INSTRUCTIONS AND DOSAGE SCHEDULE FOR TREATMENT WITH ALLERGENIC EXTRACTS

385400-H06

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Spokane, WA 99207 USA

U.S. License No. 1272 www.hsallergy.com

WARNING
This product is intended for use only by licensed medical personnel experienced in administering allergic 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. 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 REACTIONS section.

This product is not directly interchangeable with other manufacturers’ products, or with alum-adsorbed products. See WARNINGS section.

Reduced dose or extra dilutions may be required under one or more conditions. See WARNINGS section.

Consult DOSAGE AND ADMINISTRATION instructions before using this product.

This product is not approved for intravenous use, and should never be used intravenously.

Patients with cardiovascular diseases and/or pulmonary diseases such as asymptomatic 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.

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.

See WARNINGS, ADVERSE REACTIONS, and OVERDOSAGE.

DESCRIPTION: The extracts supplied in this treatment set or refill have been selected by the patient’s physician on the basis of history and skin tests for an individual patient. The extracts are sterile and intended for subcutaneous injection. Although in some rare cases, an extract will contain only one etiologically specific allergen, usually the extract will contain a mixture of allergens.

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

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

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

Epidermals include feathers, hair (clippings and/or shavings), or pelt (hair and whole epidermis), as described on product labeling. 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. Regular process epidermals are extractions of the source material without additional processing (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. Standardized Cat Hair and Standardized Cat Pelt are derived from the AP™ process.

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

Various other Environmental materials are available as allergenic extracts, and information on these materials can be obtained by contacting our Customer Service Department.

The term “Concentrate,” when used in prescription labeling, refers to the allergen manufacturing strength prescribed by the physician and used in the formulation.

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

Actual Allergen Strength × Allergen Manufacturing Strength × % Allergen in Formulation

The following is a brief description of the five methods of describing allergenic product concentration.

1. Weight by volume (w/v) refers to the weight of crude allergen added to the 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 of extracting fluid. The amount and composition of extracted materials will vary with the kind of antigen, the extracting fluid, duration of extraction, pH, temperature, and other variables.

Pollens are typically extracted at 1:20 (w/v) in Glycer-coca’s, and at 1:10 (w/v) in Coca’s.

Epidermal, environmental, 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. (i.e., 1 gram of dried precipitate in 100 mL of reconstitution fluid).

2. Protein Nitrogen Units (PNU)

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 an antigen is influenced by such factors as the kind 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. This unitage can be obtained for patient prescriptions. 10,000 PNU/mL is typically the strength of each allergen used for treatment formulation (if available).

3. Amb a 1. Of the many allergens from Short Ragweed which have been purified and characterized [Amb a 1 (also known as Antigen E)3, Amb a 2 (also known as Antigen K)3, Ra4 (BPA-R)5, Ra5, Ra6, Ra7, and Ra8, and cytochrome C4], 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. Amb a 1 units are approximately equal to micrograms previously used to measure Amb a 1 concentration. Amb a 1 assay therefore provides an absolute measure of extract potency related to the Amb a 1 antigen in Short Ragweed, rather than only an expression of extract strength.

Amb a 1 concentration of 1000 PNU/mL is equivalent to 1.75 Amb a 1 units/mL. Each concentrated lot of Short Ragweed and Giant and Short Ragweed Mix is assayed for Amb a 1 and submitted to the Center for Biologics Evaluation and Research (CBER) for release.

The Amb a 1 concentration of any extract which is diluted with a diluent or other allergenic extracts is determined by calculation.

4. 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.

5. Bioequivalent Allergy Units (BAU/mL). Other standardized allergenic extracts are labeled in Bioequivalent Allergy Units/mL (BAU/mL) based on their comparison (by ELISA inhibition or major allergen content) to CBER, FDA Reference Preparations. The FDA reference extracts have been...
assigned Bioequivalent Allergy Units based on the CBER ID50EAL technique. 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:

<table>
<thead>
<tr>
<th>BAU/mL</th>
<th>D50</th>
</tr>
</thead>
<tbody>
<tr>
<td>100,000</td>
<td>13-14.9</td>
</tr>
<tr>
<td>10,000</td>
<td>11-12.9</td>
</tr>
<tr>
<td>1,000</td>
<td>9-10.9</td>
</tr>
</tbody>
</table>

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

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

**INGREDIENTS:** Active ingredients are those allergens listed on the bottom of the package. The strength at which each allergen is added to the Concentrate will also be listed. The standardized mites are grown on a medium of brine shrimp eggs and wheat germ, and are handled and cleaned by a method in which the maximum carryover of the medium components is less than 1%. The medium contains no material of human origin.

Preservative is 50% (v/v) glycerin, or 0.4% phenol, as indicated on the product labeling. Additional ingredients present in extracting fluids are 0.275% sodium bicarbonate and 0.5% sodium chloride. Vials are diluted from the Concentrate with one of the following diluting fluids. Refer to ingredient list to determine which diluting fluid is used.

- **Sterile Buffered Saline with Phenol (BSP):** 0.5% sodium chloride, 0.275% sodium bicarbonate, and 0.4% phenol.
- **Sterile Glycerin Solution (GLY):** 50% glycerin.
- **Sterile Albumin Saline with Phenol (ABS):** 0.9% sodium chloride, 0.03% albumin (human), and 0.4% phenol.

**CLINICAL PHARMACOLOGY:** The mechanisms by which hyposensitization is achieved are 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. Well-controlled clinical studies which demonstrate the efficacy of immunotherapy are available. The allergens which have been studied are cat, mite, and some pollen extracts. Extension of these results to other allergens is generally acceptable.

**ADVERSE REACTIONS:** Patients should be informed of this, and the warnings and precautions authorized by the physician. 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. 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 to the allergen is greater than the risk of exacerbating the underlying disorder.

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

**INDICATIONS AND USAGE:** Allergic extracts are indicated for use in diagnosis and immunotherapy of patients presenting symptoms of allergy (hay fever, rhinitis, etc.) to specific environmental allergens. The use of graduated doses of specific allergenic extracts followed by maintenance doses of the most concentrated extract tolerated has long been used for immunotherapy of patients presenting symptoms of allergy (hay fever, rhinitis, etc.) to specifically identified materials. The selection of allergenic extracts to be used should be based on a thorough and carefully taken history of hypersensitivity, confirmed by skin testing. While statistically controlled, blind studies on the usefulness of aeroallergens in immunotherapy have been made, for the most part, only for some pollens, extension of these results to other allergens in certain conditions is generally considered acceptable. Avoidance 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 to the highly reactive allergen.

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.

TREATMENT VIAL DILUTIONS

<table>
<thead>
<tr>
<th>VIAL #</th>
<th>SEAL COLOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 green</td>
<td>0.5 mL of 1:10 v/v of Conc. + 4.5 mL = 1:100 v/v of Conc.</td>
</tr>
</tbody>
</table>

See Dosage and Administration for additional guidance.
A DOSAGE REDUCTION OR EXTRA DILUTIONS ARE REQUIRED IN THE FOLLOWING CIRCUMSTANCES. The actual amount of dosage reduction or the need for extra dilutions must be determined by the physician based on the clinical situation. Dose should be significantly less than 50% of the last administered dose from the previous extract. Skin testing can be helpful in determining relative potency between two extracts.

1. If one or more antigens have been deleted from the mixture as authorized by the physician.
2. If the previous extract was outdated.
3. If prolonged time has elapsed since the last injection.
4. If other changes have been made in the refill formula, such as redistribution of component parts or percentages, or a difference in extracting fluid.

INITIATE NEW COURSE OF IMMUNOTHERAPY, OR ESTABLISH INITIAL DOSE BY SKIN TITRATION FOR THE FOLLOWING SITUATIONS:

1. If one or more new antigens have been added to, or substituted for antigens in the previous formula as authorized by the physician.
2. If changing from Standardized Cat Hair to Standardized Cat Pelt extracts or vice-versa. Hair and Pelt extracts differ in their non Fel d 1 allergens and are not interchangeable.
3. If one or more previously unavailable antigens have been returned to the mixture as authorized by the physician.
4. If the previously used extract was non-standardized or was standardized and labeled in Allergy Units per mL (AU/mL).
5. If the extract previously used was from another manufacturer.
6. If changing from alum-adsorbed to aqueous or glycerinated extracts.

Proper selection of the dose and careful injection should prevent most systemic reactions. It must be remembered, however, that allergic 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 warnings and precautions should be discussed prior to immunotherapy. (See PRECAUTIONS.) Severe 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, 27, 28, 29, 30

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.

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

Sterile solutions, vials, syringes, etc. should be used and aseptic precautions observed in making dilutions. Dilutions prepared should be tested for sterility.

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 each dose from the prescribed dilution.

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 and a conservative dosage schedule 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 antigen 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 EACH TREATMENT INJECTION and instructed to return to the office promptly if symptoms of an allergic reaction or shock occur. Most severe reactions will occur within this time period, and rapid treatment measures should be instituted. See ADVERSE REACTIONS for these 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 package insert.) 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 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.

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 antihista-
mimics should be discontinued for at least 3 weeks prior to skin testing.31 Topical steroids should be discontinued at the skin test site for at least 2-3 weeks before skin testing.31,32

Tricyclic antidepressants such as Doxepin should be withheld for at least 7 days before skin testing.33 Topical local anesthetics may suppress the flare responses and should be avoided in skin test sites.34

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.

(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) Pregnancy35

Pregnancy Category C. Animal reproduction studies have not been conducted with aller-
genic extracts. It is also not known whether allergenic extracts can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity.

Allergic 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.36

(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

The dosage for the pediatric population is the same as for adults. Because of the small size of the child, 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.
**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.\(^{37}\)

**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 injections before cautiously increasing again.

Large, persistent local reactions may be treated by local applications of cold, wet dressings and/or the use of oral antihistamines. They should be considered a warning of possible severe systemic reactions and 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. Prolonged pain, or pain radiating up the arm, is usually the result of intramuscular injection, making this injection route undesirable. Subcutaneous injection is the preferred route.

(2) **Systemic Reactions**

With careful attention to dosage and administration, such reactions occur infrequently, but it must be remembered that allergenic extracts are highly potent in sensitive individuals and any injection could result in anaphylactic symptoms. 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.

It cannot be overemphasized that, under certain unpredictable combinations of circumstances, anaphylactic shock is always a possibility. Other possible systemic reaction symptoms 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.\(^{1,38}\)

If a systemic or anaphylactic reaction does occur, apply a tourniquet above the site of injection and inject 1:1000 epinephrine-hydrochloride intramuscularly 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 assured. 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 producing 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 reach 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.

**DOSE AND ADMINISTRATION:**\(^{11, 22, 23, 24}\)

(1) **General:** Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

The dosage chart on the reverse side is offered as a suggested schedule for average patients and will be satisfactory in most cases. However, the degree of sensitivity varies in many individuals. IN THESE CASES THE SIZE OF THE DOSE AND INTERVAL MAY HAVE TO BE ADJUSTED AND SHOULD BE REGULATED BY THE PATIENT’S TOLERANCE AND REACTION. (A DOSE SHOULD NEVER BE GIVEN UNTIL ALL REACTIONS RESULTING FROM A PREVIOUS DOSE HAVE ENTIRELY DISAPPEARED.) The size of the dose may also need to be varied depending upon patient’s symptoms of allergy. If symptoms recur before the expiration of the interval between injections, subsequent intervals may need to be decreased. After a period on immunotherapy, better tolerance may permit a longer interval between injections, or a larger maintenance dose, or both.

Since the individual components of the extract are those to which the patient is allergic and to which he will be exposed, typical allergic symptoms may follow shortly after the injection, particularly those experienced by the patient during exposure when the antigen from the environment plus the injected antigen exceeds the patient’s tolerance to the antigen. In such cases, decrease the size of the next scheduled dose by at least one-half of the previous dose.

The maintenance level is the largest dose tolerated by the patient that relieves symptoms without producing undesirable local or general reactions. AFTER IMMUNOTHERAPY HAS BEEN ESTABLISHED, A MAINTENANCE DOSE SHOULD BE GIVEN AT WEEKLY INTERVALS. The interval between maintenance doses can be increased gradually from one week to 10 days, to 3 weeks, to 6 weeks, and then to 8-12 weeks. Repeat doses at a given interval three or four times to check for untoward reactions before increasing the interval further. If large local (or systemic) reactions occur at one interval, do not increase the interval. Protection is lost rapidly if the interval between doses is more than 4 weeks. See WARNINGS section. It may not be possible for all patients to reach the maximum dose indicated on the suggested dose schedule.

(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.\(^{37}\)

(4) **Determining Initial Dose:**

If a patient appears to be extremely sensitive because of excessively large scratch, prick or puncture reactions, systemic reactions to testing, severe generalized symptoms during the allergy season, or for other reasons, determine the initial dose by the method of intradermal skin tests. Ten-fold dilutions of the antigen to a 1:1,000,000 v/v dilution of Concentrate, or more, can be made fresh in normal or buffered saline. Starting with the most dilute extract, 0.02 mL intradermal tests of increasing concentration can be applied every 20 to 30 minutes until a reaction of a 5 mm wheel and 10 to 20 mm erythema occurs. This dose and concentration can then serve as a starting dose for immunotherapy, and treatment can be continued according to the outlined dose schedules.

(5) **Dilutions:**

Sterile aqueous diluent containing human serum albumin [Albumin (Human) 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 dilutions constantly at 2° - 8° C. Dilutions prepared should be stored for sterility. The usual precautions
to be observed in administering allergenic extracts are necessary.

Ten-fold dilutions can be prepared from the extract as follows:

Using a sterile syringe and aseptic technique, withdraw 0.5 mL of the extract, add it to a 4.5 mL sterile diluent blank, and rock or swirl to mix thoroughly. Label this and subsequent dilutions with the appropriate strength. (See Dilution Tables below). Then withdraw 0.5 mL of the new dilution, add it to a second 4.5 mL diluent blank and rock or swirl to mix this additional dilution thoroughly.

Repeat this procedure until all necessary dilutions have been made, using a fresh 4.5 mL diluent blank for each dilution. A new syringe and needle should be used to prepare each dilution. Do not reaspirate syringe after transferring the extract.

EXAMPLE: If you are diluting the Concentrate in a ten-fold series, the dilution schedule is as follows:

<table>
<thead>
<tr>
<th>WITHDRAWAL VOLUME</th>
<th>EXTRACT STRENGTH</th>
<th>DILUENT VOLUME</th>
<th>DILUTION STRENGTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mL of</td>
<td>1.00 v/v of Conc.</td>
<td>4.5 mL</td>
<td>1:10 v/v of Conc.</td>
</tr>
<tr>
<td>0.5 mL of</td>
<td>1.00 v/v of Conc.</td>
<td>4.5 mL</td>
<td>1:100 v/v of Conc.</td>
</tr>
<tr>
<td>0.5 mL of</td>
<td>1.00 v/v of Conc.</td>
<td>4.5 mL</td>
<td>1:1,000 v/v of Conc.</td>
</tr>
<tr>
<td>0.5 mL of</td>
<td>1.00 v/v of Conc.</td>
<td>4.5 mL</td>
<td>1:10,000 v/v of Conc.</td>
</tr>
</tbody>
</table>

One or two doses from the weakest dilution can be administered to determine the patient’s tolerance to the fresh extract. If the starting dose produces no significant local or general symptoms, subsequent doses can be increased progressively until a maintenance dose is reached. Refer to product instructions for suggested dosage schedule. If the change in formula is small, the patient may tolerate an accelerated build-up schedule.

(6) Retesting:

Patients should be restested and other factors should be investigated when results are unsatisfactory after a year of treatment. Any coexisting food, non-pollen, or seasonal pollen allergies should be controlled for best results.

(7) Instructions for Specific Treatment Sets:

(a) Pollen:

Preseasonal Treatment: Preseasonal treatment is normally started 8 to 12 weeks prior to expected onset of symptoms with a 1:5,000 v/v dilution of Concentrate (Vial “5”) of the allergenic extract, or 1:50,000 v/v dilution of Concentrate (Vial “6”) if prescribed by physician for a severely sensitive patient. Commencing with the first dose, as listed in the Suggested Dosage Schedule, a dose can be administered every three to five days. In preseasonal treatment the interval between doses should be so regulated that at least the first 20 doses will have been administered by the time the hay fever symptoms are expected. Thus, the shorter the interval between start of immunotherapy and expected onset of symptoms, the shorter the interval between doses. Daily doses may be tolerated by some patients.

The dose from 1:5,000 v/v dilution of Concentrate (Vial “5”) should be gradually increased until the succeeding dose can be measured from 1:500 v/v dilution of Concentrate (Vial “4”). Continue in this manner with each succeeding vial until the dose can be measured from the Concentrate (Vial “1”), which is the most concentrated extract in the treatment. When weaker dilutions are used, start with 0.03 mL and increase by amounts identical to those shown for 1:5,000 v/v dilution of Concentrate (Vial “5”). When 0.3 mL is reached, proceed with the next higher strength.

In some areas, patients may tolerate and require either lower or higher doses; therefore, smaller or larger increments than shown on the schedule may be used. After immunotherapy has been established, A MAINTENANCE DOSE SHOULD BE GIVEN AT WEEKLY INTERVALS OR MORE OFTEN IF NECESSARY DURING THE ENTIRE HAY FEVER SEASON. The size of the maintenance dose will vary with each individual. It can be adjusted as necessary from the maximum preseasonal dose. Should symptoms develop before expiration of the maintenance interval, the interval between doses should be decreased. Should allergic symptoms develop shortly after the dose is administered, the size of the dose should be reduced. It is often advisable to cut the dose in half or a quarter of the maximum dose attained if the patient has any seasonal symptoms. This lessens the tendency to overdose the patient during the active pollination season.

ANOTHER DOSE SHOULD NEVER BE GIVEN UNDER THESE CONDITIONS:

1. IF SEVERE ALLERGIC SYMPTOMS ARE PRESENT, OR
2. UNTIL ALL LOCAL REACTION RESULTING FROM THE PREVIOUS DOSE HAS DISAPPEARED.

Perennial Treatment: After the symptom period or pollen season has passed, treatment may be continued by increasing the dose to tolerance level and lengthening the interval between doses to two or four weeks. This perennial schedule is maintained until the time of year symptoms usually occur. Then the interval between doses is decreased to one week and the dosage adjusted according to local reaction and control of symptoms. Perennial treatment may be started at any time of the year continuing from the preseasonal schedule.

See Dosage Schedule noted on the Suggested Dosage Chart.

(b) Environmental / Molds / Miscellaneous

See Determining Initial Dose above.

Treatment is normally started with the most dilute extract in the set. Beginning with the first dose as listed in the Suggested Dosage Chart, a dose can be administered every three to five days. The doses from 1:1,000 v/v dilution of Concentrate (Vial 5) should be gradually increased until the succeeding dose can be measured from 1:100 v/v dilution of Concentrate (Vial 4). Continue in this manner with Vial 3 and 1:10 v/v dilution of Concentrate (Vial 2) until the dosage can be measured from Vial 1, which is the Concentrate. When extra dilutions are used, start with the highest numbered vial, which corresponds to the weakest dilution.

In some areas, some patients may tolerate and require higher doses; therefore, larger increments than shown in the schedule may be used. The best results of immunotherapy occur when the patient is given the largest dose tolerated without excessive local or any systemic symptoms.

See Suggested Dosage Chart.

(c) Fire Ant: See Determining Initial Dose above.

If extreme sensitivity is suspected, it is recommended that 0.05 mL of the 1:1,000 v/v dilution of Concentrate (Vial 5) be added to a 4.5 mL diluent blank which can be ordered with the set. An approximate 1:100,000 v/v dilution of the Concentrate will result.

It is suggested that an intracutaneous test with 0.02 mL of a 1:1,000 v/v dilution of the Concentrate be made. Very sensitive individuals such as those who have had nearly fatal anaphylactic reactions may not tolerate even 1:100,000 v/v dilution of Concentrate as a starting point. These patients should be tested with a 1:10,000,000 v/v dilution of Concentrate. This dilution can be prepared using sterile normal or buffered saline. Treatment is started with the dilution that first gives a positive test.

An interval of four to seven days between doses is adequate. A maintenance dose of 0.3 to 0.4 mL of the Concentrate dilution is usually attainable but some patients may develop systemic symptoms before this dose is reached. When systemic symptoms appear during the course of treatment, the subsequent dose must be reduced to a point below the reaction level, and then gradually increased to a point of maximum tolerance. Extremely sensitive patients may not tolerate the Concentrate.

See Suggested Dosage Chart.

(d) Refills: If the dilution supplied in this package is of greater potency than the patient is currently receiving, it should not be used without further dilution unless tolerance to this mixture has been previously established and immunotherapy is in progress. When changing to a fresh extract of the same formula and dilution, the first dose should not exceed 50% of the last dose from the previous lot. If this first dose is tolerated satisfactorily, increase the subsequent doses to the patient’s maintenance level. The maintenance level is the largest dose tolerated by the patient that relieves symptoms without producing undesirable local or general reactions. The interval between maintenance doses can be increased gradually from 1 week to 10 days, to 2 weeks, 3 weeks, or even 4 weeks if tolerated. Repeat doses at a given interval three to four times to check for untoward reactions before increasing the interval further. If large local (or systemic) reactions occur at one interval, do not increase the interval. Protection is lost rapidly if the interval between doses is more than 4 weeks. See WARNINGS section.

The accompanying dosage chart may be used for recording the doses and dates of maintenance injections. We cannot specify a dose because it is dependent upon the dose and interval between injections previously established and recorded on your original treatment schedule. Because of minor variations in the potency of allergens between lots, changes in the patient’s reactivity, or the season of the year, the maintenance dose for different lots of the same concentrated antigen may differ to some extent.
INSTRUCTIONS:

Phylactic shock and death. Patients should be informed of the risk and the precautions prior to

IN ANOTHER SITE. To insure subcutaneous deposition of the injected material, pinch the skin

Extension of these results to other allergens is generally acceptable.

CLINICAL PHARMACOLOGY: 11

dilutions are generally required. See discussion of specific circumstances. The number of dilu-

is recommended. Intracutaneous or intramuscular injection may produce large local reactions

patients have higher antibody titers and fewer symptoms than those untreated. IgE antibodies

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

advised to use the same needle to withdraw materials from

A mild burning immediately after the injection is to be expected; this usually leaves in

The maintenance level is the largest dose tolerated by the patient that relieves symptoms

may permit a longer interval between injections, or a larger maintenance dose, or both.

There are no factors beyond our control that 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

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.

To ensure the maximum potency of extracts and their dilutions, it is recommended that they

be maintained at a temperature of 2° - 8° C, even during use.

Government regulations require a holding period for sterility tests, so please allow a minimum of four weeks for delivery when reordering.

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:


**SUGGESTED DOSAGE CHART**

THESE DOSAGE REGIMENS ARE NOT BASED ON ADEQUATE AND WELL CONTROLLED TRIALS THAT CONCLUSIVELY ESTABLISH SAFETY AND EFFICACY.

**Extract** | **Lot No.** | **Exp. Date**
---|---|---

**Physician**

**Patient**

---

*This is a suggested dose chart only. Note that one dosage schedule applies to all allergens listed below. Please read instructions before commencing immunotherapy. Observe patients for 30 minutes after injection. Certain individuals may not tolerate this suggested schedule. The physician may need to adjust both the dosage and interval accordingly.

The suggested schedule represents typical treatment dilution series prepared by Hollister-Stier Laboratories LLC. For dilution series which differ from those below, the physician may need to modify the schedule as necessary.

If it is necessary to begin treatment with weaker dilutions than those shown on schedule, consider the weaker dilution as the beginning bottle for treatment, and the same dosage volume increases should be made.

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**VIALS PROVIDED IN TREATMENT SET**

Determine the description below at left which matches the prescription formulation. Read across from left to right for most dilute to most concentrated vial strength designations. Select appropriate dosage for each vial strength from column below that strength on chart.
**Precautions:**

### Dosage and Administration

- **Concentrate:**
  - **Vial 6+**
  - **Vial 5**
  - **Vial 4**
  - **Vial 3**
  - **Vial 2**

- **Note:** Included by special request only.

---

### Table: Dosage Schedule for Vials in Same Column Above

<table>
<thead>
<tr>
<th>ONE OR MORE POLLENS</th>
<th>1:50,000 v/v dilution of Concentrate (Vial 6+)</th>
<th>1:5,000 v/v dilution of Concentrate (Vial 5)</th>
<th>1:500 v/v dilution of Concentrate (Vial 4)</th>
<th>1:50 v/v dilution of Concentrate (Vial 3)</th>
<th>1:5 v/v dilution of Concentrate (Vial 2)</th>
<th>Concentrate (Vial 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIRE ANT ONLY</td>
<td>-</td>
<td>1:10,000 v/v dilution of Concentrate (Vial 5)</td>
<td>1:1,000 v/v dilution of Concentrate (Vial 4)</td>
<td>1:100 v/v dilution of Concentrate (Vial 3)</td>
<td>1:10 v/v dilution of Concentrate (Vial 2)</td>
<td>Concentrate (Vial 1)</td>
</tr>
<tr>
<td>NO POLLENS</td>
<td>-</td>
<td>-</td>
<td>1:1,000 v/v dilution of Concentrate (Vial 4)</td>
<td>1:100 v/v dilution of Concentrate (Vial 3)</td>
<td>1:10 v/v dilution of Concentrate (Vial 2)</td>
<td>Concentrate (Vial 1)</td>
</tr>
</tbody>
</table>

**DOSAGE SCHEDULE FOR VIALS IN SAME COLUMN ABOVE**

(Progress top to bottom in each dosage column, and use vials in order shown, Left to Right.)

- **0.03 mL**
- **0.05 mL**
- **0.08 mL**
- **0.12 mL**
- **0.18 mL**
- **0.30 mL**

**NOTE:** Occasionally, higher doses are necessary to relieve symptoms. Special caution is required in administering doses greater than 0.20 mL.

**NOTE:** Increases from this point on are dependent on patient’s tolerance and amount of allergen content in air. Repeat dose if necessary. Continue immunotherapy entire season regardless of number of doses given. Unsatisfactory results are usually due to improper dosage adjustment. Avoid reactions – Check extract, dilution, and dose – Question the patient about local or systemic reaction to previous injection.

**NOTE:** If extreme sensitivity is suspected, it is recommended that 0.05 mL of the 1:1,000 v/v dilution of Concentrate (vial 5) be added to a 4.5 mL diluent blank which can be ordered with the set. This will result in an approximate 1:100,000 v/v dilution of Concentrate (91 fold) which may be used for intradermal testing, as well as starting dilution for treatment. See INSTRUCTIONS FOR SPECIFIC TREATMENT SETS.

**NOTE:** Included by special request only.
# FIRE ANT ONLY – Concentrate

<table>
<thead>
<tr>
<th>Dilution</th>
<th>Concentrate</th>
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<tbody>
<tr>
<td>1:10,000 v/v</td>
<td>Concentrate</td>
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<td>1:1,000 v/v</td>
<td>Concentrate</td>
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<td>1:10 v/v</td>
<td>Concentrate</td>
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</tbody>
</table>

- Dilution of Concentrate (91 fold) which may be used for intradermal testing, as well as starting dilution for treatment.
- 0.05 mL of the 1:1,000 v/v dilution of Concentrate (vial 5) should be added to a 4.5 mL diluent blank which can be ordered with the set. This will result in an approximate 1:100,000 v/v

**NOTE:** If extreme sensitivity is suspected, it is recommended that 0.05 mL of the 1:1,000 v/v dilution of Concentrate (vial 5) be added to a 4.5 mL diluent blank which can be ordered with the set. This will result in an approximate 1:100,000 v/v

**Stability:** Liquid extract should be stored in a refrigerator at 2 to 8°C (35.6 to 46°F).

**DOSAGE SCHEDULE FOR VIALS IN SAME COLUMN ABOVE**

<table>
<thead>
<tr>
<th>Vial</th>
<th>DOSAGE SCHEDULE FOR IMMUNOTHERAPY</th>
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<tbody>
<tr>
<td>1</td>
<td>0.03 mL 0.03 mL 0.03 mL 0.03 mL 0.03 mL</td>
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<td>2</td>
<td>0.30 mL 0.30 mL 0.30 mL 0.30 mL 0.30 mL</td>
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<tr>
<td>3</td>
<td>0.20 mL 0.20 mL 0.20 mL 0.20 mL 0.20 mL</td>
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</table>

**RECORD DOSE BELOW AS ADMINISTERED**

<table>
<thead>
<tr>
<th>DATE</th>
<th>VIAL NO.</th>
<th>DILUTION</th>
<th>DOSE (mL)</th>
<th>REMARKS: Reaction to Previous Dose, Relief of Symptoms, etc.</th>
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