
HollisterStier
Allergy
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Three Answers:

1. INNOVATIONS & DIFFERENTIATIONS

HollisterStier has been an innovator since our founding in 1921. In fact, both our histamine and AP Dog products are listed in the Allergy practice parameters.[4,5] Now approaching our 100th year, we have produced many breakthroughs.

- **ACETONE PRECIPITATED (AP) EXTRACTION**
  Our exclusive process, often using as much as 50 times the source material, creates highly potent extract.
- **PHENOL FREE**
  We do not use phenol in any of our glycerin extracts, which helps prevent denaturing of the proteins. This, in turn, helps preserve potency.[3]
- **SUBCUTANEOUS IMMUNOTHERAPY, WITHOUT COMPROMISE**
  Our focus has always been on subcutaneous immunotherapy and bulk extracts. We create products specifically for allergists and allergy specialists.

As a result, we are able to offer many high-quality products, such as:

AP DOG

The highest concentration of dog hair extract available. Studies suggest it's more effective for diagnosis and treatment.[1,2]

MITE EXTRACTS

We introduced mite extracts in 1988, and culture our source material to produce mite products—including a highly concentrated bulk extract.

VENOM EXTRACTS

Our venom products pass a minimum of 15 quality control checks. We are the only supplier of venom in the U.S.

COMFORTEN® MULTIPLE SKIN TEST SYSTEM

The only ten-test, self-loading, surgical steel skin test device on the market.

2. QUALITY CONTROL & MANUFACTURING STANDARDS

HollisterStier's facility is rigorously inspected by CBER, CDER and multiple foreign agencies, exhibiting strong GMP standards.

We strive to meet multiple agency guidelines as part of our commitment to high quality allergenic extracts for you and your patients. This requires careful control and exacting processes. It takes up to 520 staff hours to extract enough venom for one batch of raw material. We must hand extract venom from up to 130,000 insects for each batch of raw material processed.

3. COMMITMENT TO YOUR PRACTICE & PATIENTS

Our focus, subcutaneous immunotherapy, has been shown in studies to be effective for diagnosis and treatment. We continue to innovate our manufacturing methods. We've invested in equipment, technology and facilities. And we've responded to your needs and wants by creating a product portfolio that focuses on the antigens most important to you.

Finally, we are patient-focused in what we produce. We offer educational materials to help answer the questions your patients ask. For instance, we created and funded the BeeAware Program to inform the public about life-saving treatment, demonstrating our commitment to both patients and physicians.

CALL US TODAY:
1.800.992.1120
hsallergy.com

HollisterStier Allergy

Request a copy of our product catalog and schedule your complimentary consultation.

*see back for footnotes

Three Questions:

AP DOG

ALLERGENS ARE PRESENT IN EVERY ENVIRONMENT, SO CHOOSING THE RIGHT ALLERGENIC EXTRACT PARTNER ISN'T JUST IMPORTANT; IT'S VITAL FOR THE HEALTH OF YOUR PATIENTS, AND THE HEALTH OF YOUR PRACTICE. THAT MEANS FINDING A PARTNER JUST AS COMMITTED AS YOU ARE.

WE ARE THAT IDEAL PARTNER, BECAUSE WE'RE NOT AFRAID OF THE TOUGH QUESTIONS. SO ASK US, AND THEN ASK ANYONE ELSE THESE SAME QUESTIONS:

1 **WHAT ARE YOUR PRODUCT INNOVATIONS AND DIFFERENTIATIONS?**

2 **HOW DO YOU ENSURE QUALITY CONTROL AND MANUFACTURING STANDARDS?**

3 **WHAT SHOWS YOUR COMMITMENT TO MY PRACTICE AND MY PATIENTS?**

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, adverse reaction and over dosage for more detailed information.

HollisterStier Allergy *a division of Jubilant Pharma*

Jubilant HollisterStier, LLC
1.800.992.1120
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Spokane, WA 99207-5788

Footnotes

1 Turbeyville. (2008). Discordance Between Conventional and Acetone Precipitate (AP) Dog Extract in Skin Prick Testing. The Journal of Allergy and Clinical Immunology, 121(2).

2 Lent. (2006). Immunologic response to administration of standardized dog allergen extract at differing doses. The Journal of Allergy and Clinical Immunology, 118(6).

3 Nelson, H. (2004). Preparing and Mixing Allergen Vaccines for Subcutaneious Immunotheraphy. In R. Lockey, Allergens and Allergen Immunotherapy (3rd ed., p. 472). NY.

4 Cox. (2011). Allergen Immunotheraphy: A practice parameter third update. The Journal of Allergy and Clinical Immunology.

5 Bernstein, I. (2008). Allergy Diagnostic Testing: An Updated Practice Parameter. Annals of Allergy, Asthma & Immunology, 100, 1-148.

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 EXTRACTS IN BULK VIALS

HollisterStier

365107-H09

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 death.[1]

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, be observed in the office for at least 30 minutes after skin testing or treatment, and be cautioned to contact the physician's office if symptoms occur. See ADVERSE REACTION section of this package insert regarding adverse event reporting.

Standardized glycerinated extracts may be more potent than regular extracts and therefore are not directly interchangeable with non-standardized extracts, or other manufacturers' products.

Patients with cardiovascular diseases and/or pulmonary diseases such as symptomatic unstable, steroid-dependent 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]

Patients on 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.[2]

This product should never be injected intravenously.

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

DESCRIPTION The allergenic extract in this vial is referred to as a "bulk" extract or stock concentrate since it is designed primarily for the physician equipped to prepare dilutions and mixtures as required. The extract is sterile and intended for subcutaneous injection for immunotherapy and scratch, prick or puncture for diagnosis. Unless specified otherwise, the concentration of extract supplied will in most cases be expressed in weight to volume (e.g., 1:10 or 1:20 w/v) and will be the strongest available. Where mixtures of pollens and non-pollens have been ordered, the mixed extract will be treated as a pollen mixture. To insure maximum potency for the entire dating period, all bulk concentrates will contain 50% volume to volume (v/v) glycerin unless otherwise requested. Dilutions will also be prepared with 50% (v/v) glycerin unless another diluent is specified.

Source materials utilized in allergenic extract products include pollens, molds, animal epidermals, insects, foods and environmental materials.

Pollens are collected using techniques such as waterset or vacuuming, cleaned and purified to greater than 99% single specie pollen (less than 1% foreign particle presence).

Molds are typically grown on synthetic nutrient medias and are derived from the surface growth (mycelia).

Animal source materials are collected from animals deemed to be healthy at the time of collection by a veterinarian or individual trained and certified by a veterinarian. Epidermals include feathers, hair and dander, or the whole epidermal (pelt) as described on product labeling.

Regular process epidermals are extractions of the source material without additional processing, except that certain materials are defatted. AP™ (acetone precipitated) epidermal source materials are derived from the precipitate formed when acetone is added to an aqueous extract. The resulting precipitate is dried, and becomes the source material for the AP™ product.

Insects are collected in whole body form. Extractions take place as whole body or ground insects.

Information on other Environmental source materials can be obtained by contacting our Customer Service Department.

The following is a brief summary of the six methods of describing allergenic product concentration.

1. **Weight to volume (w/v).** Weight to volume (w/v) describes the weight of allergenic source material added to a given volume of extracting fluid. A 1:10 w/v extract, e.g., indicates that the solution contains the extractable material from one gram of raw material added to each 10 mL Glycero-Coca's or 10 mL Coca's extracting fluid. The amount and composition of extracted materials will vary with the type of antigen, the extracting fluid, duration of extraction, pH, temperature, and other variables.

   Pollens are typically extracted at a 1:20 w/v ratio in Glycero-Coca's while Coca's extracts are 1:10 w/v.

   Epidermal, environmental, regular molds and insect products are typically extracted at 1:10 w/v.

   AP™ (acetone precipitated) epidermal products are prepared at a 1:50 w/v concentration (i.e., 1 gram of dried precipitate in 50 mL of reconstitution fluid). AP™ Dog Hair-Dander is prepared at 1:100 w/v concentration. (i.e., 1 gram of dried precipitate in 100 mL of reconstitution fluid.)

2. **Protein Nitrogen Units per mL (PNU/mL).** One protein nitrogen unit represents 0.00001 mg phosphotungstic acid precipitable protein nitrogen dissolved in one mL of antigen extract. The PNU content of extracts of the same antigen may vary according to the method of measuring the PNU. Thus, the PNU content of extracts from different manufacturers is not comparable unless the PNU method is known to be the same and is reproducible from lot to lot. The amount of protein nitrogen extracted from the source material is influenced by such factors as the type of antigen, the extracting fluid, duration of extraction, pH, temperature and other variables. Allergenic materials make up a variable proportion of the total protein of an extract.

   Most allergenic extracts are assayed for PNU. Specific PNU information is available upon request.

3. **Amb a 1.** Of the many allergens from Short Ragweed which have been purified and characterized [Amb a 1[3] (also known as Antigen E), Amb a 2[3] (also known as Antigen K), Ra3[4], Ra4 (BPA-R)[5], Ra5[6], Ra6, Ra7, Ra8[7], and cytochrome C[8]], Amb a 1 is considered the most important and has been selected as the basis for standardization. Extracts of Short Ragweed containing Amb a 1 are diffused in agar against standard anti-serum to Amb a 1, and compared to the diffusion of standard Amb a 1 solutions. The amount of Amb a 1 is expressed as units of Amb a 1 per mL of extract. A Short Ragweed pollen extracted at 1:20 (w/v) usually assays within a range of 50,000 to 70,000 PNU/mL and 100 to 300 units of Amb a 1 per mL.

   The Amb a 1 concentration of any Short Ragweed extract which is diluted with a diluent or other allergenic extracts is determined by calculation. The resulting Amb a 1 value does not reflect the total potency of the product if Short Ragweed extract is mixed with another allergenic extract.

4. **Allergy Units per mL (AU/mL).** The potency of extracts labeled in Allergy Units (AU)/mL is determined by *in vitro* comparison to a reference standard established by the Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration (FDA).

5. **Bioequivalent Allergy Units per mL (BAU/mL).** Other standardized allergenic extracts are labeled in Bioequivalent Allergy Units/mL (BAU/mL) based on their comparison (by *in vitro* assay or major allergen content) to CBER, FDA Reference Preparations. The FDA reference extracts have been assigned Bioequivalent Allergy Units based on the CBER $ID_{50}EAL$ method.[9] Briefly, highly sensitive patients are skin tested to the reference preparation using an intradermal technique employing 3-fold extract dilutions. Depending on the dilution which elicits a summation of erythema diameter of 50, Bioequivalent Allergy Units are assigned as follows:

BAU/mL	D_{50} Range
100,000	13.9-15.9
10,000	10.9-12.9
1,000	8.8-10.8
100	6.7- 8.7

   References labeled 10,000 BAU/mL can be diluted one to a half million fold, and references labeled 100,000 BAU/mL can be diluted one to 5 million fold and produce a sum of erythema diameter of 50 mm when Intradermal testing highly reactive subjects.

6. **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%	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, or 0.4% phenol, as indicated on the vial label. Additional ingredients are 0.5% sodium chloride, and 0.275% sodium bicarbonate.

CLINICAL PHARMACOLOGY[10] The mechanism by which hyposensitization is achieved is not known completely. It has been shown that repeated injections of appropriate allergenic extracts will ameliorate the intensity of allergic symptoms upon contact with the allergen.[11, 12, 13, 14] Clinical studies which address the efficacy of immunotherapy are available. The allergens which have been studied are cat, mite, and some pollen extracts.[10, 15, 16, 17, 18, 19]

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 clear.

Further study and clarification of the relationships among changes in blocking antibody, reaginic antibody, and mediator-releasing cells, and between these three factors and successful immunotherapy, is needed.

INDICATIONS AND USAGE[20, 21, 22, 23] 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.

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 antigen.

Avoidance of allergens is to be advocated if possible, but cannot always be attained, e.g., allergy to dog dander in kennel owners and employees, dog 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 with the highly reactive allergen.

CONTRAINDICATIONS There are no known absolute contraindications to immunotherapy. See PRECAUTIONS and WARNINGS.

Patients with cardiovascular diseases and/or pulmonary diseases such as symptomatic unstable, steroid-dependent 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 by skin test reaction, have a history of symptoms on exposure, and are likely to be exposed to again.

Any injections, including immunotherapy, should be avoided in patients with a bleeding tendency. Patients on 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 systemic reactions.[2]

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

WARNINGS: See WARNINGS box at the beginning of this package insert. See also PRECAUTIONS.

Allergenic extracts must 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) any evidence of an excessively large local or any generalized reaction during the initial stages of immunotherapy or during maintenance therapy, and/or (4) exposure to excessive amounts of clinically relevant allergen prior to a scheduled injection.

Do not administer 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 MUST NOT BE INJECTED AT ANY TIME UNLESS TOLERANCE HAS BEEN ESTABLISHED. DILUTE CONCENTRATED EXTRACTS WITH STERILE DILUENT FOR SKIN TESTING AND IMMUNOTHERAPY.

INJECTIONS MUST 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 TO A DIFFERENT LOT OF EXTRACT: All extracts lose potency over time, and a fresh extract could have an effective potency that is substantially greater than that of the old extract. Even though it is the same formula and concentration, the first dose from the new vial should not exceed 50% of the previous dose.

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. In general, a dose reduction to 50% of the previous product dose should be adequate, but each situation must be evaulated separately considering the patient's history of sensitivity, tolerance of previous injections, and other factors. If the patient tolerates a 50% decrease, the next dose could be raised to the previous dose amount. If the decrease is greater than 50%, the next dose would need to be determined by the allergist, depending on the situation. Dose intervals should not exceed one week when rebuilding dose. See DOSAGE AND ADMINISTRATION.

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. See DOSAGE AND ADMINISTRATION.

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, s/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 was previously 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.

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 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, as described under ADVERSE REACTIONS. Patients should be informed of this, and the precautions should be discussed prior to immunotherapy. (See PRECAUTIONS.) Severe systemic reactions should be treated as indicated in ADVERSE REACTIONS. Refer to WARNINGS box.

PRECAUTIONS

1. **General**

The presence of asthmatic signs and symptoms appear to be an indicator for severe reactions following allergy injections. An assessment of airway obstruction either by measurement of peak flow or an alternate procedure may provide a useful indicator as to the advisability of administering an allergy injection.[1, 24, 25, 26, 27]

Concentrated extracts must not be injected unless tolerance has been established. Concentrated extracts must be diluted prior to use: See DOSAGE and ADMINISTRATION 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%) may be more potent than extracts diluted with diluents which do not contain stabilizers. When switching 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 and with a needle at least 5/8" long 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 hepatitis and other infectious agents from one person to another.

Patient reactions to previous injections should be reviewed before each new injection, so that dosage can be adjusted accordingly. See ADVERSE REACTIONS and WARNINGS.

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 AT LEAST 30 MINUTES AFTER SKIN TESTING AND EACH TREATMENT INJECTION. Most severe reactions will occur within this time period, and rapid treatment measures should be instituted. See ADVERSE REACTIONS for such treatment measures.

In order to avoid darkening and possible precipitation, do not dilute Privet pollen with solutions containing phenol. Injections of this extract discolored by reaction with phenol may produce a lasting tattoo-like discoloration of the skin.

2. **Information for Patients**

Patients should be instructed in the recognition of adverse reactions to immunotherapy, and in particular, to the symptoms of shock. (See WARNINGS box at the beginning of this package insert.) Patients should be made to understand the importance of a 30 minute observation period and be cautioned to return to the office promptly if symptoms occur after leaving.

Patients should be instructed to report any symptoms of exposure to the allergen, so the physician can adjust the dosage appropriately.

3. **Drug Interactions**

Patients with cardiovascular diseases and/or pulmonary diseases such as symptomatic unstable, steroid-dependent 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]

Patients on 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.[2] (See WARNINGS).

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.[28] Topical steroids should be discontinued at the skin test site for at least 2-3 weeks before skin testing.[28, 29]

Tricyclic antidepressants such as Doxepin should be withheld for at least 7 days before skin testing.[30] Topical local anesthetics may suppress the flare responses and should be avoided in skin test sites.[31]

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. **Pregnancy[32]**

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. The physician must carefully consider the benefit-to-risk ratio to both patient and fetus, of performing skin testing or continuing immunotherapy during pregnancy. The recommended precautions (See WARNINGS AND PRECAUTIONS) for preventing adverse reactions are especially important in the pregnant patient. Based on the physician's discretion, immunotherapy maintenance doses may be continued during pregnancy if the patient has not experienced adverse side effects. Immunotherapy is generally not initiated during pregnancy due to the risks associated with systemic reactions and their treatment.[33]

6. **Nursing Mothers**

There are no current studies on the secretion of allergenic extract components in human milk or their 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[34, 35],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.[36]

ADVERSE REACTIONS

Physicians administering allergenic extract testing or treatment materials should be experienced in the treatment of severe systemic reactions. See WARNINGS box at the beginning of this package insert.

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 subsides 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.

Most severe systemic reactions will begin within a 30 minute time period, but systemic reactions may occur at any time after skin tests or immunotherapy. Symptoms may range from mild to life-threatening (due to anaphylaxis) as described below.

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, 37]

If a systemic or anaphylactic reaction does occur, apply a tourniquet above the site of injection and inject 1:1,000 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, inhaled bronchodilators, theophylline and/or adrenal 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.

2. **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.

DOSAGE AND ADMINISTRATION

1. **General**

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

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.

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 and may be very painful.

Sterile aqueous diluent containing human serum albumin [Albumin Saline with Phenol (0.4%)] or diluent of 50% glycerin may be used when preparing dilutions of the concentrate for immunotherapy. Dilutions should be made accurately and aseptically, using sterile diluent, vials, syringes, etc. Mix thoroughly and gently by rocking or swirling. Maintain stock solutions and dilutions constantly at 2º - 8ºC. 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.

Following is 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 according to the patient's tolerance and reaction. Decrease the size of the dose if the previous injection resulted in marked local or the slightest general reaction. Another dose should never be given until all reactions resulting from the previous dose have disappeared.

The starting dose should be based on skin tests of the extract to be used for immunotherapy. 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. Subsequent doses can 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 for a pollen extract is 0.2 mL of the Concentrate, while for a non-pollen extract the maximum suggested dose is 0.5 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 is normally 3 to 7 days during dose building regimen.

Normally immunotherapy can be started with a 1:100,000 dilution of extracts labeled in weight/volume. Certain therapeutic mixtures are labeled as Concentrate, (v/v) dilutions of Concentrate, Amb a 1, Allergy units/mL or Bioequivalent Allergy Units/mL. (See DESCRIPTION.) Strength of each antigen in the mixture is indicated in the product labeling. For beginning treatment, use at least a 1,000-fold dilution of the Concentrate extract for non-pollens, and at least a 10,000-fold dilution of the Concentrate extract for pollens.

In some patients, the dosage may be increased more rapidly than recommended above. In seasonal allergies, treatment should be started and the interval between doses regulated so that at least the first twenty 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.

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.

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 extract may be painful if glycerin is present. 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.

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.)

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.

2. **Pediatric Use**
   The dose for the pediatric population is the same as for adults.

3. **Geriatric Use**
   The dose for elderly patients is the same as for adult patients under 65.[36]

HOW SUPPLIED In 10 mL, 30 mL and 50 mL vials at the w/v, Concentrate, v/v dilution of Concentrate, AU/mL (Standardized Mite Extracts: *D. farinae*, *D. pteronyssinus* 10,000 and 30,000 AU/mL; Mite Mixtures: 5,000 AU/mL each species, or 15,000 AU/mL each species), BAU/mL (Standardized Cat Hair and Cat Pelt extracts: 10,000 BAU/mL; Standardized Grass extracts: 10,000 and 100,000 BAU/mL); Amb a 1 units/mL; or PNU/mL ordered by the physician. Please see the current Allergy Product Catalog.

STORAGE The expiration date is listed on the container label. To ensure the maximum potency, the extract and its dilutions should be stored at 2° - 8°C, and kept in this temperature range at all times, even during use. Dilutions are less stable than concentrates. If loss of potency is suspected, dilutions should be checked by skin testing with equal v/v dilutions of a freshly prepared dilution on individuals known to be allergic to the specific allergen.

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.

REFERENCES

1. Lockey, R.F., L.M. Benedict, P.C. Turkletaub, S.C. Bukantz. Fatalities from immunotherapy (IT) and skin testing (ST). J. Allergy Clin. Immunol., 79 (4): 660-677, 1987.
2. Jacobs, R.L., G.W. Rake, Jr., et al. Potentiated anaphylaxis in patients with drug-induced beta-adrenergic blockade. J. Allergy Clin. Immunol., 68 (2): 125-127, August 1981.
3. Griffith, I.J., J. Pollock, D.G. Klapper, B.L. Rogers & A.K. Nault. Sequence Polymorphism of Amb a I and Amb a II, the Major Allergens in *Ambrosia artemisiifolia* (Short Ragweed). Int. Arch. Allergy Apply. Immunol., 96: 296-304, 1991.
4. Underdown, B. J. & L. Goodfriend. Isolation & characterization of an allergen from short ragweed pollen. Biochem. 8 (3): 980-989, 1969.
5. Griffiths, B. W. & R. Brunet. Isolation of a basic protein antigen of low ragweed pollen. Can. J. Biochem. 49 (3): 396-400, 1971.
6. Lapkoff, C. B. & L. Goodfriend. Isolation of a low molecular weight ragweed allergen: Ra5. Int. Arch. Allergy Appl. Immunol. 46 (2): 215-229, 1974.
7. Hussain, R. & D. G. March. Characterization and allergenic activity of ragweed allergens Ra6, Ra7, Ra8. J. Allergy Clin. Immunol. 65 (3): 230, abstr. 218, 1980.
8. Goodfriend, L., A. M. Choudhury, J. Del Carpio and T. P. King. Cytochrome C: New ragweed pollen allergen. Fed. Proc. 38 (3, part II): 1415, abstr. 6261, 1979.
9. Turkeltaub, P.C., MD, and S.C. Rastogi, PhD. Quantitative intradermal test procedure for evaluation of subject sensitivity to standardized allergenic extracts and for assignment of bioequivalent allergy units to reference preparations using the ID_{50}EAL method. Allergenics Products Testing Laboratory, Center for Biologics Evaluation and Research (CBER), FDA. Revised: November, 1994.
10. Norman, P. S. Postgraduate Course Presentation. An overview of immunotherapy, implications for the future. J. Allergy Clin. Immunol., 65 (2): 87-96, 1980.
11. Lowell, F. C. and W. Franklin. A "double-blind" study of treatment with aqueous allergenic extracts in cases of allergic rhinitis. J. Allergy, 34 (2):165-182, 1963.
12. Lowell, F. C. and W. Franklin. A double-blind study of the effectiveness and specificity of injection therapy in ragweed hay fever. N. Eng. J. Med. 273 (13): 675-679, 1965.
13. Zavazal, V. and A. Stajner. Immunologic changes during specific treatment of the atopic state. II. Acta. Allergol. 25 (1): 11-17, 1970.
14. Reisman, R. E., J. I. Wypych, and E. E. Arbesman. Relationship of immunotherapy, seasonal pollen exposure and clinical response to serum concentrations of total IgE and ragweed-specific IgE. Int. Arch. Allergy Appl. Immunol. 48 (6): 721-730, 1975.
15. Taylor, W. W., J. L. Ohman, F. C. Lowell. Immunotherapy in cat-induced asthma; double-blind trial with evaluation of bronchial responses to cat allergen and histamine. J. Allergy Clin. Immunol., 61 (5): 283-287, 1978.
16. Smith, A. P. Hyposensitization with Dermatophagoides pteronyssinus antigen: Trial in asthma induced by house dust. Br. Med. J., 4: 204-206, 1971.
17. Chapman, M. D., T. A. E. Platts-Mills, M. Gabriel, H. K. Ng, W. G. L. Allen, L. E.Hill, A. J. Nunn. Antibody response following prolonged hyposensitization with Dermatophagoides pteronyssinus extract. Int. Arch. Allergy Appl. Immunol., 61:431-440, 1980.
18. Norman, P. S., W. L. Winkenwerder. Maintenance immunotherapy in ragweed hay fever. J. Allergy, 74: 273-282, 1971.
19. Norman, P. S., W. L. Winkenwerder, L. M. Lichtenstein. Immunotherapy of hay fever with ragweed Antigen E; comparisons with whole pollen extract and placebos. J. Allergy, 42: 93-108, 1968.
20. Middleton, E., C. E. Reed & E. F. Ellis, editors. Allergy Principles and Practice. C. V. Mosby Co., St. Louis, 1978, pp. 877-898.
21. Sheldon, J. M., R. G. Lovell & K. P. Mathews. A Manual of Clinical Allergy, Second Edition. W. B. Saunders. Philadelphia, 1967, pp. 107-112.
22. Sherman, W. B. Hypersensitivity Mechanisms and Management. W. B. Saunders. Philadelphia, 1968, pp. 169-172.
23. Swineford, O. Asthma and Hay Fever. Charles C. Thomas. Springfield, IL, 1971, pp. 148-155.
24. Reid, M.J., R.F. Lockey, P.C. Turkletaub, T.A.E., Platts-Mills. Survey of fatalities from skin testing and immunotherapy. J. 0 Clin. Immunol. 92 (1): 6-15, July 1993.
25. Reid, M.J., G. Gurka. Deaths associated with skin testing and immunotherapy. J. Allergy Clin. Immunol. 97(1) Part 3:231, Abstract 195, January 1996.
26. Thompson, R.A., et al, report of a WHO/IUIS working group. The current status of allergen immunotherapy (hyposensitization). Allergy. 44: 369-379, 1989.
27. Malling, H.J., B. Weeke, et al, The European Academy of Allergology and Clinical Immunology. Position Papers. Allergy. 48 (Supplement 14): 9-82, 1993.
28. Pipkorn, U. Pharmacological influence of anti-allergic medication on *In Vivo* allergen testing. Allergy. 43: 81-86,1988.
29. Andersson, M. and U. Pipkorn. Inhibition of the dermal immediate allergic reaction through prolonged treatment with topical glucocorticosteroids. J. Allergy Clin. Immunol. 79 (2): 345-349, February 1987.
30. Rao, K.S., et al. Duration of suppressive effect of tricyclic anti-depressants on histamine induced wheal and flare reactions on human skin. J. Allergy Clin. Immunol. 82: 752-757, November 1988.
31. Pipkorn, U., and M. Andersson. Topical dermal anesthesia inhibits the flare but not the wheal response to allergen and histamine in the skin prick test. Clinical Allergy. 17: 307-311, 1987.
32. DuBuske, L.M., C.J. Ling and A.L. Sheffer. Special problems regarding allergen immunotherapy. Immunol. Allergy Clin. North Am. (USA). 12(1): 145-175, 1992.
33. Li, J.T., R.F. Lockey, I.L. Bernstein, J.M. Ortnoy, R.A. Nicklas. Allergen Immunotherapy: A Practice Parameter. Ann. Allergy, Asthma & Immunotherapy 90 (1): 26, 2003.
34. Patterson, R., et al. Allergy Principles and Practice, 2nd ed. E. Middleton, Jr., C. E. Reed, E. F. Ellis, Ed., C. V. Mosby Co., 1983, St. Louis, MO, 1983, Chapter 52.
35. Levy, D. A., L. M. Lichtenstein, E. O. Goldstein, and K. Ishizaka. Immunologic and cellular changes accompanying the therapy of pollen allergy. J. Clinical Investigation, 50:360, 1971.
36. Peebles, R.S., Jr., B. Bochner, Howard J. Zeitz, ed. Anaphylaxis in the elderly. Immunology and Allergy Clinics of North America. 13 (3): 627-646, August 1993.
37. Turkeltaub, P.C., MD, and P.J. Gergen, MD. The risk of adverse reactions from percutaneous prick-puncture allergen skin testing, venipuncture, and body measurements: Data from the second National Health and Nutrition Examination Survey 1976-80 (NHANES II). J. Allergy Clin. Immunol. 84(6): 886-890, Dec. 1989.

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INSTRUCTIONS AND DOSAGE SCHEDULE FOR ALLERGENIC EXTRACTS HYMENOPTERA VENOM PRODUCTS

(Honey Bee, Yellow Jacket, Yellow Hornet, White-Faced Hornet, Wasp, and Mixed Vespid)

VENOMIL®

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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.

Hymenoptera Venom extracts may potentially elicit a severe life-threatening systemic reaction, rarely resulting in death.[1] 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, observed in the office for at least 30 minutes after skin testing or treatment, and cautioned to contact the physician's office if symptoms occur. See ADVERSE REACTION, Section 4, of this instruction for information regarding adverse event reporting.

All patients should have available an Emergency Anaphylaxis Kit containing epinephrine and be instructed in its use for emergency treatment of possible systemic reactions occurring at times after the patient has departed the testing or treatment premises.

Patients with cardiovascular diseases and/or pulmonary diseases such as symptomatic unstable, steroid-dependent 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]

Patients on 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.[2]

Immunotherapy for insect sting allergy should be given to those patients who have experienced significant systemic reactions (for detailed description of symptoms see INDICATIONS AND USAGE and ADVERSE REACTIONS) from insect stings and who demonstrate hypersensitivity by skin testing with these products. The only approved method for diagnosing insect sting allergic patients for immunization is by skin testing.

This product must never be injected intravenously.

Refer also to CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS and OVERDOSAGE for further discussion.

DESCRIPTION

Hymenoptera Venom Products available are sterile freeze-dried venom of Honey Bee (*Apis mellifera*) and venom protein of Yellow Jacket (*Vespula sp.*), Yellow Hornet (*Dolichovespula arenaria*), White-Faced Hornet (*Dolichovespula maculata*) and Wasp (*Polistes sp.*). Mixed Vespid venom protein (Yellow Jacket, Yellow Hornet and White-Faced Hornet) is also available.

The reconstituted single venom products are intended for subcutaneous injection for immunotherapy and percutaneous use for diagnosis. The Mixed Vespid venom protein is for immunotherapy only, not for diagnosis. Diagnosis should be based on individual venoms.

Because of the difficulty in collecting all species of Yellow Jacket and Wasp, the venom raw materials for these two insects may vary in species composition from lot to lot. A listing of the exact species content for any particular lot of Yellow Jacket or Wasp venom protein may be obtained by calling Technical Services at Jubilant HollisterStier, (800) 992-1120.

Final containers of sterile freeze-dried venom products are sealed under vacuum. This will result in the diluting fluid being forcibly drawn into the sealed vial when the syringe needle penetrates the seal during reconstitution. See PRECAUTIONS.

Venom or venom protein is supplied in 2 mL diagnostic vials and in 2 mL vials for treatment maintenance. The chart below lists for each vial size the content of lyophilized venom or venom protein and reconstituted product, (mannitol and venom concentrations). Trace amounts of sodium chloride, potassium chloride, acetic acid and beta-alanine, as well as the constituents of the reconstituting fluid, will also be present.

	Vial Size	μg Venom or Venom Protein	Recon-stitution	mg/mL Mannitol	Venom Concentration
Single Venom	2 mL	120	1.2 mL	7.7 mg/mL	100 μg/mL
Mixed Vespid	2 mL	360	1.2 mL	23.1 mg/mL	300 μg/mL

See product configuration in DOSAGE AND ADMINISTRATION Section.

Maintenance sterile freeze-dried products can be reconstituted in Sterile Albumin Saline with Phenol (which contains 0.9% NaCl, 0.4% phenol and 0.03% Human Serum Albumin) to a concentration of 100 μg/mL (300 μg/mL for Mixed Vespid venom protein). The diagnostic product should be reconstituted only with Sterile Albumin Saline with Phenol (0.4%). See DOSAGE AND ADMINISTRATION for details of dilutions for diagnosis and treatment.

Space is provided on the container label to record the date (month, day, year) venom is reconstituted. Refer to dating period shown under PRECAUTIONS. At the time of reconstitution, write the calculated reconstituted product expiration date (month, day, year) on the vial label in the space provided.

CLINICAL PHARMACOLOGY

Diagnosis

Diluted solutions of stinging insect venom injected intradermally will produce wheal and erythema reactions in patients who have significant IgE-mediated, Type I immediate hypersensitivity to stings of these insects.

Treatment

Repeated injections of increasing doses of insect venom extracts have been shown to ameliorate the intensity of allergic symptoms upon subsequent insect stings.[3, 4]

The mechanism by which hyposensitization is achieved is not known completely. IgG antibodies (blocking antibodies) appear in the serum of patients treated with injected venom. No direct relationship has been identified between the level of blocking antibody (or the ratio of blocking antibody to IgE antibody directed to the same venom antigens) and the degree of hyposensitization. However, patients who show protection from symptoms after stings have been found to have significant levels of specific blocking antibody.[3, 4]

Initially, after a period of immunotherapy with specific venom antigens, levels of IgE antibody may increase.[4] However, from studies carried out with other venom preparations, these levels are reported to decline after a time.[5] After maintenance level has been reached and maintained, symptoms after stings have been shown to decrease considerably.[3, 4]

It is not known if skin-sensitizing antibody can be eradicated or if the patient can be entirely cured, nor is it known how long immunotherapy must be continued.

In a clinical study with Jubilant HollisterStier venom products, injections (using the Suggested Dose Schedule under DOSAGE AND ADMINISTRATION) were given once per week at one study center, and twice or more per week at another center.[4] (For further discussion, see below). It must be considered important to achieve the 100 μg per venom maintenance dose (the maintenance dose for Mixed Vespid venom protein is 300 μg), since there are no data on effectiveness of maintenance levels below 100 μg per venom.

In the clinical trial, 97% of patients at the maintenance dosage (100 μg per venom) showed no systemic reaction following an insect sting challenge.[4] The remaining 3% had a milder reaction than noted prior to treatment. The patients in this study reached maintenance (100 μg per venom) usually within $2\frac{1}{2}$-$3\frac{1}{2}$ months after beginning therapy.[4] Whether efficacy of therapy is influenced by the time required to reach maintenance has not yet been determined.

Large local reactions occurred in approximately 60% of the patients given immunotherapy. Some form of systemic response occurred, often repeatedly, in one-third of the patients treated in the clinical trial.[4] Only one systemic response occurred on the first dose given. The rest occurred at various times in the course of immunotherapy. Some systemic manifestations may have occurred because of the patient's apprehension, and did not require treatment. Approximately one-fourth of the patients experiencing systemic responses were given some form of specific therapy (epinephrine, theophylline, or metaproteranol), some on several occasions.[4]

In deciding the criteria for proceeding from dose to dose of the Suggested Dose Schedule (see DOSAGE AND ADMINISTRATION), the results of the clinical study[4] should be considered. A study center "A" reporting the least number of systemic reactions during pre-maintenance treatment held the dose constant in most of the cases where significant local reactions occurred. With the systemic reactions reported, this center held the dose the same in approximately 80% of the incidences. The treatment injections were given at this center usually once per week, and if a patient missed an appointment, the next dose was often the same as the preceding dose (depending on the previous reactivity of the patient). Patients treated at this center reached maintenance in an average of 17-19 visits.

Another study center "B", reporting a higher incidence of systemic reactions, was more regimented in following the Suggested Dose Schedule. This center reduced or held the dose the same in less than 10% of the cases reporting significant local reactions. With the systemic reactions reported, this center held the dose the same or reduced the dosage in approximately 20% of the cases. At this center, more than one injection per week was given at the outset as circumstances and sensitivity allowed. Patients treated at this center reached maintenance in an average of 14 visits.

Following the achievement of maintenance level (100 μg per venom), approximately 80% or more patients were given a second maintenance injection at a 1-week interval. The third maintenance injection was usually (in approximately 60% of the patients) at a 2-week interval. The next injection was usually within 3 weeks, and thereafter, the patients were injected for ongoing maintenance at approximately monthly intervals.[4]

INDICATIONS AND USAGE

Insect stings may induce a wide range of allergic symptoms in sensitive patients. A normal sting response is initial burning or stinging pain that may be intense and last several minutes to an hour

or more. There is usually some local swelling coming on immediately and persisting for several days. The location of the sting has considerable influence on the intensity of the pain and extent of swelling. Stings on the fingers or feet produce much pain, but less swelling; whereas a sting on the head or face produces extensive swelling with variable pain.

Local reactions coming on rapidly and larger than the usual local reaction, particularly if the swelling spans both adjacent joints on the extremities, can indicate hypersensitivity. Systemic symptoms come on shortly after the sting, often within seconds to minutes. Symptoms may range from generalized flushing, itching, redness, diffuse swelling of the skin or urticarial wheals, abdominal cramps, nausea, vomiting, or incontinence of urine or stool, to faintness, blurring or loss of vision, unconsciousness, seizures, respiratory or cardiac arrest, or death. Later reactions may consist of fever, achiness, malaise, joint swelling, urticaria or other signs of vascular damage typical of serum sickness, a Type III reaction. Typical delayed Type IV reactions may also occur.[6]

Rarely, other types of severe reactions to insect stings have been reported.[6] These include serum sickness, hematologic abnormalities, and neurological disorders commencing some time after a sting, and not associated with anaphylactoid reactions. These patients are not candidates for immunotherapy using insect venoms.

(1) Diagnosis

Skin testing with insect venoms is useful to demonstrate the presence of IgE antibodies which account for the patient's symptoms.[3] Patients are seldom able to identify the insect which stung them, so skin testing is used to determine the insect culprit. Dilutions of these venom products will help judge the sensitivity of the patient and whether the patient should be treated.[7]

It is not absolutely known what levels (micrograms) of venom, that elicit positive skin tests, are diagnostic of clinical sensitivity. However, patients with a history of reactions (any of three types: generalized urticaria or angioedema; respiratory difficulty due either to laryngeal edema or to bronchospasm; or vascular collapse, with or without loss of consciousness) to previous stings and a positive skin test to a venom intradermal injection of approximately 1 μg/mL had about a 60% chance of reacting again when stung by the same insect. These patients should receive venom immunotherapy.[3]

Patients with a history of reaction (any of the three reaction types described above) to previous stings, but who did **not** demonstrate a positive skin test reaction to venom, were considered in a previous study not to be clinically sensitive, and were not treated.[3] We cannot recommend treatment for such patients.

Another study demonstrated false positive reactions when skin testing with venom concentrations of 10 μg/mL and 100 μg/mL was carried out.[8] Thus there can be a nonspecific skin test reaction potentially due to the pharmacological action of the venom at higher concentrations.

The best statement that can be made, at present, is that patients with significant positive history (reactions of the three types described above) following an insect sting, **and** who do react with a positive skin test to a venom concentration of 1 μg/mL or less, are recommended for treatment. Patients who have the history described above, but who do not react to a 1 μg/mL intradermal venom skin test, cannot be recommended for treatment. At present, the data does not exist, to determine whether a patient who might react to a higher concentration, e.g., 2-10 μg/mL, is at risk from a subsequent sting or not. Since it is not known if sting-sensitive patients who subsequently lose their IgE anti-venom antibody can be resensitized by further stings, it is advisable to retest these patients after any subsequent stings.[3] However, since the level of venom-specific IgE may fall to low levels briefly after a sting, patients should not be re-tested until 2 to 4 weeks after any sting.

(2) Treatment

Immunotherapy is indicated for those patients diagnosed as sensitive (see Diagnosis above) and is accomplished by using graduated dilutions of the appropriate insect venom or venoms to control the severity of the patient's symptoms from subsequent stings.

Increasing doses of venom are given at intervals, dependent on the patient's ability to tolerate the venoms, until a maintenance dosage (100 μg per venom is recommended – 300 μg in the case of the Mixed Vespid venom protein) is reached and maintained.

Venom sensitivity differs for individual patients, thus it is not possible to provide a dosage schedule that is universally suited to all patients. The dosage schedule shown under DOSAGE AND ADMINISTRATION is a summary of the schedule used in clinical trials of our product and found suitable for the majority of patients.

In highly sensitive patients, the physician may be required to use a modified dose schedule, based on the patient's sensitivity to and tolerance of the injections. Lower initial doses and smaller dosage increments than shown under DOSAGE AND ADMINISTRATION may be necessary.

CONTRAINDICATIONS

There are no **known** absolute contraindications to immunotherapy using Hymenoptera Venom Products. See also PRECAUTIONS and WARNINGS.

Patients showing negative intradermal skin tests to specific venoms at 1 μg/mL are not recommended for venom treatment.

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

Patients with cardiovascular diseases and/or pulmonary diseases such as symptomatic unstable, steroid-dependent 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]

Patients on 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 systemic reactions.[2]

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

WARNINGS

See WARNINGS box at the beginning of this Instruction Sheet. See also PRECAUTIONS.

Venom extract must 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) any evidence of an excessively large local or any generalized reaction during the initial stages of immunotherapy, or during maintenance therapy; and/or (4) insect sting prior to a scheduled injection. Do not administer venom injections during a period of symptoms following an insect sting or on the day the patient received an insect sting, since this could result in an allergen load that exceeds the patient's tolerance.

THE CONCENTRATE MUST NOT BE INJECTED AT ANY TIME UNLESS TOLERANCE HAS BEEN ESTABLISHED. DILUTE CONCENTRATED EXTRACTS WITH STERILE ALBUMIN SALINE WITH PHENOL (0.4%) FOR SKIN TESTING AND IMMUNOTHERAPY.

INJECTIONS MUST NEVER BE GIVEN INTRAVENOUSLY. Subcutaneous injection is recommended. Intracutaneous or intramuscular injections 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.

Patients with hypersensitivity to insect venom who undergo desensitization treatment while under concomitant therapy with ACE (angiotensin-converting enzyme) inhibitors, may have an increased risk of life-threatening anaphylactic reactions.[9] Patients without insect venom hypersensitivity, who take ACE inhibitors, and are stung by insects such as bee or wasp can show such reactions as well.[10]

Two patients undergoing desensitization treatment with Hymenoptera Venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenge.[11]

IF CHANGING TO A DIFFERENT LOT OR A FRESHLY RECONSTITUTED VIAL OF VENOM EXTRACT: All extracts lose potency over time, and a fresh extract could have an effective potency that is substantially greater than that of the old extract. The first dose from the new vial should not exceed 50% of the previous dose.

IF THE VENOM 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 venom extract therefore should be greatly decreased even though the extract is the same formula and dilution. In general, a dose reduction to 50% of the previous product dose should be adequate, but each situation must be evaluated separately considering the patient's history of sensitivity, tolerance of previous injections, and other factors. If the patient tolerates a 50% decrease, the next dose could be raised to the previous dose amount. If the decrease is greater than 50%, the next dose would need to be determined by the allergist, depending on the situation. Dose intervals should not exceed one week when rebuilding dose. See DOSAGE AND ADMINISTRATION.

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. See DOSAGE AND ADMINISTRATION.

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, s/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 when starting the fresh extract.

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, ranging from mild to life-threatening anaphylaxis, or even death, as described under INDICATIONS AND USAGE and ADVERSE REACTIONS. Patients should be informed of this, and the warnings and precautions should be discussed prior to immunotherapy. See PRECAUTIONS below. Systemic reactions should be treated as indicated in ADVERSE REACTIONS.

PRECAUTIONS

(1) General

The presence of asthmatic signs and symptoms appear to be an indicator for severe reactions following allergy injections. An assessment of airway obstruction either by measurement of peak flow or an alternate procedure may provide a useful indicator as to the advisability of administering an allergy injection.[1, 12-16]

Concentrated extracts must not be injected unless tolerance has been established.

Diluting fluid should be forcibly drawn into the sealed vial when the syringe needle penetrates the seal during reconstitution. Failure of this to occur for a particular vial indicates possible loss of vacuum. Vials without vacuum should be returned to the manufacturer.

Record date of reconstitution and expiration date of reconstituted product in the space provided on the product label. Date of expiration after reconstitution must not exceed the Final Expiration Date indicated on the container label. (See table below for expiration dates, including dilutions).

Store freeze-dried and reconstituted venom product, stock solutions and venom dilutions constantly at 2° - 8°C.

Venom Concentration	Diluent	Recommended Expiration Date*
100 µg/mL	Albumin Saline with Phenol (0.4%)	6 months
10 µg/mL	Albumin Saline with Phenol (0.4%)	1 month
1 µg/mL	Albumin Saline with Phenol (0.4%)	1 month
0.1 µg/mL	Albumin Saline with Phenol (0.4%)	14 days
Less than 0.1 µg/mL	Albumin Saline with Phenol (0.4%)	Prepare fresh daily

*But not to exceed Final Expiration Date indicated on the container label.

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, with a needle at least 5/8" long and graduated in 0.01 mL units, should be used to measure carefully each dose from the appropriate dilution. Aseptic techniques should always be employed when injections are being administered.

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

Patient reactions to previous injections should be reviewed before each new injection so that dose can be adjusted accordingly. See ADVERSE REACTIONS and WARNINGS.

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. It is suggested that 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 AT LEAST 30 MINUTES AFTER SKIN TESTING AND AFTER EACH TREATMENT INJECTION. Most severe reactions will occur within this time period, and rapid treatment measures should be instituted. See ADVERSE REACTIONS 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. (See WARNINGS box at the beginning of this Instruction Sheet). Patients should be made to understand the importance of a 30 minute observation period following skin testing or therapeutic injections, and be cautioned to return to the office promptly if symptoms occur after leaving. Patients should be instructed in the use of, and have available, an Emergency Anaphylaxis Kit for self-administration of epinephrine.

Patients must be instructed to report any insect stings that have occurred, since a venom injection should not be given on the same day as the sting, nor during a time when the patient is still experiencing symptoms from the sting.

(3) Drug Interactions

Patients with cardiovascular diseases and/or pulmonary diseases such as symptomatic, unstable, steroid-dependent 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]

Patients on 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.[2]

See WARNINGS section regarding concurrent treatment with ACE inhibitors.

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.[17] Topical steroids should be discontinued at the skin test site for at least 2-3 weeks before skin testing.[17, 18]

Tricyclic antidepressants such as doxepin, should be withheld for at least 7 days before skin testing.[19] Topical local anesthetics may suppress the flare responses and should be avoided on skin test sites.[20]

When using other drugs in patients receiving allergenic extracts, always consult the product labeling of the other drugs to determine any possible interaction with use of allergenic extracts, and specifically with stinging insect (Hymenoptera) venom extracts.

(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) Pregnancy[12, 21]

Animal reproduction studies have not been conducted with Hymenoptera Venom Products. It is also not known whether Hymenoptera Venom Products can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Hymenoptera Venom Products should be given to a pregnant woman only if clearly needed.

On the basis of histamine's known ability to contract uterine muscle, theoretically, a systemic reaction, whether occurring from insect sting or from venom skin testing or treatment dose, should be avoided. Therefore, the physician must carefully consider the benefit-to-risk ratio, to both patient and fetus, of continuing venom immunotherapy during pregnancy, or performing venom skin testing, and especially of initiating a venom immunotherapy program where there is a possibility that the patient may not be able to reach the recommended maintenance dose without significant risk of a systemic reaction.

(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, 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. A study done in children ages 4 to 17 showed no special problems with venom immunotherapy in this population.[22]

(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.[23]

ADVERSE REACTIONS

Physicians administering Hymenoptera Venom testing or treatment materials should be experienced in the treatment of severe systemic reactions (see WARNINGS box at the beginning of this Instruction Sheet).

(1) Local Reactions

Some erythema, swelling or pruritis at the site of injection are common, the extent varying with the patient. Excessively large, painful or persistent local reactions can occur from skin tests or immunotherapy. Frequent application of cold, wet dressings to the area and/or the use of oral antihistamines will ameliorate the discomfort. Reactions usually subside in 24-36 hours. Large local reactions occurred in approximately 60% of the patients given immunotherapy in a clinical study. None of the local reactions required specific treatment; however, subsequent injections in many instances were held to the previous dose or a reduced dose. Some patients had repeated large local reactions that slowed the increase in the immunotherapy dose.[4]

See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION Sections.

A mild burning immediately after the injection is to be expected. This usually leaves in 10 to 20 seconds. See also WARNINGS and PRECAUTIONS regarding proper method and route of injection.

(2) Systemic Reactions

Most severe systemic reactions will begin within a 30 minute time period, but systemic reactions may occur at any time after skin tests or immunotherapy. Symptoms may range from mild to life-threatening from anaphylaxis as described under INDICATIONS AND USAGE.

With careful attention to dosage and administration, severe 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. See CLINICAL PHARMACOLOGY for clinical incidence of systemic reactions and course of action following these reactions.

If a systemic or anaphylactic reaction does occur, inject 1:1000 epinephrine-hydrochloride intramuscularly or subcutaneously.

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 antihistamines, inhaled bronchodilators, theophylline and/or corticosteroids may be used if necessary after adequate epinephrine and circulatory support have 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; epinephrine usually produces a prompt response. However, the physician should be prepared in advance for all contingencies. Promptness in beginning emergency treatment measures is of utmost importance.

For recommendations regarding how to proceed with venom extract dose following systemic reactions, see WARNINGS, PRECAUTIONS and DOSAGE AND ADMINISTRATION.

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

(1) General

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

Reconstitute and dilute the freeze-dried venom as directed below. Sterile Albumin Saline with Phenol (0.4%) must be used to reconstitute and dilute the venoms for skin testing and treatment.

Reconstitute the freeze-dried venoms by adding 1.2 mL Sterile Albumin Saline with Phenol (0.4%) to the vial using a sterile syringe. Swirl or rock the container to dissolve the venom completely. DO NOT SHAKE, since shaking can cause foaming.

Dilutions (see table below) must be made in Sterile Albumin Saline with Phenol (0.4%). They must be made accurately and aseptically, using sterile solutions, vials, syringes, etc., and thoroughly mixed by rocking or swirling. DO NOT SHAKE. Maintain stock solutions and dilutions constantly at 2° - 8°C.

Extract Volume	Extract Concentration		Diluent Volume		Dilution Concentration
1 part of	100 µg/mL	+	9 parts	=	10 µg/mL
1 part of	10 µg/mL	+	9 parts	=	1 µg/mL
1 part of	1 µg/mL	+	9 parts	=	0.1 µg/mL
1 part of	0.1 µg/mL	+	9 parts	=	0.01 µg/mL
1 part of	0.01 µg/mL	+	9 parts	=	0.001 µg/mL
1 part of	0.001 µg/mL	+	9 parts	=	0.0001 µg/mL

As an example of the preceding dilution table:

Extract Volume	Extract Concentration		Diluent Volume		Dilution Concentration
0.2 mL of	100 µg/mL	+	1.8 mL	=	10 µg/mL
0.2 mL of	10 µg/mL	+	1.8 mL	=	1 µg/mL
0.2 mL of	1 µg/mL	+	1.8 mL	=	0.1 µg/mL
0.2 mL of	0.1 µg/mL	+	1.8 mL	=	0.01 µg/mL
0.2 mL of	0.01 µg/mL	+	1.8 mL	=	0.001 µg/mL
0.2 mL of	0.001 µg/mL	+	1.8 mL	=	0.0001 µg/mL

NOTE: Mixed Vespid venom protein concentrations will be three times that shown above.

USE OF VENOMIL DIAGNOSTIC SETS

The Venomil® Diagnostic Sets from Jubilant HollisterStier contain a vial of freeze-dried venom protein that when reconstituted as instructed below will contain 100 µg venom or venom protein/mL.

To use the Venomil Diagnostic set, follow these steps:

1. Open box and remove contents. Be sure to read the complete package Instruction Sheet paying particular attention to the WARNINGS, PRECAUTIONS, CONTRAINDICATIONS, and ADVERSE REACTIONS.

2. Remove the freeze-dried venom vial and the vial of diluent provided with the kit. Withdraw 1.3 mL of Albumin Saline with Phenol (0.4%) from the diluent vial using a 2 or 3 mL disposable syringe. Expel some Albumin Saline with Phenol (0.4%) from the syringe until exactly 1.2 mL are remaining in the syringe. The remaining Albumin Saline with Phenol (0.4%) in the diluent vial may be marked "Control" and used as a negative control for prick testing.

3. Insert the needle of the diluent syringe into the vial of venom and expel the diluent. Remove the syringe. Swirl or rock the vial to dissolve the venom completely. DO NOT SHAKE. Shaking can cause foaming of the extract.

At this point, you have completed the reconstitution of the freeze-dried venom. The reconstituted products contain 100 µg of venom or venom protein per mL. DO NOT USE THIS STRENGTH FOR INTRADERMAL SKIN TESTING. DISCARD AFTER THE DILUTIONS HAVE BEEN PREPARED.

4. Remove six vial labels from the kit and mark them: 10 µg/mL, 1 µg/mL, 0.1 µg/mL, 0.01 µg/mL, 0.001 µg/mL and 0.0001 µg/mL. Withdraw 0.2 mL of venom extract in a 1 mL syringe from the vial reconstituted in step #3. Insert the syringe needle into one vial of 1.8 mL Albumin Saline with Phenol (0.4%). Slowly expel the 0.2 mL venom into it. Swirl or rock to mix, and label 10 µg/mL.

5. Withdraw 0.2 mL of the 10 µg/mL venom extract and inject into another vial of 1.8 mL Albumin Saline with Phenol (0.4%). Mix and label 1 µg/mL.

6. The four additional dilutions should be prepared in the same manner.

(2) Diagnosis

Since the level of insect venom specific IgE **may** fall to low levels briefly after a reaction to a sting, patients should not be tested until 2 to 4 weeks after any sting.

Skin testing should be carried out with **all** five individual venoms, since many patients have multiple sensitivities.[4] Mixed Vespid venom protein should be used only for therapy – not for diagnosis.

Prick testing should be done **before** intradermal testing to determine appropriate concentration for intradermal testing. See Intradermal Tests. Skin testing (prick and intradermal) provides information to assist in identifying those patients who are to be classified as extremely sensitive and who may not tolerate the Suggested Dose Schedule. See DOSAGE AND ADMINISTRATION, Immunotherapy CAUTION.

In **both** the prick and intradermal tests, a negative control test with diluent alone must be performed. A histamine positive control test is also recommended.

The flexor surface of the forearm is the usual location for skin testing. It is important that a separate sterile syringe and needle be used for each extract and each patient.

Prick Tests: Prick tests are accomplished by applying one drop of the 1 µg/mL venom extract to the forearm, and by pricking the skin through the surface of the drop with a sterile 27 gauge needle. The prick is superficial and should not draw blood.

Skin response should be assessed after approximately 15-20 minutes.

For prick tests, a positive reaction (reaction greater than diluent control) at the 1 µg/mL concentration indicates a high level of sensitivity to the test venom.

Intradermal Tests: Patients showing a positive reaction to the prick test at the 1 µg/mL concentration should begin intradermal tests at concentrations of not more than 0.0001 to 0.001 µg/mL. Patients with negative prick tests may begin intradermal tests at a concentration of 0.001 µg/mL.

A 1 mL tuberculin syringe with a short 27-gauge needle should be used to deliver a volume of 0.05 mL for intradermal testing. Introduce the needle into the superficial skin layers, bevel down, until the bevel is completely buried, then slowly inject a 0.05 mL aliquot of the venom dilution, making a small bleb.

Start intradermal tests with the most dilute solution. If after 20 minutes no skin reaction is obtained, continue the intradermal testing using ten-fold increments in the concentration until a reaction of 5-10 mm wheal and 11-20 mm erythema is obtained, or until a concentration of 1 µg/mL has been tested, whichever occurs first.

A patient should be considered sensitive to the test venom when a skin response of 5-10 mm wheal and 11-20 mm erythema (or greater) occurs at a concentration of 1 µg/mL or less,[8] providing that this reaction is greater than that of the diluent control.

(3) Immunotherapy

For proper method and route of injection, see WARNINGS, PRECAUTIONS and ADVERSE REACTIONS.

The most common site of injection is the lateral aspect of the upper arm.

Patients who have multiple venom sensitivities should be given each specific venom injection in a separate site. (Except, if the patient has sensitivities to Yellow Jacket, Yellow Hornet, and White-Faced Hornet venoms concurrently, s/he can be injected with Mixed Vespid venom protein, an equal mixture of these three vespid venoms). Note which venom preparation is injected at a specific site, so that dosage of that venom preparation can be adjusted if an excessive local reaction occurs. In patients receiving more than one venom, there is theoretically a greater risk of systemic reactions.

CAUTION: Sensitivity to venom differs from patient to patient. Thus, it is not possible to provide a dosage schedule suitable for all patients. The Suggested Dose Schedule shown below was used in clinical trials[4] and should be suitable for a majority of patients.

IN EXTREMELY SENSITIVE PATIENTS, however, an individualized dose schedule must be employed which will be dictated by the patient's sensitivity. This individualized schedule will probably include weaker dilutions and smaller increments between doses in progressing to the maintenance level (100 µg per venom).

In identifying those patients to be classified as extremely sensitive, individuals reacting with significant skin test (wheal greater than 5 mm and erythema greater than 20 mm) at intradermal skin test concentrations of 0.01 µg/mL or less, or those patients experiencing a systemic reaction to any venom skin test concentration, should be considered highly sensitive.

Suggested Dose Schedule for a Single Venom:

Dose No.	*Volume of 1 µg/mL	Dose No.	Volume of 10 µg/mL	Dose No.	Volume of 100 µg/mL
1	0.05 mL	5	0.05 mL	9	0.05 mL
2	0.10 mL	6	0.10 mL	10	0.10 mL
3	0.20 mL	7	0.20 mL	11	0.20 mL
4	0.40 mL	8	0.40 mL	12	0.40 mL
Mixed Vespid venom will contain three times the				13	0.60 mL
venom protein per mL shown in this table.				14	0.80 mL
*See preceding CAUTION Section.				15	1.00 mL

ALTERNATE MAINTENANCE DOSE SCHEDULE

If the above suggested dosage schedule has been followed, Dose #15 will have emptied the third vial of venom. There should now be three vials of freeze-dried venom remaining in the maintenance set. If a smaller volume maintenance dose is desired, then the remaining vials of venom may be reconstituted with 0.6 mL of Sterile Albumin Saline with Phenol (0.4%) instead of the previously recommended 1.2 mL. When 0.6 mL is used for reconstitution, the maintenance dose volume then becomes 0.5 mL instead of 1.0 mL. The 0.5 mL injection will still contain 100 micrograms of venom or venom protein.

Precautions should be taken to ensure that maintenance level injections of 0.5 mL are given only from those vials of venom that have been reconstituted with 0.6 mL of diluting fluid. Any other volume used for reconstitution will not give 100 micrograms of venom or venom protein at a dosage of 0.5 mL.

In proceeding with the Suggested Dose Schedule, or modified schedules (for highly sensitive patients) it is recommended that injections be given at least once per week, as in the clinical studies. (See CLINICAL PHARMACOLOGY and INDICATIONS AND USAGE). When building the dose, it is important that dose intervals not exceed one week since longer intervals may decrease the patient's tolerance of the extract.

Based on the clinical studies[4] it is suggested that if a systemic, extremely large local (10 cm or more in duration, or other severe local symptoms), or persistent and severe delayed local reaction occurs during the dose building phase, the dose at the next visit be held constant (or reduced, depending on judgment of the severity of the reaction) as was done at Study Center "A," which reported the least number of systemic reactions during the course of therapy.

It must be considered important to achieve the 100 µg per venom maintenance dose (the maintenance dose for Mixed Vespid venom protein is 300 µg), since there are no data on effectiveness of maintenance levels below 100 µg per venom. Following the achievement of maintenance level (100 µg per venom), it is recommended that a second maintenance injection be given at a 1-week interval, and a third maintenance injection at a 2-week interval. Administer the next injection at a 3-week interval, and then monthly for ongoing maintenance.

See CLINICAL PHARMACOLOGY and INDICATIONS AND USAGE for further information regarding clinical studies on which the above recommendations are based.

The optimum duration for immunotherapy is not known, so current recommendations are that maintenance injections be continued indefinitely, year around, particularly in patients experiencing life-threatening anaphylaxis after insect stings.

Pediatric Use

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

Geriatric Use

The dose for elderly patients is the same as for adult patients under 65.[23] (See PRECAUTIONS).

HOW SUPPLIED

Jubilant HollisterStier sterile freeze-dried Hymenoptera Venom Products are supplied in vacuum-sealed vials containing venom extract and excipients: mannitol (for Vespid Venom Protein), and mannitol and sodium chloride (for Honey Bee Venom). (See the chart under DESCRIPTION or the latest Allergy Product Price List for vial sizes and content.) Reconstituting fluid [Sterile Albumin Saline with Phenol (0.4%)] is supplied with the Venomil® kits, and is also available separately. (Note: Diagnostic kits also contain Sterile Empty Vials.)

Storage: Store freeze-dried and reconstituted venom product, and venom dilutions, at 2° - 8°C, and keep at this temperature range during office use.

LIMITED WARRANTY

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

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

REFERENCES

1. Lockey, Richard F., Linda M. Benedict, Paul C. Turkeltaub, Samuel C. Bukantz. Fatalities from immunotherapy (IT) and skin testing (ST). J. Allergy Clin. Immunol. 79 (4): 660-677, 1987.
2. Jacobs, Robert L., Goeffrey W. Rake, Jr., et. al. Potentiated anaphylaxis in patients with drug-induced beta-adrenergic blockade. J. Allergy Clin. Immunol. 68 (2): 125-127, August 1981.
3. Hunt, K. J., M. D. Valentine, A. K. Sobotka, A. W. Benton, F. J. Amodio, L. M. Lichtenstein. A controlled trial of immuotherapy in insect hypersensitivity. New Eng. J. Med. 299: 157-161, July 27, 1978.
4. Summary of data from BB-IND 1292 clinical studies, 1978-79, on Hollister-Stier products.
5. Amodio, F., L. Markley, M. D. Valentine, A. K. Sobotka, L. M. Lichtenstein. Maintenance immunotherapy for Hymenoptera sensitivity. J. Allergy Clin. Immunol. 61 (3): 134, 1978.
6. Reisman, R. E. Allergy Principles and Practice. E. Middleton, C. E. Reed, E. F. Ellis, ed. C. V. Mosby Co., 1978.
7. Sobotka, A. K., N. F. Adkinson, Jr., M. D. Valentine, L. M. Lichtenstein. Allergy to insect stings. IV. Diagnosis by R.A.S.T. J. Immunol. 121 (6): 2477-2484, 1978.
8. Hunt, K. J., M. D. Valentine, A. K. Sobotka, L. M. Lichtenstein. Diagnosis of allergy to stinging insects by skin testing with Hymenoptera venoms. Annals Int. Med. 85: 56-59, 1976.
9. Annals of Allergy, Asthma & Immunology. Inhibitors of angiotensin II: Potential hazards for patients at risk for anaphylaxis.Editorial. 78: 527-529, June 1997.
10. Pharm. Ind. (Germany). Anaphylactoid reactions in patients treated with ACE inhibitor treatment in combination with desensitization treatment or after insect bites. 56 (9): IX226-227, 1994.
11. Tunon-De-Lara, J.M., et al. ACE inhibitors and anaphylactoid reactions during venom immunotherapy. The Lancet (United Kingdom). 340(8824): 908, Oct. 10, 1992.
12. Weinstien, A.M., B.D. Dubin, W.K. Podleski, S.L. Spector, R.S. Farr. Asthma and pregnancy. JAMA. 124 (11): 1161-1165, 1979.
13. Reid, M. J., R. F. Lockey, P. C. Turkletaub, T.A.E. Platts-Mills. Survey of fatalities from skin testing and immunotherapy. J. Allergy Clin. Immunol. 92 (1): 6-15, July 1993.
14. Reid, M. J., G. Gurka. Deaths associated with skin testing and immunotherapy. J. Allergy Clin. Immunol. 97 (1) Part 3:231, Abstract 195, January 1996.
15. Thompson, R. A. et al. Report of a WHO/IUIS working group. The current status of allergen immunotherapy (hyposensitization). Allergy. 44: 369-379, 1989.
16. Malling, H.J., B. Weeke, et al. The European Academy of Allergology and Clinical Immunology. Position Papers. Allergy. 48 (Supplement 14): 9-82, 1993.
17. Pipkorn, Ulf. Pharmacological influence of anti-allergic medication on *In Vivo* allergen testing. Allergy. 43: 81-86, 1988.
18. Andersson, M., U. Pipkorn. Inhibition of the dermal immediate allergic reaction through prolonged treatment with topical glucocorticosteroids. J. Allergy Clin. Immunol. 79 (2): 345-349, February 1987.
19. Rao, Kamineni S., et al. Duration of suppressive effect of tricyclic anti-depressants on histamine induced wheal and flare reactions on human skin. J. Allergy Clin. Immunol. 82: 752-757, November 1988.

20. Pipkorn, Ulf, M. Andersson. Topical dermal anesthesia inhibits the flare but not the wheal response to allergen and histamine in the skin prick test. Clinical Allergy. 17: 307-311, 1987.

21. DuBuske, L.M., C.J. Ling, A.L. Sheffer. Special problems regarding allergy immunotherapy. Immunol. Allergy Clin. North Am. (USA). 12 (1): 145-175, 1992.

22. Graft, D., K. Schuberth, A. Kagey-Sobotka, K. Kwiterovich, Y. Niv, L. Lichtenstein, M. Valentine. Assessment of prolonged venom immunotherapy in children. J. Allergy Clin. Immunol. 80 (2): 162-169, August 1987.

23. Peebles, Ray Stokes, Jr., B. Bochner, Howard J. Zeitz, ed. Anaphylaxis in the elderly. Immunol. Allergy Clin. of North Am. 13 (3): 627-646, August 1993.

SUGGESTED DOSAGE CHART
FOR HYMENOPTERA VENOM PRODUCTS

Schedule for Immunotherapy

Dr. | Patient | Venom Product | Lot No.

Dose No.	Volume of 1 µg/mL	Dose No.	Volume of 10 µg/mL	Dose No.	Volume of 100 µg/mL
1	0.05 mL	5	0.05 mL	9	0.05 mL
2	0.10 mL	6	0.10 mL	10	0.10 mL
3	0.20 mL	7	0.20 mL	11	0.20 mL
4	0.40 mL	8	0.40 mL	12	0.40 mL
				13	0.60 mL
				14	0.80 mL
				15	1.00 mL

Mixed Vespid Venom will contain three times the venom protein per mL shown in this table.

See CAUTION Section in DOSAGE AND ADMINISTRATION, Immunotherapy.

CAUTION

See INDICATIONS AND USAGE, TREATMENT, and DOSAGE AND ADMINISTRATION in this Instruction Sheet.

DOSE NO.	DILUTION	mL	DATE	REMARKS
1				
2				
3				
4				
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PLEASE NOTE: Minor leakage of vial contents may occur after stopper is punctured several times if excessive amounts of air are injected into the vial. To prevent leakage, avoid buildup of air pressure, or store vial in upright position.

To reorder Venom Product, cut on dotted line and send to Spokane address.

☐ Bulk-5 Dose
☐ Bulk-12 Dose
☐ Venomil®

Dr. Name: _____

Address: _____

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Phone: _____

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(Dr. Signature)

Honey Bee _____
Yellow Jacket _____
Yellow Hornet _____
White-Faced Hornet _____
Wasp _____
Mixed Vespid _____
Diluent _____

HollisterStier

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February 2018

INSTRUCTIONS AND DOSAGE SCHEDULE
ALLERGENIC EXTRACTS
STANDARDIZED MITES

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Printed in U.S.A.
Rev. 02/18

HollisterStier Allergy

Jubilant HollisterStier, LLC
Spokane, WA 99207
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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 death[1]. Therefore, emergency measures and personnel trained in their use should be available immediately in the event of such a reaction. Patients should be instructed to recognize adverse reaction symptoms and cautioned to contact the physician's office if symptoms occur. Standardized glycerinated extracts may be more potent than regular extracts and therefore, are not directly interchangeable with non-standardized extracts, or other manufacturers' products. This product should never be injected intravenously. Refer also to the WARNINGS, PRECAUTIONS, ADVERSE REACTIONS and OVERDOSE Sections for further discussion.

DESCRIPTION:

Mite extract is a sterile solution containing the extractables of Dermatophagoides farinae or Dermatophagoides pteronyssinus, 0.5% sodium chloride, 0.275% sodium bicarbonate, and 50% glycerin by volume as a preservative. Source material for the extract is the whole bodies of the mites. The mites are grown on a medium of brine shrimp eggs and wheat germ, and are handled and cleaned in a manner that the maximum carryover of the medium components is less than 1%. The medium contains no material of human origin. Sterile, diluted mite extracts available for intradermal testing contain 0.9% sodium chloride, not more than 0.5% glycerin by volume, 0.03% albumin (human), not more than 0.003% sodium bicarbonate, and 0.4% phenol as a preservative.

Skin test trials were conducted to evaluate the skin reactivity of medium components mixed in the approximate proportion used for mite growth. Twenty-three individuals who were puncture test reactive ($\sum E \geq 40$mm) to either D. farinae or D. pteronyssinus were tested with an extract of medium components at an estimated 1% carryover level. None of these patients had a $\sum E$ response more than 3mm larger than the negative control by puncture test with the concentrate of the medium components extract. One of the 23 patients had a reaction with $\sum E \geq 20$mm when tested intradermally with a 1:100 (v/v) dilution of the concentrate of the medium components extracts. Standardized D. farinae and D. pteronyssinus extract concentrates (stock concentrates) containing 30,000 Allergy Units/mL (AU/mL) are supplied in dropper vials for scratch, prick or puncture tests. Stock concentrates are also available in multiple-dose vials containing 10,000 AU/mL and 30,000 AU/mL to be diluted for intradermal testing and immunotherapy. Standardized D. farinae and D. pteronyssinus extract dilutions (at 30 AU/mL and 300 AU/mL) are supplied for intradermal diagnostic tests described in Section DOSAGE AND ADMINISTRATION, Diagnosis, Part 2.a.

Product Concentration:

1. Allergy Units (AU/mL). The potency of extracts labeled in Allergy Units (AU/mL) is determined by in vitro comparison to a reference standard established by the Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration.

2. Bioequivalent Allergy Units (BAU/mL). Other standardized allergenic extracts are labeled in Bioequivalent Allergy Units/mL (BAU/mL) based on their comparison (by in vitro assay or major allergen content) to CBER, FDA Reference Preparations. The FDA reference extracts have been assigned Bioequivalent Allergy Units based on the CBER ID_{50}EAL method.[5] Briefly, highly sensitive patients are skin tested to the reference preparation using an intradermal technique employing 3-fold extract dilutions. Depending on the dilution which elicits a summation of erythema diameter of 50, Bioequivalent Allergy Units are assigned as follows:

BAU/mL	D_{50}
100,000	13-15
10,000	10.9-12.9
1,000	8.8-10.8
100	6.7-8.7

3. 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:

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

CLINICAL PHARMACOLOGY:[26]

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. Mites belonging to the genus Dermatophagoides are found in approximately 80% of house dust samples throughout the world[22, 23]. D. farinae is common in much of the United States[24], although D. pteronyssinus is predominant in certain coastal regions, and both species are commonly found in homes[25]. Persons suspected of having allergy to house dust should be tested for sensitivity to each mite.

INDICATIONS AND USAGE:[16, 17, 18, 26]

Standardized glycerinated 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[20, 21]. 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. 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 to the allergen 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 or she 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 ALBUMIN SALINE WITH PHENOL (0.4%) FOR INTRADERMAL TESTING. INJECTIONS SHOULD NEVER BE GIVEN INTRAVENOUSLY. Subcutaneous injection is recommended. Intracutaneous or intramuscular injections 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 TO A DIFFERENT LOT OF STANDARDIZED 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 STANDARDIZED 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 standardized glycerinated 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. In highly sensitive individuals, the skin test method may be preferable. 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 THE PREVIOUS EXTRACT WAS NON-STANDARDIZED: Standardized extracts may be more potent than non-standardized extracts. Initiate therapy as though the 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 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

The presence of asthmatic signs and symptoms appear to be an indicator for severe reactions following allergy injections[1, 32, 33, 34, 35]. An assessment of airway obstruction either by measurement of peak flow or an alternate procedure may provide a useful indicator as to the advisability of administering an allergy injection. Concentrated extracts must be diluted prior to use; See DOSAGE AND ADMINISTRATION Section for detailed instructions on the dilution of standardized glycerinated allergenic extracts. Any evidence of 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 Albumin Saline with Phenol (0.4%) may be more potent than extracts diluted with diluents which do not contain stabilizers. When switching 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 homologous 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. Carcinogenesis, Mutagenesis, Impairment of Fertility.

Long-term studies in animals have not been conducted with allergenic extracts to determine their potential for carcinogenicity, mutagenicity or impairment of fertility.

4. Pregnancy[30]

Allergenic Extracts. 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.

5. Nursing Mothers

There are no current studies on secretion of the allergenic extract components in human milk, or of their effect on the nursing infant. Because many drugs are excreted in human milk, caution should be exercised when allergenic extracts are administered to a nursing woman.

6. Pediatric Use

Since dosage for the pediatric population is the same as for adults[26, 27], 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.

7. 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[29].

8. Drug Interactions

Patients on non-selective beta blockers may be more reactive to allergens given for diagnosis or treatment, and may be unresponsive to the usual doses of epinephrine used to treat allergic reactions[19]. 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[2]. Topical steroids should be discontinued at the skin test site for at least 2-3 weeks before skin testing[2, 3]. Tricyclic antidepressants such as Doxepin should be withheld for at least 7 days before skin testing[31]. Topical local anesthetics may suppress the flare responses and should be avoided in skin test sites[4].

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, 28] **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 DOSAGE: 0.3 to 0.5 mL should be injected. Repeat in 5 to 10 minutes if necessary.

PEDIATRIC DOSAGE: The usual initial dose is 0.01 mg (mL) per kg body weight or 0.3 mg (mL) per square meter of body surface area. Suggested dosage for infants to 2 years of age is 0.05 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:

1. General

Sterile aqueous diluent containing human serum albumin [Albumin Saline with Phenol (0.4%)], or diluent of 50% glycerin may be used when preparing dilutions of the concentrate for immunotherapy. For intradermal testing dilutions, Albumin Saline with Phenol is recommended. 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 scratch, 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 testing is performed by placing a drop of extract concentrate on the skin and puncturing the skin through the drop with a small needle such as a Prick Lancetter. Fifteen minutes after puncture is made the diameter of wheal and erythema reactions are measured, and the sensitivity class of the patient determined by the table presented at end of Diagnosis Section. Less sensitive individuals (Class 0 to 1+) can be tested intradermally with the recommended dilutions of the extract concentrate (See intradermal testing instructions). The skin test concentration of 30,000 AU/mL in dropper vials is used for scratch, prick or puncture testing. Puncture tests performed on 12 selected highly sensitive subjects showed the following:

Species	Mean ∑ Wheal ± 1 Std. Dev. (mm)	Mean ∑ Erythema ± 1 Std. Dev. (mm)
D. farinae	22.4 ± 10.7	82.3 ± 21.7
D. pteronyssinus	24.0 ± 9.9	89.3 ± 24.5

∑ equals the sum of the longest diameter and the mid-point orthogonal diameter. Extract for intradermal testing should be prepared by diluting the 30,000 AU/mL stock concentrate, provided in multiple-dose vials, with sterile aqueous diluent (refer to the dilution table displayed in the immunotherapy section below). To administer the intradermal strength dilutions, a 1 mL tuberculin syringe with a short 27-gauge needle should be used. The needle is inserted intradermally at a 30° angle, bevel down, and 0.02 to 0.05 mL of the extract is injected. Fifteen minutes following injection, the diameter of wheal and erythema reactions are measured, and the patient's sensitivity class is determined by the table on the following page. Intradermal skin test results in selected highly sensitive subjects are presented for reference purposes:

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

Intradermal extract should be used as follows:

a. Patients with a negative scratch, prick or puncture test:

Patients who do not react to a valid scratch, prick or puncture test should be tested intradermally with 0.02 to 0.05 mL of a 30 AU/mL extract solution. If this test is negative, a second intradermal test may be performed using a 300 AU/mL extract solution. The negative control used with this latter dilution should contain 0.5% glycerin.

b. Patients tested only by the intradermal method:

Patients suspected of being highly allergic should be tested with 0.02 to 0.05 mL of a solution containing 0.03 AU/mL. A negative test should be followed by repeat tests using progressively stronger concentrations until the maximum recommended strength of 300 AU/mL is reached. The negative control used with this latter dilution should contain 0.5% glycerin. Skin tests are graded in terms of the wheal and erythema response noted at 10 to 20 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 ∑E (sum of the longest diameter and the mid-point orthogonal diameters of erythema) is also presented.

Class	Wheal Diameter	Erythema Diameter	Corresponding ∑E
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	> 80mm

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 Albumin Saline with Phenol (0.4%). 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 11-20 mm erythema (SE 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 this 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 twenty 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 glycerin concentrate may be painful due to the glycerin content. The dosage of the 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 30,000 AU/mL

Dilution	Extract	+ Diluent	=	AU/mL Concentration
0	Concentrate	+ 0 mL	=	30,000
1	1 mL concentrate	+ 9 mL	=	3,000
2	1 mL dilution #1	+ 9 mL	=	300
3	1 mL dilution #2	+ 9 mL	=	30
4	1 mL dilution #3	+ 9 mL	=	3
5	1 mL dilution #4	+ 9 mL	=	0.3
6	1 mL dilution #5	+ 9 mL	=	0.03
7	1 mL dilution #6	+ 9 mL	=	0.003

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[29].

HOW SUPPLIED:

Standardized allergenic extracts are supplied for diagnostic and therapeutic use:

Diagnostics:

Extracts: D. pteronyssinus and D. farinae
Scratch, prick or puncture tests, 30,000 AU/mL [50% glycerin (v/v)] in 5 mL dropper vial.
Intradermal Tests [Aqueous] of 30 AU/mL in 5 mL vial, and 300 AU/mL in 5 mL vial.

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

Extracts: D. pteronyssinus and D. farinae
10 mL vial, 30,000 AU/mL or 10,000 AU/mL
30 mL vial, 30,000 AU/mL or 10,000 AU/mL
50 mL vial, 10,000 AU/mL

A mixture of the two mite species, in equal parts, resulting in D. pteronyssinus at 15,000 AU/mL and D. farinae at 15,000 AU/mL is available for therapeutic use in 10 mL and 30 mL vials. A mixture of the two species is also available at 5,000 AU/mL each species in 10 mL, 30 mL and 50 mL.

Storage:

The expiration date of the mite extract in 50% glycerin is listed on the container label. The extract should be stored at 2° - 8°C and kept in this temperature range during office use. Dilutions containing less than 50% glycerin are less stable, and if loss of potency is suspected, should be checked by skin testing with equal units of a freshly prepared dilution on known mite allergic individuals.
The expiration date of the intradermal tests is listed on container labels. Store at 2° - 8°C.

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.

REFERENCES

1. Lockey, Richard F., Linda M. Benedict, Paul C. Turkeltaub, Samuel C. Bukantz. Fatalities from immunotherapy (IT) and skin testing (ST). J. Allergy Clin. Immunol., 79 (4): 660-677, 1987.
2. Pipkorn, Ulf. Pharmacological influence of anti-allergic medication on In Vivo allergen testing. Allergy. 43: 81-86, 1988.
3. Andersson, M. and U. Pipkorn. Inhibition of the dermal immediate allergic reaction through prolonged treatment with topical glucocorticosteroids. J. Allergy Clin. Immunol. 79 (2): 345-349, February 1987.
4. Pipkorn, Ulf, and M. Andersson. Topical dermal anesthesia inhibits the flare but not the wheal response to allergen and histamine in the skin prick test. Clinical Allergy. 17: 307-311, 1987.
5. Turkeltaub, Paul C., MD, and Suresh C. Rastogi, PhD. Quantitative intradermal test procedure for evaluation of subject sensitivity to standardized allergenic extracts and for assignment of allergy units to reference preparations using the ID50EAL method, Allergenics Products Testing Laboratory, Center for Biologics Evaluation and Research (CBER), FDA. Revised: November 1994.
6. Lowell, F.C., W. Franklin. A "double-blind" study of treatment with aqueous allergenic extracts in cases of allergic rhinitis. J. Allergy, 34 (2): 165-182, 1983.
7. Lowell, F.C., W. Franklin. A double-blind study of the effectiveness and specificity of injection therapy in ragweed hay fever. N. Eng. J. Med., 273 (13): 675-679, 1965.
8. Zavazal, V., A. Stajner. Immunologic changes during specific treatment of the atopic state. II. Acta. Allergol., 25 (1): 11-17, 1970.
9. Reisman, R.E., J.I. Wypych, E.E. Arbesman. Relationship of immunotherapy, seasonal pollen exposure and clinical response to serum concentrations of total IgE and ragweed-specific IgE. Int. Arch. Allergy Appl. Immunol., 48 (6): 721-730, 1975.
10. Taylor, W.W., J.L. Ohman, F.C. Lowell. Immunotherapy in cat-induced asthma; double-blind trial with evaluation of bronchial responses to cat allergen and histamine. J. Allergy Clin. Immunol., 61 (5): 283-287, 1978.
11. Smith. A.P. Hyposensitization with Dermatophagoides pteronyssinus antigen: Trial in asthma induced by house dust. Br. Med. J., 4: 204-206, 1971.
12. Chapman, M.D., T.A.E. Platts-Mills, M. Gabriel, H.K. Ng, W.G.L. Allen, L.E. Hill, A.J. Nunn. Antibody response following prolonged hyposensitization with Dermatophagoides pteronyssinus extract. Int. Arch. Allergy Appl. Immunol., 61: 431-440, 1980.
13. Norman, P.S. Postgraduate course presentation. An overview of immunotherapy, implications for the future. J. Allergy Clin. Immunol., 65 (2): 87-96, 1980.
14. Norman, P.S., W.L. Winkenwerder. Maintenance immunotherapy in ragweed hay fever. J. Allergy, 74: 273-282, 1971.
15. Norman, P.S., W.L. Winkenwerder, L.M. Lichtenstein. Immunotherapy of hay fever with ragweed antigen E; comparisons with whole pollen extract and placebos. J. Allergy, 42: 93-108, 1968.
16. Sheldon, J.M., R.G. Lovell, K.P. Matthews. A Manual of Clinical Allergy. Second Edition. W.B. Saunders, Philadelphia, 1967, pp. 107-112.
17. Sherman, W.B. Hypersensitivity Mechanism and Management. W.B. Sanders, Philadelphia, 1968, pp. 169-172.
18. Swineford, O. Asthma and Hay Fever. Charles C. Thomas, Springfield, IL, 1971, pp. 148-155.
19. Jacobs, R.L., G.W. Rake, Jr., et al. Potentiated anaphylaxis in patients with drug-induced beta-adrenergic blockade. J. Allergy Clin. Immunol., 68 (2): 125-127, August 1981.
20. Pauli, G., J.C. Bessot, R. Thierry, and A. Lamensons. Correlation between skin tests, inhalation tests and specific IgE in a study of 120 subjects to house dust and D. pteronyssinus. Clin. Allergy, 7:337, 1977.
21. Murray, A.B., A.C. Ferguson and B.J. Morrison. Diagnosis of house dust mite allergy in asthmatic children: what constitutes positive history? J. Allergy Clin. Immunol. 71:21, 1983.
22. Wharton, G.W. House Dust Mites. J. Med. Entomol. 12:577, 1976.
23. Voorhorst, R., F.Th.M. Spieksma and H. Varekamp. House Dust Atopy and the House Mite. Leiden, Stafleu's Scientific Publishing Co., 1969.
24. Baer, H. Allergy to House Dust Mites. Immuno. Allergy Practice, 5:356, 1983.
25. Lang, J.D. and S. Mulla. Distribution and abundance of house dust mites, Dermatophagoides (spp.) in different climatic zones of southern California. Environmental Entomology, 6:213-216, 1977.
26. Patterson, Roy, et al. Allergy Principles and Practice, 2nd ed. E. Middleton, Jr., C.E. Reed, E.F. Ellis, Ed., C.V. Mosby Co., 1983, St. Louis, MO, 1983, Chapter 52.
27. Levy, D.A., L.M. Lichtenstein, E.O. Goldstein, and K. Ishizaka. Immunologic and cellular changes accompanying the therapy of pollen allergy. J. Clinical Investigation, 50:360, 1971.
28. Turkeltaub, Paul C., MD, and Peter J. Gergen, MD. The risk of adverse reactions from percutaneous prick-puncture allergen skin testing, venipuncture, and body measurements: data from the second National Health and Nutrition Examination Survey, 1976-80 (NHANES II). J. Allergy Clin. Immunol. 84(6): 886-890, Dec. 1989.
29. Peebles, Ray Stokes, Jr., B. Bochner, Howard J. Zeitz, ed. Anaphylaxis in the elderly. Immunology and Allergy Clinics of North America. 13 (3): 627-646, August 1993.
30. Metzger, W.J., E. Turner and R. Patterson. The study of immunotherapy during pregnancy. J. Allergy Clin. Immunol. 61 (4): 268-272, 1978.
31. Rao, Kamineni S., et al. Duration of suppressive effect of tricyclic anti-depressants on histamine induced wheal and flare reactions on human skin. J. Allergy Clin. Immunol. 82: 752-757, November 1988.
32. Reid, M.J., R.F. Lockey, P.C. Turkletaub, T.A.E. Platts-Mills. Survey of fatalities from skin testing and immunotherapy. J. Allergy Clin. Immunol. 92 (1): 6-15, July 1993.
33. Reid, M.J., G. Gurka. Deaths associated with skin testing and immunotherapy. J. Allergy Clin. Immunol. 97 (1) Part 3:231, Abstract 195, January 1996.
34. Thompson, R.A. et al, report of a WHO/IUIS working group. The current status of allergen immunotherapy (hyposensitization). Allergy. 44: 369-379, 1989.
35. Malling, H.-J., B. Weeke, et al, The European Academy of Allergology and Clinical Immunology. Position Papers. Allergy. 48 (Supplement 14): 9-82, 1993.