (flare) response compared to the appropriate controls. Wheal and flare sizes may be recorded by actual measurements. The largest diameter of the wheal and flare may be recorded, or the sum of the largest diameter and the orthogonal (right angle) diameter wheal or flare may be used.

Puncture, prick or scratch testing:

The skin test concentration of 10,000 BAU/mL is used for puncture, prick or scratch testing. Puncture tests with Standardized Cat Hair Extract performed on ten highly sensitive cat puncture-positive patients showed a mean diameter wheal of 6.0 mm \pm 2.2 mm and a mean erythema of 36.7 mm \pm 6.7 mm. 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; 1:1000 w/v) may be used as a positive control. A 50% glycerosaline solution may be used as the negative control.

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.

Intradermal testing:

Extract for intradermal testing must be prepared by diluting the stock concentrate with sterile diluent (use normal or buffered saline or normal saline with human serum albumin) or obtained by ordering the appropriate dilutions ready made. 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). As a negative control, use 0.5% to 1% glycerosaline solution.

Intradermal skin tests with 0.05 mL of three-fold serial dilutions in ten highly sensitive cat puncture test positive (sum of erythema >57 mm) persons showed the results in Table I:

TABLE I
BAU/mL to Elicit 50mm
Sum of Diameter Erythema Reaction

Geometric	
<u>Mean</u>	<u>Range</u>
0.0542	0.0050 - 0.4809

Intradermal extract is used as follows:

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 with 0.02 to 0.05 mL of a 50 BAU/mL extract dilution. If this test is negative, a second intradermal test may be performed using a 200 BAU/mL extract dilution.

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 and the dose adjusted according to puncture test reactivity. Other patients suspected of being moderately allergic may be tested with an intradermal test dose of 0.02 to 0.05 mL of a 0.05 BAU/mL dilution. A negative test should be followed by repeat tests using progressively stronger concentrations until the maximum recommended strength of 200 BAU/mL is reached.

Skin tests are graded in terms of the wheal and erythema response noted at 15 to 20 minutes. Wheal and erythema size may be recorded by actual measurement of the extent of both responses.

IMMUNOTHERAPY

Immunotherapy is administered by subcutaneous injection. **Not for intravenous use!**

Dosage of allergenic extracts is individualized according to the patient's sensitivity, the clinical response, and tolerance to the extract administered during the early phases of an injection regimen. The initial dose of the extract should be calculated based on the puncture test reactivity. The initial dose of the extract may be as low as 0.1 mL of a 0.005 to 0.05 BAU/mL dilution (dilution 5 or 6 in Table II below) or even less for the exquisitely sensitive patient. Patients with lesser sensitivity may be started at 0.1 mL of a 0.5 to 5 BAU/mL dilution. The amount of allergenic extract is increased at each injection by no more than 50% of the previous amount; 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. Any evidence of systemic reaction is an indication for a significant reduction (at least 50%) in the subsequent dose. The upper limits of dosage have not been established; however, doses larger than 0.2 mL of 5,000 BAU/mL may cause discomfort upon injection because of the high glycerin content. The dosage of allergenic extract does not vary significantly with the respiratory allergic disease under treatment.

To prepare dilutions for intradermal and therapeutic use starting from a 5,000 or 10,000 BAU/mL stock concentrate proceed as follows: (Note add 1 mL of concentrate to 9.0 mL of sterile diluent and make additional dilutions in the same manner.)

TABLE II

<u>Dilution</u>	<u>Extract</u>	<u>Diluent</u>	<u>BAU/mL</u>	
0	Concentrate		5,000	10,000
1	1 mL concentrate	9.0	500	1,000
2	1 mL dilution 1	9.0	50	100
3	1 mL dilution 2	9.0	5	10
4	1 mL dilution 3	9.0	0.5	1.0
5	1 mL dilution 4	9.0	0.05	0.1
6	1 mL dilution 5	9.0	0.005	0.01

The optimal interval between doses of allergenic extract has not been definitely established. However, as is customarily practiced, injections are given 1, 2 or 3 times per week until the maintenance dose of extract is reached. At this time, the injection interval 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 after the last injection, 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 depending on a consideration of 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 one-quarter of the previous dose.

The usual duration of immunotherapy 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 extract containing 10,000 Bioequivalent Allergy Units per mL (10,000 BAU/mL) in 50% glycerin v/v or other dilutions as requested by the physician are supplied in 5, 10, 30 and 50 mL vials. Cat extracts are also supplied in 5 mL dropper vials for puncture, prick or scratch testing. All dilutions of cat extracts are supplied in 50% Glycero-Coca's solution.

STORAGE

Standardized Cat Hair Extract should be stored at 2-8 degrees C and kept at this temperature range during office use. Refer to vial label for expiration date of concentrated extract. Dilutions should not be used past the expiry dating on the concentrate. Dilutions of concentrated extract result in a glycerin content of less than 50% which is less stable, particularly for the serum component. Potency of the dilution can be checked by skin test in comparison to a fresh dilution of the extract on a known cat allergic individual.

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