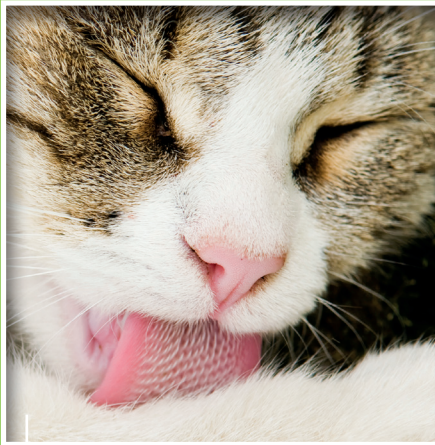




HollisterStier
Allergy



□ ITEM NO. 4815

WARNING Important Safety Information
(See full prescribing information for complete boxed warning.)

Intended for use only by licensed health care provider experienced in administering allergenic extracts and trained to provide immediate emergency treatment in the event of a life-threatening reaction. Observe patients for at least 30 minutes following administration. Immunotherapy may not be suitable for patients with medical conditions that reduce their ability to withstand a systemic reaction. Allergenic extracts can cause serious systemic reactions, including anaphylactic shock and in rare cases death, especially in patients who have severe or steroid-dependent asthma, cardiovascular disease, or in patients who use beta blockers. Do not inject intravenously. This product is intended for subcutaneous injection for immunotherapy and percutaneous use for diagnosis. Refer to contraindications, warnings, precautions, and adverse reaction sections for more detailed information.

STANDARDIZED CAT Extracts

This product line offers the diversity of two testing and treatment options with Fel d 1 and albumin.

ITEM NO.	DESCRIPTION	UNIT
4815	AP Cat Hair – Scratch (Standardized)	5 mL 10,000 BAU/mL
	AP Cat Hair – Bulk (Standardized)	10 mL, 50 mL Glycerinated 10,000 BAU/mL
4810	AP Cat Pelt – Scratch (Standardized)	5 mL 10,000 BAU/mL
	AP Cat Pelt – Bulk (Standardized)	50 mL Glycerinated 10,000 BAU/mL

Fel d 1 is universally present in U.S. homes (even homes without pets)¹, meaning all of your patients have some home exposure to cat allergens. Because everyone is at risk for possible allergic sensitization, it's important you have the most exacting options for diagnosis and treatment.

Our manufacturing process allows us to target specific levels of Fel d 1 for greater lot to lot consistency.

Why It Matters

- While our standardized cat extracts are produced using our exclusive Acetone Precipitated (AP) process, potency is standardized by the FDA.
- Tighter release limits than the FDA means more consistent lot to lot product. For instance, our cat hair release limit is 12.5-19.9 units/mL and our cat pelt release limit is 13.3-19.9 Fel d 1 Units/mL vs. the FDA limit of 10-19.9 units/mL.²
- Approximately 22% of patients with a cat allergy have specific IgE antibodies to cat albumin.³ Cat pelt extracts have a greater amount of albumin than cat hair extracts.³ Therefore, testing for both cat hair and cat pelt is beneficial.
- Like all of our antigens, our standardized cat extracts don't contain phenol which can denature the proteins in allergenic extracts.⁴

QUALITY. PURITY. RELIABILITY.

SEE INSERT INSIDE.



HollisterStier
Allergy

3525 North Regal Street | Spokane, WA 99207-5788
hsallergy.com | 800.495.7437

Footnotes

- 1 Arbes, S. C. (2004). Dog Allergen (Can f1) and Cat Allergen (Fel D1) in U.S. Homes: Results from the National Survey of Lead Allergens in Housing. *The Journal of Allergy and Clinical Immunology*, 114(1), 111-117.
- 2 Internal data on file.
- 3 Cox, L., Nelson, H., Lockey, R., Calabria, C., Chacko, T., Finegold, I., Nelson, M., Weber, R., Bernstein, D. I., Blessing-Moore, J., Khan, D. A., Lang, D. M., Nicklas, R. A., Oppenheimer, J., Portnoy, J. M., Randolph, C., Schuller, D. E., Spector, S. L., Tilles, S., & Wallace, D. (2011). Allergen immunotherapy: a practice parameter third update. *The Journal of allergy and clinical immunology*, 127(1 Suppl), S1-S55. <https://doi.org/10.1016/j.jaci.2010.09.034>
- 4 H.S. Nelson. Preparing and mixing allergen vaccines for subcutaneous immunotherapy. R.F. Lockey, S.C. Bukantz, & J. Bousquet (Eds.), *Allergens and allergen immunotherapy*, 4th ed., p. 315, 2008.

Adverse reactions on our products can be reported by calling 800-495-7437, or by emailing adversereactions@jhs.jubl.com. You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch, or call 800-FDA-1088.

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INSTRUCTIONS AND DOSAGE SCHEDULE

**ALLERGENIC EXTRACT
STANDARDIZED CAT HAIR
AP™ Acetone Precipitated**


HollisterStier

WARNINGS

This product is intended for use only by licensed medical personnel experienced in administering allergenic extracts and trained to provide immediate emergency treatment in the event of a life-threatening reaction.

Allergenic extracts may potentially elicit a severe life-threatening systemic reaction, rarely resulting in death¹. Therefore, emergency measures and personnel trained in their use must 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.

This standardized extract may be more potent than regular extracts and therefore is not directly interchangeable with Jubilant HollisterStier LLC non-standardized extracts, or other manufacturers' products. Standardized pelt and hair extracts are manufactured from different source materials and are not interchangeable. Standardized cat extracts labeled in AU/mL are not interchangeable with extracts labeled in BAU/mL. See DESCRIPTION Section.

This product should never be injected intravenously.

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

DESCRIPTION: Allergenic extracts are sterile solutions containing the extractables of the source material and components of the extraction fluid. Standardized Cat Hair is available as an extract from acetone precipitated source material in the extraction fluid described below.

Source Material:

Cat Hair Source Material consists of hair clippings and/or shavings which have undergone an acetone precipitation process. AP™ Acetone Precipitated Cat Hair is derived from the precipitate formed when acetone is added to an aqueous extract.

Extracting Fluid:

Glycero-Coca's: Contains 0.5% sodium chloride, 0.275% sodium bicarbonate, and 50% glycerin (v/v) as a preservative.

Product Concentration:

1. **Bioequivalent Allergy Units.** When originally licensed, standardized cat extracts containing 10 to 20 Fel d 1 units/mL were arbitrarily assigned 100,000 Allergy Units (AU)/mL. Subsequently, quantitative skin testing by the ID₅₀EAL method²³ was used to determine that standardized cat extracts containing 10 to 19.9 Fel d 1 units/mL should be assigned 10,000 AU/mL rather than 100,000 AU/mL. To avoid possible confusion about this change in allergy unit assignment, the nomenclature changed for cat extracts, and such products are labeled in Bioequivalent Allergy Units (BAU/mL).

Each lot of Standardized Cat Hair extract is standardized by quantitating the Fel d 1 content based on standards on file with the Center for Biologics Evaluation and Research (CBER) of the U.S. Food and Drug Administration. Test extracts are diffused in agar containing standard anti-serum to Fel d 1, and compared to the diffusion of a reference cat allergen preparation². The potency of the extract is expressed as units of Fel d 1 per mL, and extracts containing 10-19.9 Fel d 1 units per mL are labeled at 10,000 BAU/mL.

It has been recognized that there are differences in the levels of non Fel d 1 allergens among standardized cat extracts which utilize different source materials. Isoelectric focusing (IEF) patterns have been shown to be predictive of the presence of non Fel d 1 allergens. Therefore, each lot of Standardized Cat Hair is compared by IEF to a Cat Pelt Extract Reference and a Cat Hair Extract Reference on file with the CBER. The labeled name of the cat extract (i.e., Cat Hair Extract or Cat Pelt Extract) must be supported by matching the IEF profile of the corresponding reference.

2. **Concentrate.** Concentrate label terminology applies to allergenic extract **mixtures** where the individual allergens being combined vary in strength or the designation of strength.

e.g. Concentrate	
50% Short Ragweed 1:20 w/v	
25% Std. Cat Hair 10,000 BAU/mL	
25% Std. Mite D. farinae 10,000 AU/mL	

Should the physician choose to calculate the actual strength of each component in the "Concentrate" mixture, the following formulation may be used:

$$\text{Actual Allergen Strength in Concentrate Mixture} = \text{Allergen Manufacturing Strength} \times \% \text{ Allergen in Formulation (by volume or parts)}$$

Ingredients:

Active ingredients are the allergen(s) noted on the vial label. Preservative is 50% (v/v) glycerin. Glycerinated extracts contain 0.5% sodium chloride, 0.275% sodium bicarbonate and 50% glycerin (v/v) as a preservative.

CLINICAL PHARMACOLOGY:¹³ The mechanisms by which hyposensitization is achieved are not completely understood. It has been shown that repeated injections of appropriate allergenic extracts will ameliorate the intensity of allergic symptoms upon contact with the allergen.^{6, 7, 8, 9} Clinical studies which address the efficacy of immunotherapy are available. The allergens which have been studied are cat, mite, and some pollen extracts.^{10, 11, 12, 13, 14, 15}

IgE antibodies bound to receptors on mast cell membranes are required for the allergic reaction, and their level is probably related to serum IgE concentrations. Immunotherapy has been associated with decreased levels of IgE, and also with increases in allergen specific IgG "blocking" antibody.

The histamine release response of circulating basophils to a specific allergen is reduced in some patients by immunotherapy, but the mechanism of this change is not yet clear.

The relationships among changes in blocking antibody, reaginic antibody, and mediator-releasing cells, and successful immunotherapy need study and clarification.

INDICATIONS AND USAGE:^{3, 16, 17, 18} Allergenic extracts are indicated for use in diagnosis and immunotherapy of patients presenting symptoms of allergy (hay fever, rhinitis, etc.) to specific environmental allergens. The selection of allergenic extracts to be used should be based on a thorough and carefully taken history of hypersensitivity, and confirmed by skin testing.^{19, 20}

The use of mixed or unrelated antigens for skin testing is not recommended since, in the case of a positive reaction, it does not indicate which component of the mix is responsible for the reaction, while, in the case of a negative reaction, it fails to indicate whether the individual antigens at full concentration would give a positive reaction. Utilization of such mixes for compounding a treatment may result, in the former case, in administering unnecessary antigens and, in the latter case, in the omission of a needed allergen.

Avoidance of allergens is to be advocated if possible, but cannot always be attained, e.g., allergy to cat dander in kennel owners and employees, cat breeders, research workers, veterinarians, etc.

Allergens to which a patient is extremely sensitive should not be included in treatment mixes with allergens to which there is much less sensitivity, but should be administered separately. This allows individualized and better control of dosage increases, including adjustments in dosage becoming necessary after severe reactions which may occur to the highly reactive allergen.

CONTRAINDICATIONS: There are no known absolute contraindications to immunotherapy. However, see PRECAUTIONS for pregnancy risks.

Patients with cardiovascular diseases or pulmonary diseases such as symptomatic asthma, and/or those 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 allergy treatment regimen. Patients should be treated only if the benefit of treatment outweighs the risks.¹

Treat patients only with allergens to which they are allergic as shown by skin test reaction, have a history of symptoms on exposure to the allergen, and are likely to be exposed again.

Any injections, including immunotherapy, should be avoided in patients with a bleeding tendency.

Since there are differences of opinion concerning the possibility of routine immunizations exacerbating autoimmune diseases, immunotherapy should be given cautiously to patients with autoimmune diseases and only if the risk from exposure is greater than the risk of exacerbating the autoimmune process.

WARNINGS: See WARNINGS at the beginning of this instruction sheet.

Allergenic extract 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; or (3) exposure to excessive amounts of clinically relevant allergen prior to a scheduled injection. Do not start immunotherapy during a period of symptoms due to exposure. Since

the individual components of the extract are those to which the patient is allergic, and to which he will be exposed, typical allergic symptoms may follow shortly after the injection, particularly when the antigen load from exposure plus the injected antigen exceeds the patient's antigen tolerance.

THE CONCENTRATE SHOULD NOT BE INJECTED AT ANY TIME UNLESS TOLERANCE HAS BEEN ESTABLISHED. DILUTE CONCENTRATED EXTRACTS WITH STERILE DILUENT FOR INTRADERMAL TESTING.

INJECTIONS SHOULD NEVER BE GIVEN INTRAVENOUSLY. Subcutaneous injection is recommended. Intracutaneous or intramuscular injection may produce large local reactions or be excessively painful.

AFTER INSERTING NEEDLE SUBCUTANEOUSLY, BUT BEFORE INJECTING, ALWAYS WITHDRAW THE PLUNGER SLIGHTLY. IF BLOOD APPEARS IN THE SYRINGE, CHANGE NEEDLE AND GIVE THE INJECTION IN ANOTHER SITE.

IF CHANGING FROM HAIR TO PELT EXTRACTS OR VICE-VERSA: Hair and pelt extracts differ in their non Fel d 1 allergens and are not interchangeable. Therefore, if patients are switched from one type of cat extract to another, the initial dose should be based on skin tests as noted under DOSAGE AND ADMINISTRATION, 3. Immunotherapy.

IF THE PREVIOUS EXTRACT WAS NON-STANDARDIZED OR WAS STANDARDIZED AND LABELED IN ALLERGY UNITS PER mL (AU/mL): This standardized extract may be more potent than non-standardized extracts. Initiate therapy as though patient had not been receiving immunotherapy, or determine initial dose by skin test using serial dilutions of the extract. See PRECAUTIONS and DOSAGE AND ADMINISTRATION Sections.

IF CHANGING TO A DIFFERENT LOT OF JUBILANT HOLLISTERSTIER EXTRACT: Even though it is the same formula and concentration, the first dose of the new extract should not exceed 50% of the last administered dose from the previous extract.

IF THE EXTRACT PREVIOUSLY USED WAS FROM ANOTHER MANUFACTURER: Since manufacturing processes and sources of raw materials differ among manufacturers, the interchangeability of extracts from different manufacturers cannot be insured. The starting dose of the extract therefore should be greatly decreased even though the extract is the same formula and dilution. Initiate therapy as though patient had not been receiving immunotherapy, or determine initial dose by skin test using serial dilutions of the extract. See DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS Sections.

IF A PROLONGED PERIOD OF TIME HAS ELAPSED SINCE THE LAST INJECTION: Patients may lose tolerance for allergen injections during prolonged periods between doses. The duration of tolerance is an individual characteristic and varies from patient to patient. In general, the longer the lapse in the injection schedule, the greater dose reduction required. If the interval since last dose is over four weeks, perform skin tests to determine starting dose.

IF THE PREVIOUS EXTRACT WAS OUTDATED: The dating period for allergenic extracts indicates the time that they can be expected to remain potent under refrigerated storage conditions (2° - 8° C). During the storage of extracts, even under ideal conditions, some loss of potency occurs. For this reason, extracts should not be used beyond their expiration date. If a patient has been receiving injections of an outdated extract, he may experience excessive local or systemic reactions when changed to a new, and possibly more potent, extract. In general, the longer the material has been outdated, the greater the dose reduction necessary for the fresh extract.

IF CHANGING FROM ALUM-ADSORBED TO AQUEOUS OR GLYCERINATED EXTRACTS: When the patient previously has been receiving alum-adsorbed or alum-precipitated extract, the safest course is to start over as though the patient had not been receiving immunotherapy. See DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS in product instructions.

IF ANY OTHER CHANGES HAVE BEEN MADE IN THE EXTRACT CONCENTRATE FORMULA: Changes other than those listed above may include situations such as a redistribution of component parts or percentages, a difference in extracting fluid (i.e., change from non-glycerin extracts to 50% glycerin extracts), combining two or more stock concentrates, or any other change.

It should be recognized that any change in formula can affect a patient's tolerance of the treatment. The usual 1/2 of the previous dose for a new extract may produce an adverse reaction: extra dilutions are recommended whenever starting a revised formula. The greater the change, the greater the number of dilutions required.

Proper selection of the dose and careful injection should prevent most systemic reactions. It must be remembered, however, that allergenic extracts are highly potent in sensitive individuals, and that systemic reactions of varying degrees of severity may occur, including urticaria, rhinitis, conjunctivitis, wheezing, coughing, angioedema, hypotension, bradycardia, pallor, laryngeal edema, fainting, or even anaphylactic shock and death. Patients should be informed of this, and the precautions should be discussed prior to immunotherapy. (See PRECAUTIONS below.) Severe systemic reactions should be treated as indicated in the ADVERSE REACTIONS Section.

PRECAUTIONS:

(1) General

Concentrated extracts must be diluted prior to use: See DOSAGE AND ADMINISTRATION Section below for detailed instructions on the dilution of allergenic extracts.

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 diluted with sterile Albumin Saline with Phenol (0.4%) diluent may be more potent than extracts diluted with diluents which do not contain stabilizers. When changing from non-stabilized to stabilized diluent, consider weaker initial dilutions for both intradermal testing and immunotherapy.

Sterile solutions, vials, syringes, etc. should be used and aseptic precautions observed in making dilutions. To avoid cross-contamination, do not use the same needle to withdraw materials from vials of more than one extract, or extract followed by diluent.

A sterile tuberculin syringe graduated in 0.01 mL units should be used to measure each dose from the appropriate dilution. Aseptic techniques should always be employed when injections of allergenic extracts are being administered.

A separate sterile syringe should be used for each patient to prevent transmission of serum hepatitis and other infectious agents from one person to another.

Patient reactions to previous injections should be reviewed before each new injection. A conservative dosage schedule should be followed by the physician until a pattern of local responses is established which can be used to monitor increases in dosage.

Rarely, a patient is encountered who develops systemic reactions to minute doses of allergen and does not demonstrate increasing tolerance to injections after several months of treatment. If systemic reactions or excessive local responses occur persistently at very small doses, efforts at immunotherapy should be stopped.

PATIENTS SHOULD BE OBSERVED IN THE OFFICE FOR 30 MINUTES AFTER EACH TREATMENT INJECTION. Most severe reactions will occur within this time period, and rapid treatment measures should be instituted. See ADVERSE REACTIONS Section for such treatment measures.

(2) Information for Patients

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

(3) 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.⁵

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.²⁴ Topical steroids should be discontinued at the skin test site for at least 2-3 weeks before skin testing.^{24, 25}

Tricyclic antidepressants such as Doxepin should be withheld for at least 7 days before skin testing.²⁶ Topical local anesthetics may suppress the flare responses and should be avoided in skin test sites.²⁷

(4) 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.

(5) Pregnancy²²

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.

For women who have been getting maintenance doses of allergen without side effect, the occurrence of pregnancy is not an indication to stop immunotherapy.

(6) 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.

(7) Pediatric Use

Since dosage for the pediatric population is the same as for adults^{3,4}, the larger volumes of solution may produce excessive discomfort. Therefore, in order to achieve the total dose required, the volume of the dose may need to be divided into more than one injection per visit.

(8) **Geriatric Use**

The reactions from immunotherapy can be expected to be the same in elderly patients as in younger ones. Elderly patients may be more likely to be on medication that could block the effect of epinephrine which could be used to treat serious reactions, or they could be more sensitive to the cardiovascular side effect of epinephrine because of pre-existing cardiovascular disease.²⁶

ADVERSE REACTIONS:

(1) **Local Reactions**

Some erythema, swelling or pruritus at the site of injection are common, the extent varying with the patient. Such reactions should not be considered significant unless they persist for at least 24 hours. Local reactions (erythema or swelling) which exceed 4-5 cm in diameter are not only uncomfortable, but also indicate the possibility of a systemic reaction if dosage is increased. In such cases the dosage should be reduced to the last level not causing the reaction and maintained at this level for two or three treatments before cautiously increasing again.

Large persistent local reactions may be treated by local cold, wet dressings and/or the use of oral antihistamines. They should be considered a warning of possible severe systemic reactions and an indication of the need for temporarily reduced dosages.

A mild burning immediately after the injection is to be expected. This usually leaves in 10 to 20 seconds.

(2) **Systemic Reactions**

With careful attention to dosage and administration, systemic reactions occur infrequently, but it cannot be overemphasized that in sensitive individuals, any injection could result in anaphylactic shock. Therefore, it is imperative that physicians administering allergenic extracts understand and be prepared for the treatment of severe reactions.

Other possible systemic reactions which may occur in varying degrees of severity are laryngeal edema, fainting, pallor, bradycardia, hypotension, angioedema, cough, wheezing, conjunctivitis, rhinitis, and urticaria. Adverse reaction frequency data for allergenic extract administration for testing and treatment show that risk is low.^{1, 21}

If a systemic or anaphylactic reaction does occur, apply a tourniquet above the site of injection and inject 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 DOSAGE

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

PEDIATRIC: 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. Airway patency should be insured. Oxygen should be given by mask. Intravenous antihistamine, theophylline and/or corticosteroids may be used if necessary after adequate epinephrine and circulatory support has been given.

Emergency resuscitation measures and personnel trained in their use must be available immediately in the event of a serious systemic or anaphylactic reaction not responsive to the above measures [Ref. J. Allergy and Clinical Immunology, 77(2):p. 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.

Severe systemic reactions mandate a decrease of at least 50% in the next dose, followed by cautious increases. Repeated systemic reactions, even of a mild nature, are sufficient reason for the cessation of further attempts to increase the reaction-causing dose.

(3) **Adverse Event Reporting**

Report all adverse events to Jubilant HollisterStier LLC, Customer Technical Services Department at 1 (800) 992-1120. A voluntary adverse event reporting system for health professionals is available through the FDA MEDWATCH program. Preprinted forms (FDA Form 3500) are available from the FDA by calling 1 (800) FDA-1088. Completed forms should be mailed to MEDWATCH, 5600 Fisher Lane, Rockville, MD 20852-9787 or Fax to: 1 (800) FDA-0178.

OVERDOSAGE: See ADVERSE REACTIONS Section.

DOSAGE AND ADMINISTRATION:^{3, 16, 17, 18}

(1) **General**

Sterile aqueous diluent containing human serum albumin is recommended when preparing dilutions of the concentrate for intradermal testing or immunotherapy.

Dilutions should be made accurately and aseptically, using sterile diluent, vials, syringes, etc. Mix thoroughly and gently by rocking or swirling.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

(2) **Diagnosis**

To identify highly sensitive individuals and as a safety precaution, it is recommended that a prick or puncture test using a drop of the extract concentrate be performed prior to initiating intradermal testing. Prick tests are performed by placing a drop of extract on the skin and piercing through the drop into the skin with a slight lifting motion. Puncture tests are performed by placing a drop of extract on the skin and piercing through the drop perpendicular to the skin with a device such as a Prick Lancetter. After about 1 minute the extract may be wiped away with a dry sponge. The diameter of wheal and erythema reactions are measured 15 minutes after the prick or puncture is made, and the sensitivity class of the patient determined by the table presented at the end of the diagnosis section. Less sensitive individuals (Class 0 to 1+) can be tested intradermally with the recommended dilutions of the extract concentrate (see intradermal testing information below).

The skin test concentration of 10,000 BAU/mL (10-19.9 Fel d 1 Units/mL) in dropper vials is used for prick or puncture testing. Puncture tests performed on 15 highly sensitive subjects showed the following:

Product	Mean Sum of Wheal ± 1 Std. Dev. (mm)	Mean Sum of Erythema ± 1 Std. Dev. (mm)
Standardized Cat Hair	15.1 ± 3.8	73.3 ± 14.3

The sum of a skin response is the sum of the longest diameter and the midpoint orthogonal diameter.

Intradermal endpoint titration (IET) tests were completed using the same 15 subjects to determine the mean concentration required to produce a ΣE of 50mm (D₅₀). 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% glycerol.

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.

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

Class	Wheal	Erythema	Corresponding ΣE
	Diameter	Diameter	
0	<5 mm	<5 mm	<10 mm
±	5-10 mm	5-10 mm	10-20 mm
1+	5-10 mm	11-20 mm	20-40 mm
2+	5-10 mm	21-30 mm	40-60 mm
3+	10-15 mm ^a	31-40 mm	60-80 mm
4+	>15 mm ^b	>40 mm	>80 mm

a. or with pseudopods

b. or with many pseudopods

(3) **Immunotherapy**

Allergen extracts should be administered using a sterile syringe with 0.01 mL gradations and a 25-27 gauge x 1/2" to 5/8" needle. The injections are given subcutaneously. The most common sites of injection are the lateral aspect of the upper arm or thigh. Intracutaneous or intramuscular injections may produce large local reactions which may be very painful.

Dosage of allergenic extracts is a highly individualized matter and varies according to the degree of sensitivity of the patient, his clinical response, and tolerance to the extract administered during the early phases of an injection regimen. The starting dose should be based on skin tests of the extract to be used for immunotherapy. To prepare dilutions for intradermal and therapeutic use, make a 1:10 dilution by adding 1.0 mL of the concentrate to 9.0 mL of sterile aqueous diluent.

Subsequent serial dilutions are made in a similar manner. (See Table I.) To determine the starting dose, begin intradermal testing with the most dilute extract preparation. Inject 0.02 mL and read the reaction after 15 minutes. Intradermal testing is continued with increasing concentrations of the extract until a reaction of 10-20 mm erythema (ΣE 20-40 mm) and/or a 5 mm wheal occurs. This concentration at a dose of 0.03 mL then can serve as a starting dose for immunotherapy and be increased by 0.03 mL to as high as 0.12 mL increments each time until 0.3 mL is reached, at which time a dilution 10 times as strong can be used, starting with 0.03 mL. Proceed in this way until a tolerance dose is reached or symptoms are controlled. Suggested maintenance dose is 0.2 mL of the concentrate. Occasionally, higher doses are necessary to relieve symptoms. Special caution is required in administering doses greater than 0.2 mL. The interval between doses normally is 3 to 7 days.

This is offered as a suggested schedule for average patients and will be satisfactory in most cases. However, the degree of sensitivity varies in many patients. The size of the dose should be adjusted and should be regulated by the patient's tolerance and reaction. The size of the dose should be decreased if the previous injection resulted in marked local or the slightest general reaction. Another dose should never be given until all local reactions resulting from the previous dose have disappeared.

In some patients, the dosage may be increased more rapidly than called for in the schedule. In seasonal allergies, treatment should be started and the interval between doses regulated so that at least the first 20 doses will have been administered by the time symptoms are expected. Thus, the shorter the interval between the start of immunotherapy and the expected onset of symptoms, the shorter the interval between each dose. Some patients may even tolerate daily doses. A maintenance dose, the largest dose tolerated by the patient that relieves symptoms without producing undesirable local or general reactions is recommended for most patients. The upper limits of dosage have not been established; however, doses larger than 0.2 mL of the glycerinated concentrate may be painful due to the glycerin content. The dosage of allergenic extract does not vary significantly with the respiratory allergic disease under treatment. The size of this dose and the interval between doses will vary and can be adjusted as necessary. Should symptoms develop before the next injection is scheduled, the interval between doses should be decreased. Should allergic symptoms or local reactions develop shortly after the dose is administered, the size of the dose should be decreased. In seasonal allergies, it is often advisable to decrease the dose to one-half or one-quarter of the maximum dose previously attained if the patient has any seasonal symptoms.

The interval between maintenance doses can be increased gradually from one week to 10 days, to two weeks, to three weeks, or even to four weeks if tolerated. Repeat the doses at a given interval three or four times to check for untoward reactions before further increasing the interval. Protection is lost rapidly if the interval between doses is more than four weeks. (See WARNINGS Section.)

The usual duration of treatment has not been established. A period of two or three years of injection therapy constitutes an average minimum course of treatment.

TABLE I
TEN-FOLD DILUTION SERIES
Standardized Extracts Labeled 10,000 BAU/mL

Dilution	Extract	+ Diluent	=	BAU/mL Concentration
0	Concentrate	+ 0 mL	=	10,000
1	1 mL concentrate	+ 9 mL	=	1,000
2	1 mL dilution #1	+ 9 mL	=	100
3	1 mL dilution #2	+ 9 mL	=	10
4	1 mL dilution #3	+ 9 mL	=	1
5	1 mL dilution #4	+ 9 mL	=	0.1
6	1 mL dilution #5	+ 9 mL	=	0.01
7	1 mL dilution #6	+ 9 mL	=	0.001

(4) Pediatric Use (See PRECAUTIONS)

HOW SUPPLIED: Standardized Cat Hair allergenic extract is supplied for diagnostic and therapeutic use:

Diagnostics:

Prick or puncture testing, 10,000 BAU/mL [50% glycerin (v/v)] in 5 mL dropper vial.

Bulk Therapeutics, multiple dose vials in 50% glycerin (v/v).

- 10 mL vial, 10,000 BAU/mL
- 30 mL vial, 10,000 BAU/mL
- 50 mL vial, 10,000 BAU/mL

STORAGE:

The expiration date of the Standardized Cat Hair extract containing 10,000 BAU/mL is listed on the container label. The extract should be stored at 2° - 8° C. Dilutions of the BAU/mL concentrates are less stable and, if loss of potency is suspected, should be checked by skin testing with equal bioequivalent allergen units of a freshly prepared dilution on known cat allergic individuals.

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.

The foregoing statement is made in lieu of any other warranty of merchantability or fitness. Representatives of the Company are not authorized to vary the terms of this warranty or the contents of any printed labeling 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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INSTRUCTIONS AND DOSAGE SCHEDULE

ALLERGENIC EXTRACT STANDARDIZED CAT PELT AP™ Acetone Precipitated



HollisterStier

345040-H05

WARNINGS

This product is intended for use only by licensed medical personnel experienced in administering allergenic extracts and trained to provide immediate emergency treatment in the event of a life-threatening reaction.

Allergenic extracts may potentially elicit a severe life-threatening systemic reaction, rarely resulting in death¹. Therefore, emergency measures and personnel trained in their use must 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.

This standardized extract may be more potent than regular extracts and therefore is not directly interchangeable with our non-standardized extracts, or other manufacturers' products. Standardized pelt and hair extracts are manufactured from different source materials and are not interchangeable. Standardized cat extracts labeled in AU/mL are not interchangeable with extracts labeled in BAU/mL. See DESCRIPTION Section.

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.⁵

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

DESCRIPTION: Allergenic extracts for subcutaneous injection and prick or puncture for diagnosis are sterile solutions containing the extractables of the source material and components of the extraction fluid. Standardized Cat Pelt is available as an extract from acetone precipitated source material in two different extraction fluids described below.

Source Material:

Cat Pelt source material consists of hair and whole epidermis which have undergone an acetone precipitation process. AP™ Acetone Precipitated Cat Pelt is derived from precipitate formed when acetone is added to an aqueous extract.

Extracting Fluids:

Glycero-Coca's: Contains 0.5% sodium chloride, 0.275% sodium bicarbonate, and 50% glycerin (v/v) as a preservative.

Product Concentration:

- Bioequivalent Allergy Units.** When originally licensed, standardized cat extracts containing 10 - 20 Fel d 1 units/mL were arbitrarily assigned 100,000 Allergy Units (AU)/mL. Subsequently, quantitative skin testing by the ID₅₀EAL method²³ was used to determine that standardized cat extracts containing 10 to 19.9 Fel d 1 units/mL should be assigned 10,000 AU/mL rather than 100,000 AU/mL. To avoid possible confusion about this change in allergy unit assignment, the nomenclature changed for cat extracts, and such products are labeled in Bioequivalent Allergy Units (BAU/mL).

Each lot of Standardized Cat Pelt extract is standardized by quantitating the Fel d 1 content based on standards on file with the Center for Biologics Evaluation and Research (CBER) of the U.S. Food and Drug Administration. Test extracts are diffused in agar containing standard anti-serum to Fel d 1, and compared to the diffusion of a reference cat allergen preparation². The potency of the extract is expressed as units of Fel d 1 per mL, and extracts containing 10-19.9 Fel d 1 units per mL are labeled at 10,000 BAU/mL.

It has been recognized that there are differences in the levels of non Fel d 1 allergens among standardized cat extracts which utilize different source materials. Isoelectric focusing (IEF) patterns have been

shown to be predictive of the presence of non Fel d 1 allergens. Therefore, each lot of Standardized Cat Pelt is compared by IEF to a Cat Pelt Extract Reference and a Cat Hair Extract Reference on file with the CBER. The labeled name of the cat extract (i.e., Cat Hair Extract or Cat Pelt Extract) must be supported by matching the IEF profile of the corresponding reference.

- Concentrate.** Concentrate label terminology applies to allergenic extract **mixtures** where the individual allergens being combined vary in strength or the designation of strength.

e.g. Concentrate
50% Short Ragweed 1:20 w/v
25% Std. Cat Pelt 10,000 BAU/mL
25% Std. Mite <i>D. farinae</i> 10,000 AU/mL

Should the physician choose to calculate the actual strength of each component in the "Concentrate" mixture, the following formulation may be used:

$$\begin{array}{rcc} \text{Actual Allergen Strength} & & \text{Allergen Manufacturing} \\ \text{in Concentrate Mixture} & = & \text{Strength} \\ & & \times \\ & & \text{\% Allergen in Formulation} \\ & & \text{(by volume or parts)} \end{array}$$

Ingredients:

Active ingredients are the allergen(s) noted on the vial label. Preservative is 50% (v/v) glycerin. Glycerinated extracts contain 0.5% sodium chloride, 0.275% sodium bicarbonate and 50% glycerin (v/v) as a preservative.

CLINICAL PHARMACOLOGY:¹³ The mechanisms by which hyposensitization is achieved are not completely understood. It has been shown that repeated injections of appropriate allergenic extracts will ameliorate the intensity of allergic symptoms upon contact with the allergen.^{6, 7, 8, 9} Clinical studies which address the efficacy of immunotherapy are available. The allergens which have been studied are cat, mite, and some pollen extracts.^{10, 11, 12, 13, 14, 15}

IgE antibodies bound to receptors on mast cell membranes are required for the allergic reaction, and their level is probably related to serum IgE concentrations. Immunotherapy has been associated with decreased levels of IgE, and also with increases in allergen specific IgG "blocking" antibody.

The histamine release response of circulating basophils to a specific allergen is reduced in some patients by immunotherapy, but the mechanism of this change is not yet clear.

The relationships among changes in blocking antibody, reaginic antibody, and mediator-releasing cells, and successful immunotherapy need study and clarification.

INDICATIONS AND USAGE:^{3, 16, 17, 18} Allergenic extracts are indicated for use in diagnosis and immunotherapy of patients presenting symptoms of allergy (hay fever, rhinitis, etc.) to specific environmental allergens. The selection of allergenic extracts to be used should be based on a thorough and carefully taken history of hypersensitivity, and confirmed by skin testing.^{19, 20}

The use of mixed or unrelated antigens for skin testing is not recommended since, in the case of a positive reaction, it does not indicate which component of the mix is responsible for the reaction, while, in the case of a negative reaction, it fails to indicate whether the individual antigens at full concentration would give a positive reaction. Utilization of such mixes for compounding a treatment may result, in the former case, in administering unnecessary antigens and, in the latter case, in the omission of a needed allergen.

Avoidance of allergens is to be advocated if possible, but cannot always be attained, e.g., allergy to cat dander in kennel owners and employees, cat breeders, research workers, veterinarians, etc.

Allergens to which a patient is extremely sensitive should not be included in treatment mixes with allergens to which there is much less sensitivity, but should be administered separately. This allows individualized and better control of dosage increases, including adjustments in dosage becoming necessary after severe reactions which may occur to the highly reactive allergen.

CONTRAINDICATIONS: There are no known absolute contraindications to immunotherapy. See PRECAUTIONS for pregnancy risks.

Patients with cardiovascular diseases or pulmonary diseases such as symptomatic asthma, and/or those 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 allergy treatment regimen. Patients should be treated only if the benefit of treatment outweighs the risks.¹

Any injections, including immunotherapy, should be avoided in patients with a bleeding tendency.

Since there are differences of opinion concerning the possibility of routine immunizations exacerbating autoimmune diseases, immunotherapy should be given cautiously to patients with autoimmune diseases and only if the risk from exposure is greater than the risk of exacerbating the autoimmune process.

WARNINGS: See WARNINGS at the beginning of this instruction sheet.

Allergenic extract 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; or (3) exposure to excessive amounts of clinically relevant allergen prior to a scheduled injection. Do not start immunotherapy during a period of symptoms due to exposure. Since the individual components of the extract are those to which the patient is allergic, and to which s/he will be exposed, typical allergic symptoms may follow shortly after the injection, particularly when the antigen load from exposure plus the injected antigen exceeds the patient's antigen tolerance.

THE CONCENTRATE SHOULD NOT BE INJECTED AT ANY TIME UNLESS TOLERANCE HAS BEEN ESTABLISHED. DILUTE CONCENTRATED EXTRACTS WITH STERILE DILUENT FOR INTRADERMAL TESTING.

INJECTIONS SHOULD NEVER BE GIVEN INTRAVENOUSLY. Subcutaneous injection is recommended. Intracutaneous or intramuscular injection may produce large local reactions or be excessively painful.

AFTER INSERTING NEEDLE SUBCUTANEOUSLY, BUT BEFORE INJECTING, ALWAYS WITHDRAW THE PLUNGER SLIGHTLY. IF BLOOD APPEARS IN THE SYRINGE, CHANGE NEEDLE AND GIVE THE INJECTION IN ANOTHER SITE.

IF CHANGING FROM HAIR TO PELT EXTRACTS OR VICE-VERSA: Hair and pelt extracts differ in their non-Fel d 1 allergens and are not interchangeable. Therefore, if patients are switched from one type of cat extract to another, the initial dose should be based on skin tests as noted under DOSAGE AND ADMINISTRATION, 3. Immunotherapy.

IF THE PREVIOUS EXTRACT WAS NON-STANDARDIZED OR WAS STANDARDIZED AND LABELED IN ALLERGY UNITS PER mL (AU/mL): This standardized extract may be more potent than non-standardized extracts. Initiate therapy as though patient had not been receiving immunotherapy, or determine initial dose by skin test using serial dilutions of the extract. See PRECAUTIONS and DOSAGE AND ADMINISTRATION Sections.

IF CHANGING TO A DIFFERENT LOT OF EXTRACT: Even though it is the same formula and concentration, the first dose of the new extract should not exceed 50% of the last administered dose from the previous extract.

IF THE EXTRACT PREVIOUSLY USED WAS FROM ANOTHER MANUFACTURER: Since manufacturing processes and sources of raw materials differ among manufacturers, the interchangeability of extracts from different manufacturers cannot be insured. The starting dose of the extract therefore should be greatly decreased even though the extract is the same formula and dilution. Initiate therapy as though patient had not been receiving immunotherapy, or determine initial dose by skin test using serial dilutions of the extract. See DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS Sections.

IF A PROLONGED PERIOD OF TIME HAS ELAPSED SINCE THE LAST INJECTION: Patients may lose tolerance for allergen injections during prolonged periods between doses. The duration of tolerance is an individual characteristic and varies from patient to patient. In general, the longer the lapse in the injection schedule, the greater dose reduction required. If the interval since last dose is over four weeks, perform skin tests to determine starting dose.

IF THE PREVIOUS EXTRACT WAS OUTDATED: The dating period for allergenic extracts indicates the time that they can be expected to remain potent under refrigerated storage conditions (2° - 8°C). During the storage of extracts, even under ideal conditions, some loss of potency occurs. For this reason, extracts should not be used beyond their expiration date. If a patient has been receiving injections of an outdated extract, he may experience excessive local or systemic reactions when changed to a new, and possibly more potent, extract. In general, the longer the material has been outdated, the greater the dose reduction necessary for the fresh extract.

IF CHANGING FROM ALUM-ADSORBED TO AQUEOUS OR GLYCERINATED EXTRACTS: When the patient previously has been receiving alum-adsorbed or alum-precipitated extract, the safest course is to start over as though the patient had not been receiving immunotherapy. See DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS in product instructions.

IF ANY OTHER CHANGES HAVE BEEN MADE IN THE EXTRACT CONCENTRATE FORMULA: Changes other than those listed above may include situations such as a redistribution of component parts or percentages, a difference in extracting fluid (i.e., change from non-glycerin extracts to 50% glycerin extracts), combining two or more stock concentrates, or any other change.

It should be recognized that any change in formula can affect a patient's tolerance of the treatment. The usual 1/2 of the previous dose for a new extract may produce an adverse reaction: extra dilutions are recommended whenever starting a revised formula. The greater the change, the greater the number of dilutions required.

Proper selection of the dose and careful injection should prevent most systemic reactions. It must be remembered, however, that allergenic extracts are highly potent in sensitive individuals, and that systemic reactions of varying degrees of severity may occur, including urticaria, rhinitis, conjunctivitis, wheezing, coughing, angioedema, hypotension, bradycardia, pallor, laryngeal edema, fainting, or even anaphylactic shock and death. Patients should be informed of this, and the precautions should be discussed prior to immunotherapy. (See

PRECAUTIONS below.) Severe systemic reactions should be treated as indicated in the ADVERSE REACTIONS Section. Refer to boxed WARNINGS Section.

PRECAUTIONS:

1. General

Concentrated extracts must be diluted prior to use: See DOSAGE AND ADMINISTRATION Section below for detailed instructions on the dilution of allergenic extracts.

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 diluted with sterile Albumin Saline with Phenol (0.4%) diluent may be more potent than extracts diluted with diluents which do not contain stabilizers. When changing from non-stabilized to stabilized diluent, consider weaker initial dilutions for both intradermal testing and immunotherapy.

Sterile solutions, vials, syringes, etc. should be used and aseptic precautions observed in making dilutions.

To avoid cross-contamination, do not use the same needle to withdraw materials from vials of more than one extract, or extract followed by diluent.

A sterile tuberculin syringe graduated in 0.01 mL units should be used to measure each dose from the appropriate dilution. Aseptic techniques should always be employed when injections of allergenic extracts are being administered.

A separate sterile syringe should be used for each patient to prevent transmission of serum hepatitis and other infectious agents from one person to another.

Patient reactions to previous injections should be reviewed before each new injection. A conservative dosage schedule should be followed by the physician until a pattern of local responses is established which can be used to monitor increases in dosage.

Rarely, a patient is encountered who develops systemic reactions to minute doses of allergen and does not demonstrate increasing tolerance to injections after several months of treatment. If systemic reactions or excessive local responses occur persistently at very small doses, efforts at immunotherapy should be stopped.

PATIENTS SHOULD BE OBSERVED IN THE OFFICE FOR 30 MINUTES AFTER EACH TREATMENT INJECTION. Most severe reactions will occur within this time period, and rapid treatment measures should be instituted. See ADVERSE REACTIONS Section for such treatment measures.

2. Information for Patients

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

3. 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.⁵

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.²⁴ Topical steroids should be discontinued at the skin test site for at least 2-3 weeks before skin testing.^{24, 25}

Tricyclic antidepressants such as Doxepin should be withheld for at least 7 days before skin testing.²⁶ Topical local anesthetics may suppress the flare responses and should be avoided in skin test sites.²⁷

4. 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.

5. Pregnancy²²

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.

For women who have been getting maintenance doses of allergen without side effect, the occurrence of pregnancy is not an indication to stop immunotherapy.

6. 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.

7. Pediatric Use

Since dosage for the pediatric population is the same as for adults^{3, 4}, the larger volumes of solution may produce excessive discomfort. Therefore, in order to achieve the total dose required, the volume of the dose may need to be divided into more than one injection per visit.

8. Geriatric Use

The reactions from immunotherapy can be expected to be the same in elderly patients as in younger ones. Elderly patients may be more likely to be on medication that could block the effect of epinephrine which could be used to treat serious reactions, or they could be more sensitive to the cardiovascular side effect of epinephrine because of pre-existing cardiovascular disease.²⁸

ADVERSE REACTIONS:

1. Local Reactions

Some erythema, swelling or pruritus at the site of injection are common, the extent varying with the patient. Such reactions should not be considered significant unless they persist for at least 24 hours. Local reactions (erythema or swelling) which exceed 4-5 cm in diameter are not only uncomfortable, but also indicate the possibility of a systemic reaction if dosage is increased. In such cases the dosage should be reduced to the last level not causing the reaction and maintained at this level for two or three treatments before cautiously increasing again.

Large persistent local reactions may be treated by local cold, wet dressings and/or the use of oral antihistamines. They should be considered a warning of possible severe systemic reactions and an indication of the need for temporarily reduced dosages.

A mild burning immediately after the injection is to be expected. This usually leaves in 10 to 20 seconds.

2. Systemic Reactions

With careful attention to dosage and administration, systemic reactions occur infrequently, but it cannot be overemphasized that in sensitive individuals, any injection could result in anaphylactic shock. Therefore, it is imperative that physicians administering allergenic extracts understand and be prepared for the treatment of severe reactions.

Other possible systemic reactions which may occur in varying degrees of severity are laryngeal edema, fainting, pallor, bradycardia, hypotension, angioedema, cough, wheezing, conjunctivitis, rhinitis, and urticaria. Adverse reaction frequency data for allergenic extract administration for testing and treatment show that risk is low.^{1, 21}

If a systemic or anaphylactic reaction does occur, apply a tourniquet above the site of injection and inject 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 DOSAGE

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

PEDIATRIC: 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. Airway patency should be insured. Oxygen should be given by mask. Intravenous antihistamine, theophylline and/or corticosteroids may be used if necessary after adequate epinephrine and circulatory support has 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 and Clinical Immunology*, 77(2):p. 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.

Severe systemic reactions mandate a decrease of at least 50% in the next dose, followed by cautious increases. Repeated systemic reactions, even of a mild nature, are sufficient reason for the cessation of further attempts to increase the reaction-causing dose.

3. Adverse Event Reporting

Report all adverse events to Jubilant HollisterStier LLC, Customer Technical Services Department at 1 (800) 992-1120. A voluntary adverse event reporting system for health professionals is available through the FDA MEDWATCH program. Preprinted forms (FDA Form 3500) are available from the FDA by calling 1 (800) FDA-1088. Completed forms should be mailed to MEDWATCH, 5600 Fisher Lane, Rockville, MD 20852-9787 or Fax to: 1 (800) FDA-0178.

OVERDOSAGE: See ADVERSE REACTIONS Section.

DOSAGE AND ADMINISTRATION:^{3, 16, 17, 18}

1. General

Sterile aqueous diluent containing human serum albumin is recommended when preparing dilutions of the concentrate for intradermal testing or immunotherapy.

Dilutions should be made accurately and aseptically, using sterile diluent, vials, syringes, etc. Mix thoroughly and gently by rocking or swirling.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

2. Diagnosis

To identify highly sensitive individuals and as a safety precaution, it is recommended that a prick or puncture test using a drop of the extract concentrate be performed prior to initiating intradermal testing. Prick tests are performed by placing a drop of extract on the skin and piercing through the drop into the skin with a slight lifting motion. Puncture tests are performed by placing a drop of extract on the skin and piercing through the drop perpendicular to the skin with a device such as a Prick Lancetter. After about 1 minute the extract may be wiped away with a dry sponge. The diameter of wheal and erythema reactions are measured 15 minutes after the prick or puncture is made, and the sensitivity class of the patient determined by the table presented at the end of the diagnosis section. Less sensitive individuals (Class 0 to 1+) can be tested intradermally with the recommended dilutions of the extract concentrate (see Intradermal Testing).

The skin test concentration of 10,000 BAU/mL (10-19.9 Fel d 1 Units/mL) in dropper vials is used for prick or puncture testing. Puncture tests performed on 15 highly sensitive subjects showed the following:

Product	Mean Sum of Wheal	Mean Sum of Erythema
	± 1 Std. Dev. (mm)	± 1 Std. Dev. (mm)
Standardized Cat Pelt	13.9 ± 4.3	67.3 ± 13.3

The sum of a skin response is the sum of the longest diameter and the midpoint orthogonal diameter.

Intradermal endpoint titration (IET) tests were completed using the same 15 subjects to determine the mean concentration required to produce a ΣE of 50mm (D₅₀). That concentration contained 0.042 BAU/mL (range 0.002 to 0.890 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% glycerol.

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.

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

Class	Wheal Diameter	Erythema Diameter	Corresponding ΣE
0	<5 mm	<5 mm	<10 mm
±	5-10 mm	5-10 mm	10-20 mm
1+	5-10 mm	11-20 mm	20-40 mm
2+	5-10 mm	21-30 mm	40-60 mm
3+	10-15 mm ^a	31-40 mm	60-80 mm
4+	>15 mm ^b	>40 mm	>80 mm

a. or with pseudopods

b. or with many pseudopods

3. Immunotherapy

Allergen extracts should be administered using a sterile syringe with 0.01 mL gradations and a 25-27 gauge x 1/2" to 5/8" needle. The injections are given subcutaneously. The most common sites of injection are the lateral aspect of the upper arm or thigh. Intracutaneous or intramuscular injections may produce large local reactions which may be very painful.

Dosage of allergenic extracts is a highly individualized matter and varies according to the degree of sensitivity of the patient, his clinical response, and tolerance to the extract administered during the early phases of an injection regimen. The starting dose should be based on skin tests of the extract to be used for immunotherapy. To prepare dilutions for intradermal and therapeutic use, make a 1:10 dilution by adding 1.0 mL of the concentrate to 9.0 mL of sterile aqueous diluent. Subsequent serial dilutions are made in a similar manner. (See Table I.) To determine the starting dose, begin intradermal testing with the most

dilute extract preparation. Inject 0.02 mL and read the reaction after 15 minutes. Intradermal testing is continued with increasing concentrations of the extract until a reaction of 10-20 mm erythema (\geq E 20-40 mm) and/or a 5 mm wheal occurs. This concentration at a dose of 0.03 mL then can serve as a starting dose for immunotherapy and be increased by 0.03 mL to as high as 0.12 mL increments each time until 0.3 mL is reached, at which time a dilution 10 times as strong can be used, starting with 0.03 mL. Proceed in this way until a tolerance dose is reached or symptoms are controlled. Suggested maintenance dose is 0.2 mL of the concentrate. Occasionally, higher doses are necessary to relieve symptoms. Special caution is required in administering doses greater than 0.2 mL. The interval between doses normally is 3 to 7 days.

This is offered as a suggested schedule for average patients and will be satisfactory in most cases. However, the degree of sensitivity varies in many patients. The size of the dose should be adjusted and should be regulated by the patient's tolerance and reaction. The size of the dose should be decreased if the previous injection resulted in marked local or the slightest general reaction. Another dose should never be given until all local reactions resulting from the previous dose have disappeared.

In some patients, the dosage may be increased more rapidly than called for in the schedule. In seasonal allergies, treatment should be started and the interval between doses regulated so that at least the first 20 doses will have been administered by the time symptoms are expected. Thus, the shorter the interval between the start of immunotherapy and the expected onset of symptoms, the shorter the interval between each dose. Some patients may even tolerate daily doses. A maintenance dose, the largest dose tolerated by the patient that relieves symptoms without producing undesirable local or general reactions is recommended for most patients. The upper limits of dosage have not been established; however, doses larger than 0.2 mL of the glycerinated concentrate may be painful due to the glycerin content. The dosage of allergenic extract does not vary significantly with the respiratory allergic disease under treatment. The size of this dose and the interval between doses will vary and can be adjusted as necessary. Should symptoms develop before the next injection is scheduled, the interval between doses should be decreased. Should allergic symptoms or local reactions develop shortly after the dose is administered, the size of the dose should be decreased. In seasonal allergies, it is often advisable to decrease the dose to one-half or one-quarter of the maximum dose previously attained if the patient has any seasonal symptoms.

The interval between maintenance doses can be increased gradually from one week to 10 days, to two weeks, to three weeks, or even to four weeks if tolerated. Repeat the doses at a given interval three or four times to check for untoward reactions before further increasing the interval. Protection is lost rapidly if the interval between doses is more than four weeks. (See WARNINGS Section.)

The usual duration of treatment has not been established. A period of two or three years of injection therapy constitutes an average minimum course of treatment.

TABLE I
TEN-FOLD DILUTION SERIES
Standardized Extracts Labeled 10,000 BAU/mL

Dilution	Extract	+ Diluent	=	BAU/mL Concentration
0	Concentrate	+ 0 mL	=	10,000
1	1 mL concentrate	+ 9 mL	=	1,000
2	1 mL dilution #1	+ 9 mL	=	100
3	1 mL dilution #2	+ 9 mL	=	10
4	1 mL dilution #3	+ 9 mL	=	1
5	1 mL dilution #4	+ 9 mL	=	0.1
6	1 mL dilution #5	+ 9 mL	=	0.01
7	1 mL dilution #6	+ 9 mL	=	0.001

4. Pediatric Use

The dose for the pediatric population is the same as for adults. (See PRECAUTIONS.)

5. Geriatric Use

The dose for elderly patients is the same as for adult patients under 65.²⁸

HOW SUPPLIED: Standardized Cat Pelt allergenic extract is supplied for diagnostic and therapeutic use:

Diagnostics:

Prick or puncture testing, 10,000 BAU/mL [50% glycerin (v/v)] in 5 mL dropper vial.

Bulk Therapeutics: multiple dose vials in 50% glycerin (v/v).

10 mL vial, 10,000 BAU/mL
30 mL vial, 10,000 BAU/mL
50 mL vial, 10,000 BAU/mL

STORAGE:

The expiration date of the Standardized Cat Pelt extract containing 10,000 BAU/mL is listed on the container label. The extract should be stored at 2° - 8°C. Dilutions of the BAU/mL concentrates are less stable and, if loss of potency is suspected, should be checked by skin testing with equal bioequivalent allergy units of a freshly prepared dilution on known cat allergic individuals.

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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