STANDARDIZED MITE, DERMATOPHAGOIDES PTERONYSSINUS - standardized mite, dermatophagoides pteronyssinus injection, solution
STANDARDIZED MITE, DERMATOPHAGOIDES FARINAE - standardized mite, dermatophagoides farinae injection, solution
MIXTURE OF STANDARDIZED MITES - mixture of standardized mites injection, solution
Antigen Laboratories, Inc.

Allergenic Extract

WARNINGS

Standardized allergenic extract is intended for use by physicians who are experienced in the administration of standardized (AU/ml) allergenic extracts for immunotherapy and the emergency care of anaphylaxis, or for use under the guidance of an allergy specialist. Standardized allergenic extracts are not directly interchangeable with other allergenic extracts. The initial dose must be based on skin testing as described in the "DOSAGE AND ADMINISTRATION" section of this insert. Patients being switched from other types of extract to standardized allergenic extracts should be started as though they were coming under treatment for the first time. Patients should be instructed to recognize adverse reaction symptoms and cautioned to contact the physician's office if reaction symptoms occur. As with all allergenic extracts, severe systemic reactions may occur. *In certain individuals, these life-threatening reactions may result in death***. Patients should be observed for at least 20 minutes following treatment and emergency measures, as well as personnel trained in their use, should be immediately available in the event of a life-threatening reaction. Patients being switched from one lot of extract to another from the same manufacturer should have the dose reduced by 75%.**

This product should not be injected intravenously. Deep subcutaneous routes have proven to be safe, see "WARNINGS", "PRECAUTIONS", "ADVERSE REACTIONS" and "OVERDOSAGE" sections.

Sensitive patients may experience severe anaphylactic reactions resulting in respiratory obstruction, shock, coma and/or death.

Patients receiving beta-blockers may not be responsive to epinephrine or inhaled bronchodilators. Respiratory obstruction not responding to parenteral or inhaled bronchodilators may require theophylline, oxygen, intubation and the use of life support systems. Parenteral fluid and/or plasma expanders may be utilized for treatment of shock. Adrenocorticosteroids may be administered parenterally or intravenously. Refer to "WARNINGS", "PRECAUTIONS", and "ADVERSE REACTIONS" sections.

DESCRIPTION

The extract is sterile and intended for dilution prior to skin testing and/or immunotherapy. The routes of administration for diagnostic purposes are intradermal or prick-puncture of the skin. The route of administration for immunotherapy is subcutaneous. The designation AU/ml (Allergy Units per ml) is unitage based upon the relative potency of this standardized mite extract when compared by ELISA competition to the F.D.A. Mite Allergenic Reference Standard labeled 10,000 AU/ml assigned on the basis of quantitative skin testing by the ID_{50}EAL Method.[1,2,3,4,5,16] Lower concentrations (e.g. 5,000 AU/ml and 3,000 AU/ml) are prepared by dilution of stock concentrates. Mite mixtures containing equal volumes of *D. farinae* and *D. pteronyssinus* are available at 5,000 AU/ml, 2,500 AU/ml and 1,500 AU/ml.

Active allergens are described by common and scientific name on the stock concentrate container label.

INGREDIENTS: Extract of Standardized Mites contain at least 99.0% adult mites and mite stages.

This product may contain trace amounts of yeast and/or pork products; sodium chloride 0.95%; sodium bicarbonate 0.24%; 50% v/v glycerine as stabilizing agent and preservative.

Following is a brief description of the *standardized quality procedures* applied to these extracts:

1. The source material is carefully selected from whole body adult mites and mite stages cultured from a medium containing *no material of human origin.* The source material is extracted with a saline buffer and 50% v/v glycerine.

2. Several manufacturers submitted intradermal skin test data on Biopol Laboratories mite medium extract using patients who were puncture test positive (erythema greater than 40 mm) to either *D. farinae* or *D. pteronyssinus* extracts. By intradermal testing, there was 1 positive (erythema greater than 20 mm) in 44 individuals at an estimated 1% level of medium contamination of mites, and 4 positives in 40 individuals at an estimated 10% contamination. Two of the individuals who were skin test positive to the mite extract and who were also skin test positive to the mite medium extract were also skin tested by the puncture method with an extract of yeast (*Saccharomyces sp.*) and were positive.

3. A ninhydrin protein analysis is completed to compare with the standard extract.

4. Each lot is standardized against the F.D.A. reference standard extract for total biologic activity by means of ELISA competition.

5. The standardized mite extract is analyzed for glycerine content to insure a minimum of 50% v/v glycerine for optimal stability during the entire dating period.

CLINICAL PHARMACOLOGY

As a consequence of the discovery of IgE and the development of methods to identify and quantify antiallergen IgE levels, interest in recent years has centered around the utilization of in vivo and in vitro diagnostic procedures. [3,5]

The mode of action of immunotherapy with allergenic extracts is still under investigation. Subcutaneous injections of increasing doses of Standardized Mite allergenic extract into patients with allergic disease have been shown to result in both humoral and cellular changes including the production of allergen-specific IgG antibodies, the suppression of histamine release from target cells, decrease in circulating levels of antigen specific IgE antibody over long periods of time and suppression of peripheral blood T-Iymphocyte cell responses to antigen.[10,14,15]

INDICATIONS AND USAGE

Standardized Mite allergenic extract is indicated for diagnostic testing and for the treatment (immunotherapy) of patients whose histories indicate that upon natural exposure to the allergen, they experience allergic symptoms. Confirmation is determined by skin testing. An orderly approach to the diagnostic use of allergenic extracts usually begins with direct skin testing. This product is not intended for treatment of patients who do not manifest immediate hypersensitivity reactions to the allergenic extract following skin testing.

Mite mixtures should not be used for diagnostic skin testing. The individual mites should be used. Mite mixtures may be used for immunotherapy to treat patients who demonstrated sensitivity to both *D. farinae* and *D. pteronyssinus* mites. Patients who react to both D. farinae and D. pteronyssinus have demonstrated a significant cross-reactivity. Caution should be used in escalating treatment with mite mixtures.[21]

PRICK-PUNCTURE TESTING: A positive control using Histamine Phosphate is important to identify those patients whose skin may not be reactive due to medications, metabolic or other reasons. A diluent control, if negative, would exclude false-positive reactions due to ingredients in the diluent or patients who have dermatographism.

To identify highly sensitive individuals and as a safety precaution, it is recommended that prick-puncture test using a drop of the extract concentrate (10,000 AU/ml) be performed prior to initiating very dilute intradermal testing. Prick-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 bifurcated vaccinating needle. The most satisfactory sites on the back for skin testing are from the posterior

axillary fold to 2.5 cm from the spinal column, and from the top of the scapula to the lower rib margins. The best areas on the arms are the volar surfaces from the axilla to 2.5 or 5 cm above the wrist, skipping the anticubital space. Glycerinated Mite extracts containing 10,000 AU/ml are recommended for prick-puncture testing. Skin reactions are based on size of erythema and wheal. For interpretation of skin reactions, refer to chart below.

GRADE	**mm ERYTHEMA**	**mm WHEAL**
0	less than 5	less than 5
+/-	5-10	5-10
1+	11-20	5-10
2+	20-30	5-10
3+	31-40	10-15 or with pseudopods
4+	greater than 40	greater than 15 or with many pseudopods

Smaller, less conclusive reactions may be considered positive in conjunction with a definitive history of symptoms on exposure to the mite allergen. The more sensitive the patient the higher the probability that he/she will have symptoms related to the exposure of the offending allergen. Hence, the importance of a good patient history. Less sensitive individuals can be tested intradermally with an appropriately diluted extract.

A clinical study using the same patients with positive prick-puncture test (10) using the **ID_{50}EAL Method, Intradermal Dilution for 50 mm Sum of Erythema D50 Determines the Allergy Unit**, has demonstrated the following:

Skin test by prick-puncture test using Standardized *D. farinae* Mite, 10,000 AU/ml was performed in 10 patients. The mean sum of erythema diameter was 76.6 mm (Range 45-104 mm). Skin test by prick-puncture test using Standardized *D. pteronyssinus* Mite, 10,000 AU/ml in 10 patients, the mean sum of erythema diameter was 74.7 mm (Range 43-109 mm).

TABLE 1
STANDARDIZED MITE ALLERGENIC EXTRACTS
LABELED 10,000 AU/ml

10,000 AU/ml 1:3 Dilutions	10,000 AU/ml 1:5 Dilutions	10,000 AU/ml 1:10 Dilutions
*C 10,000 3^{-1} 3,333 3^{-2} 1,111 3^{-3} 370.37 3^{-4} 123.45 3^{-5} 41.15 3^{-6} 13.71 3^{-7} 4.57 3^{-8} 1.52 3^{-9} 0.508 3^{-10} 0.169 3^{-11} 0.056 3^{-12} **0.018** 3^{-13} 0.0063 3^{-14} 0.0021	*C 10,000 5^{-1} 2,000 5^{-2} 400 5^{-3} 80 5^{-4} 16 5^{-5} 3.20 5^{-6} 0.64 5^{-7} 0.128 5^{-8} **0.0256** 5^{-9} 0.00512 5^{-10} 0.00102	*C 10,000 10^{-1} 1,000 10^{-2} 100 10^{-3} 10 10^{-4} 1 10^{-5} 0.10 10^{-6} **0.01** 10^{-7} 0.001 10^{-8} 0.0001 10^{-9} 0.00001

3^{-15}	0.0007		

*C = Concentration

SINGLE DILUTION INTRADERMAL TESTING: The surface of the upper and lower arm is the usual location for skin testing. It is important that a new, sterile, disposable syringe and needle be used for each extract tested. Intracutaneous test dilutions should be made with aqueous diluent. (1) Start testing with the most dilute allergenic extract concentration. (2) A volume of 0.02-0.05 ml should be injected slowly into the superficial skin layers making a small bleb (superficial wheal). (3) For patients without a history of extreme sensitivity, a prick-puncture test of less than 2+, the initial dilution for skin testing should contain 0.02 to 0.06 AU/ml (see Table I). For very sensitive patients with a prick-puncture of greater than 2+, a further dilution should be made to 0.002 to 0.006 AU/ml (see Table I). If after 20 minutes no skin reaction is obtained, continue the testing using five-fold or ten-fold increments in potency until a reaction of 1+ or until the concentration of 2,000 AU (five-fold) or 1,000 AU (ten-fold) has been tested with a glycerine control. Glycerine may be used at a dilution of 0.5% as long as 0.5% glycerine produces negative control. The diluent should be tested and included in the interpretation of the skin reactions.[16]

INTRADERMAL TESTING–SKIN ENDPOINT TITRATION: The allergenic extracts to which the patient is sensitive, the patient's degree of sensitivity and the dose of allergen to be used in immunotherapy can be determined through the use of intracutaneous skin tests involving progressive five-fold dilutions of allergenic extracts, prepared and refrigerated at 2-8° C. The critical variable is the size if the wheal and erythema produced by the intracutaneous injection of 0.01 to 0.02 ml of the test allergen producing a 4 mm diameter superficial skin wheal. For patients demonstrating a prick-puncture skin test of less than 2+, an initial screening dilution of 0.02-0.06 AU/ml is safe (see Table I). For patients demonstrating a prick-puncture skin test greater than 2+, an initial screening dilution of 0.002 to 0.006 AU/ml is safe. The skin endpoint is detected by noting the dilution that produces a wheal 2 mm larger than non-reacting dilutions (5 mm negative wheal) until progressive whealing with each five-fold increase in test potency occurs, i.e., a 5 mm (negative), 7 mm, 9 mm, 11 mm is the normal sequence of whealing. The 7 mm wheal would be the endpoint. The endpoint dilution is used as an initial dose concentration for immunotherapy. An endpoint dose of 0.15 ml is a safe initial dose to be followed by escalation to the optimal maximum tolerated dose for each individual.

Using Standardized *D. farinae Mite*, 10,000 AU/ml on 10 patients, the mean AU for 50 mm sum of erythema was 0.02 AU (Standard deviation was 1.4). Using Standardized *D. pteronyssinus* Mite 10,000 AU/ml in 10 patients, the mean AU for 50 mm sum of erythema was 0.02 AU (Standard deviation was 1.7).

CONTRAINDICATIONS

Do not administer in the presence of diseases characterized by bleeding diathesis. Individuals with autoimmune disease may be at risk of exacerbating symptoms of the underlying disease, possibly due to routine immunization. Patients who have experienced a recent myocardial infarction may not be tolerant of immunotherapy. Children with nephrotic syndrome probably should not receive injections due to a variety of seemingly unrelated events, such as immunization causing exacerbation of their nephrotic disease.

WARNINGS

Extreme caution is necessary when using diagnostic skin tests or injection treatment in highly sensitive patients, who have experienced severe symptoms or anaphylaxis by natural exposure or previous skin testing or treatment. *IN THESE CASES BOTH THE POTENCY FOR SKIN TESTS AND THE ESCALATION OF THE TREATMENT DOSE MUST BE ADJUSTED TO THE PATIENT'S SENSITIVITY TOLERANCE.* Refer to boxed “WARNINGS" and "OVERDOSAGE" section.

Epinephrine 1:1000 should be available. When *changing immunotherapy from an unstandardized to an*

AU/ml standardized allergenic extract, dose adjustment, if indicated, should be based on such considerations as the results of skin endpoint titration (see "INDICATIONS AND USAGE" section). Patient re-evaluation may be necessary. Injections should never be given intravenously. A 5/8 inch, 25 gauge needle on a sterile syringe will allow deep subcutaneous injection. Precaution of withdrawing the plunger slightly after inserting the needle is advisable to determine if a blood vessel has been entered. DO NOT INJECT INTRAVENOUSLY. Proper measurement of the dose and caution in making the injection will minimize reactions. Patients should be detained for twenty to thirty minutes after injection and advised to notify the office immediately if symptoms or reactions occur.

Patients being switched from one lot of extract to another from the same manufacturer should have the *dose reduced to 75%.* Also, this extract should be temporarily withheld or dosage reduced in the following conditions: 1) flu or other infection with fever; 2) exposure to excessive amounts of allergen prior to injection; 3) rhinitis and/or asthma exhibiting severe symptoms.

PRECAUTIONS

General:

Immunotherapy must be given under physician's supervision. Sterile solutions, vials, syringes, etc. must be used. Aseptic technique should be observed in making dilutions, skin testing and extracts for treatment. The usual precautions in administering allergenic extracts are necessary. Disposable, sterile syringe and needle should be used for each individual patient to prevent transmission of serum hepatitis, HIV and other infectious agents from one person to another. The current standard method of immunotherapy dates back to the earliest studies by Noon. Therapy is begun with a low dose which has been shown to be tolerated by both experience and skin testing. The initial dilution of allergenic extract, starting dose, and progression of dosage must be carefully determined on the basis of the patient's history and results of skin tests. Patients with a history of severe sensitivity and markedly positive skin tests in high dilutions of the allergenic extract should be started with low doses of highly diluted extract. Pregnancy or a history of prior reactions to allergen immunotherapy dictates the need to start with small quantities of antigen.

It cannot be overemphasized that, under certain unpredictable combinations of circumstances, anaphylactic shock is always a possibility. Other possible systemic reaction symptoms are, in varying degrees of severity, fainting, pallor, bradycardia, hypotension, angioedema, cough, wheezing, conjunctivitis, rhinitis, and urticaria.[13,14]

With careful attention to dosage and administration, such reactions occur infrequently, but it must be remembered that allergenic extracts are highly potent to sensitive individuals and OVERDOSE could result in anaphylactic symptoms. Therefore, it is imperative that physicians administering allergenic extracts understand and be prepared for the treatment of severe reactions.

Refer to "OVERDOSAGE" section for description of treatment for anaphylactic reactions.

Information for Patients:

Patient should remain under observation of a nurse, physician, or personnel trained in emergency measures for at least 20 minutes following injection of immunotherapy. Any adverse reactions during or after leaving office should be reported to the physician or his qualified personnel.

Carcinogenicity, Mutagenicity, Impairment of Fertility:

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

Pregnancy Category C:

Animal reproduction studies have not been conducted with allergenic extracts. It is not known whether allergenic extracts cause fetal harm during pregnancy or affect reproductive capacity. A systemic reaction to allergenic extracts could cause uterine contractions leading to spontaneous abortion or premature labor. Allergenic extracts should be used during pregnancy only if potential benefit justifies potential risk to fetus.[11]

Nursing Mothers:

It is not known whether allergenic extracts are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when allergenic extracts are administered to a nursing woman.

Pediatric Use:

Although standardized mite extract has not been studied in children, allergenic extracts (including mite) have been used in children with no evidence of special problems related to safety or other specific hazards.[17,18,19,20,21,22]

Drug Interactions:

Antihistamines. The H_1 antagonists which block the capillary effects of histamine, inhibit the wheal-and-flare reaction. Moreover, H_1 antagonists reduce the wheal reaction induced by mast cell secretagogues or allergens in sensitized patients. The most potent H_1 antagonists seems to be astemizole, which blocks the wheal and flare induced by histamine for a long period of time, ranging from a few days to 40 days. Although a large interpatient variation exists, hydroxyzine and clemastine seem to be more potent inhibitors than chlorpheniramine, and promethazine. On the other hand, tripelennamine, diphenhydramine, cyproheptadine, and perphenazine induce a variable, but rather low, degree of inhibition.[23] The duration of the inhibitory effect varies from 1 day to up to 10 days, according to the drug and the patient's sensitivity. Hydroxyzine and clemastine usually exhibit a longer blockade. Sustained-release H_1 antagonists may produce a longer inhibitory effect. Long-term treatment with antihistamines may reduce the inhibitory effects of these drugs on skin tests. Long et al. noticed that after 3 weeks of treatment with hydroxyzine, its suppressive effect, as well as that induced by other H_1 blockers, was significantly reduced. These data indicate that the 24-hour period without antihistamine sometimes recommended prior to skin testing may not be sufficient for reliable testing. If the histamine control is normal, it suggests that accurate testing can be performed, because the reactions to histamine and allergen were found to be equally suppressed by hydroxyzine. [23]

Tricyclic antidepressants exert a potent and sustained decrease of skin reactions to histamine. This effect may last for a few weeks. Tranquilizers and antiemetic agents of the phenothiazine class have H1 antihistaminic activity and can block skin tests.[23]

Corticosteroids. Short-term (less than 1 week) administration of corticosteroids at the therapeutic doses used in asthmatic patients does not modify the cutaneous reactivity to histamine, compound 48/80, or allergen. Long-term corticosteroid therapy modifies the skin texture and makes the interpretation of immediate skin tests more difficult.[23]

Theophylline. It appears that theophylline need not be stopped prior to skin testing. [23]

Beta-adrenergic agents. Inhaled $beta_2$ agonists in the usual doses used for the treatment of asthma do not usually inhibit allergen-induced skin tests. However, oral terbutaline and parenteral ephedrine were shown to decrease the allergen-induced wheal. Such an effect seems to be related to the antianaphylactic properties of $beta_2$ agonists and, to a lesser extent, to a direct action on the dermal vasculature. Conversely, beta-blocking agents such as Propanolol can significantly increase skin reactivity. [23]

Cromolyn. Cromolyn inhaled or injected prior to skin tests with allergens or degranulating agents does not alter the skin whealing response. [23]

Other drugs. Other drugs have been shown to decrease skin test reactivity. Among them, dopamine is the best-documented compound. [23]

Specific Immunotherapy. A decreased skin test reactivity has been noticed by many authors for patients undergoing specific immunotherapy with pollen extracts, grass pollen allergoids, mites, or hymenoptera venoms, or in professional beekeepers who are spontaneously desensitized. Finally, it was shown that specific immunotherapy in patients treated with ragweed pollen extract induced a decreased late-phase reaction. [23]

ADVERSE REACTIONS

Adverse reactions include, but are not necessarily limited to urticaria; itching; edema of extremities; respiratory wheezing or asthma; dyspnea; cyanosis; tachycardia; lacrimation; marked perspiration; flushing of face, neck or upper chest; mild persistent clearing of throat; hacking cough or persistent sneezing.

1) Local Reactions

Small amounts of erythema and swelling 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 or exceed 50 mm in diameter.

Larger local reactions are not only uncomfortable, but 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 or minor exacerbations of the patient's allergic symptoms may be treated by local cold applications and/or use of oral antihistamines, but 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 10-20 seconds. Prolonged pain is usually the result of intramuscular injection, making this injection route undesirable. Subcutaneous injection is the recommended route.

2) Systemic Reactions

Systemic reactions range from mild exaggeration of patient's allergic symptoms to anaphylactic reactions. Very sensitive patients may show a rapid response. In some instances, a severe systemic reaction with blood pressure fall and/or shock may occur. Quantitation of patient's sensitivity combined with careful early observation is essential for safe skin testing and treatment.

Reports from regulatory authorities in Sweden to the F.D.A. indicated that several deaths have been associated with the use of mite extracts. The F.D.A. was subsequently informed that these deaths may have been related to use by physicians untrained in the administration of potent extracts rather than a product defect. It should be noted that anaphylaxis and deaths following the injection of mite and other extracts have also been reported by the British Committee on Safety in Medicine in the British Medical Journal, Vol. 293, p. 948, 1986.[24]

Patients receiving beta-blockers may not be responsive to epinephrine or inhaled bronchodilators. The following are commonly prescribed **beta-blockers**: Levatol, Lopressor, Propanolol Intersol, Propanolol HCL, Blocadren, Propanolol, Inderal-LA, Visken, Corgard, Ipran, Tenormin, Timoptic. Ophthalmic beta-blockers: Betaxolol, Levobunolol, Timolol, Timoptic. Chemicals that are beta-blockers and may be components of other drugs: Acebutolol, Atenolol, Esmolol, Metoprolol, Nadolol, Penbutolol, Pindolol, Propanolol, Timolol, Labetalol, Carteolol.

OVERDOSAGE

If a systemic or anaphylactic reaction does occur, the first treatment should be injection intra-muscularly or subcutaneously 0.3 to 0.5 ml of 1:1000 epinephrine-hydrochloride into the opposite arm or gluteal area. Apply tourniquet above the site of allergenic extract injection and loosen briefly at 5 minute intervals to prevent circulatory impairment. If oxygen is indicated, it may be administered by nasal cannula or ambu bag.

The epinephrine HCL 1:1000 dose for infants to 2 years is 0.05 to 0.1 ml; for children 2 to 6 years it is 0.15 ml; for children 6 to 12 years it is 0.2 ml.

Studies on asthmatic subjects reveal that plasma concentrations of theophylline of 5 to 20 ug/ml are associated with therapeutic effects. Toxicity is particularly apparent at concentrations greater than 20 ug/ml. A loading dose of aminophylline of 5.6 mg/kg intravenously followed by 0.9 mg/kg per hour results in plasma concentrations of approximately 10 ug/ml (Mitenko and Ogilvie 1973b; Nicholson and Chick 1973).[4]

Other beta-adrenergic drugs such as isoproterenol, isoetharine, or albuterol may be used by inhalation. The usual dose to relieve broncho-constriction in asthma is 0.5 ml or the 0.5% solution for isoproterenol HCL; albuterol is longer acting than isoproterenol by any route of administration. The albuterol inhaler delivers approximately 90 mcg of albuterol from the mouthpiece. The usual dosage for adults and children would be two inhalations repeated every 4 to 6 hours. Isoetharine supplied in the Bronkometer unit delivers approximately 340 mcg isoetharine. The average adult dose is one to two inhalations.

Patients who have been taking a beta-blocker may be unresponsive to epinephrine. Epinephrine or beta-adrenergic drugs (Alupent) may be ineffective. These drugs should be administered even though a beta-blocker may have been taken. The following treatment will be effective whether or not patient is taking a beta-blocker: Aminophylline IV, slow push or drip, Atrovent (Ipratropium bromide) Inhaler, 3 inhalations repeated, Atropine, 0.4 mg/ml, 0.75 to 1.5 ml lM or IV, Solu-Cortef, 100-200 mg IM or IV, Solu-Medrol, 125 mg IM or IV, Glucagon, 0.5-1 mg IM or IV, Benadryl, 50 mg IM or IV, Cimetidine, 300 mg IM or IV, Oxygen via ambu bag.

DOSAGE AND ADMINISTRATION

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

Normally, immunotherapy with standardized mite allergenic extracts can be started with 0.15 ml of the endpoint of reaction.

If the first injection of the initial dilution of extract is tolerated without significant local reaction, increasing doses by 5-20% increments of that dilution may be administered. The rate of increase in dosage in the early stages of treatment with highly diluted extracts is usually more rapid than the rate of increase possible with more concentrated extracts. This schedule is intended only as a guide and must be modified according to the reactivity of the individual patient. Needless to say, the *physician must proceed cautiously in the treatment of the highly sensitive patient who develops large local or systemic reactions.*

Some patients may tolerate larger doses of the standardized mite allergenic extract depending on patient response.[7] Because dilute extracts tend to lose activity on storage, the first dose from a more concentrated vial should be the same or less than the previous dose.[8,12]

The physician who undertakes immunotherapy should be concerned with the degree of sensitivity of the patient. See "INDICATIONS AND USAGE" section. Strongly positive skin tests may be risk factors for systemic reactions. Less aggressive immunotherapy schedules may be indicated for such patients. *Maintenance dose potency must be established by the physician's clinical observation and experience.*[6,13]

Serial five-fold or ten-fold dilutions of the extract are used to make more dilute extract concentrations. Other concentrations can be prepared by appropriate dilutions. In brief, the allergist can prepare any dilution of extract that is considered appropriate for the patient.

Dosages progressively increase thereafter according to the tolerance of the patient at intervals of one to seven days until, (1) the patient achieves relief of symptoms, (2) induration at site of injection is no larger than 50 mm in 36 to 48 hours, (3) a maintenance dose, the largest dose tolerated by the patient short of aggravating existing symptoms, systemic symptoms, or anaphylaxis, or demonstrates untoward reactions that indicate the dose to be excessive. This maintenance dose may be continued at regular intervals perennially. It may be necessary to adjust the progression of dosage downward to avoid local and constitutional reactions.

HOW SUPPLIED

The concentrate of standardized mite allergenic extract is expressed in AU/ml. It is supplied in 10,000, 5,000 and 3,000 AU/ml. The mite extract is available in 10 ml, 30 ml, and 50 ml containers. Extracts in dropper bottles are available for prick-puncture testing.

Mite mixtures for immunotherapy only containing equal volumes of *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus* are available in the following potencies-5,000 AU/ml, 2,500 AU/ml,

and 1,500 AU/ml.

STORAGE

Store all stock concentrates and dilutions at 2-8 degrees C. Keep at this temperature during office use. The expiration date of allergenic extracts containing 10,000 AU/ml is listed on the container label. Dilutions of 10,000 AU/ml concentrate containing less than 50% glycerol are less stable. If loss of potency is suspected, concentrate can be checked by skin testing with equal units of a freshly prepared dilution on known mite allergic individuals.

REFERENCES

1. Evans, R., Pence, H., Kaplan, H., Rocklin, R.: The effect of Immunotherapy on Humoral and Cellular Response in Ragweed Hay Fever. J. Clin. lnv. 57: 1378-1385, 1976.
2. Gleich, G.J., Yunginger, J.W.: The Radio Allergo Sorbent Test: A Method to Measure IgE Antibodies, IgG Blocking Antibodies, and the Potency of Allergy Extracts. Bull. N.Y. Acad. Sci. 57 (7): 559-567, 1981.
3. Allergenic Products: Antigen E. Potency Test: Additional Standards for Miscellaneous Products, 21 CFR Part 680, Federal Register, Vol. 46, No. 147, Friday, July 31, 1981, Rules and Regulations, pp. 39128-39136.
4. Goodman, L.S., Gillman, A.: Editors The Pharmacological Basis of Therapeutics, MacMillan Publishing Co., Inc., Chapter 19, p. 375.
5. Kniker, W.T.: "Clinical Science and Common Sense in the Diagnosis and Immunotherapy of Respiratory Allergy," Continuing Education for the Family Physician, Vol. 10, No. 5, May 1979, pp.16-33.
6. Matthews, K., et al: Rhinitis, Asthma and the Other Allergic Diseases, NIAID Task Force Report, U.S. Dept. HEW, NIH Publication No. 79-387, Chapter 4, pp. 213-217, May 1979.
7. Ishizaka, K.: Control of IgE Synthesis, Third Edition, Allergy Principles and Practices, C.V. Mosby Co.,Vol. l, Chap. 4, p. 52,1988.
8. Nelson, H.S.: "The Effect of Preservatives and Dilution on the Deterioration of Russian Thistle (Salsola pestifer), a pollen extract." The Journal of Allergy and Clinical Immunology. Vol. 63, No.6, pp. 417-425, June 1979.
9. Norman, P.S., Lichtenstein, L.M., Ishizaka, K.: "Diagnostic tools in ragweed hay fever. A comparison of direct skin tests IgE antibody measurements and basophil histamine release." The Journal of Allergy and Clinical lmmunology, Vol. 52, 1973, pg. 210.
10. Rocklin, R.E., Sheffer, A.L., Grainader, D.K. and Melmon, K.: "Generation of antigen-specific suppressor cells during allergy desensitization", New England Journal of Medicine, Vol. 302, pp. 1213-1219, May 29,1980.
11. Seebohm, P.M., et al: Panel on Review of Allergenic Extracts, Final Report, Food and Drug Administration, pp. 9-48, March 13, 1981.
12. Stevens, E.: Cutaneous Tests, Regulatory Control and Standardization of Allergenic Extracts, First lnternational Paul Ehrlich Seminar, Frankfurt, Germany, pp. 133-138, May 20-22, 1979.
13. Van Metre, T., Adkinson, N., Amodio, F., Lichtenstein, L., Mardinay, M., Norman, P., Rosenberg, G., Sobotka, A., Valentine, M.: "A Comparative Study of the Effectiveness of the Rinkel Method and the Current Standard Method of Immunology for Ragweed Pollen Hay Fever," The Journal of Clinical Allergy and Immunology, Vol. 66, No. 6, p. 511, December 1980.
14. Wasserman, S.: The Mast Cell and the Inflammatory Response. The Mast Cell–its role in health and disease. Proceedings of an International Symposium, Davos, Switzerland, Pitman Medical Publishing Co., pp. 9-20, 1979.
15. Perelmutter, L.: IgE Regulation During Immunotherapy of Allergic Diseases. Annals of Allergy, Vol. 57, August 1986.
16. Baer, H., Anderson, M.C., Turkeltaub, P.C.: Allergenic Extracts, Third Edition, Allergy Principles and Practice, C.V. Mosby Co., Vol. I, Chap. 17, p. 373, 1988.
17. Wasserman, S., Marquart, D.: Anaphylaxis, Third Edition, Allergy Principles and Practice, C.V.

Mosby Co., Vol. 1, Chap. 58, pp. 1365-1376, 1988.
18. Solomon, W., Matthews, K.: Aerobiology and inhalant allergens, Third Edition, Allergy Principles and Practice, Vol. I, Chapt. 16, pg. 312, edited by Middleton et al.
19. Bullock, J., Frick, O.: Mite Sensitivity in House Dust Allergic Children, Am. J. Dis. Child., pp.123222, 1972.
20. Kawai, T., Marsh, D., Lichtenstein, L., Norman, P.: The Allergens Responsible for House Dust Allergy. I. Comparison of Dermatophagoides pteronyssinus and House Dust Extracts by Assay of Histamine Release from Allergic Human Leukocytes. J. Allergy Clin. Immunol. 50: 117, 1972.
21. Willoughby, J.W.: Inhalant Allergy Immunotherapy with Standardized and Nonstandardized Allergenic Extracts, American Academy of Otolaryngology-Head and Neck Surgery: Instructional Courses, C.V. Mosby Co., Vol. 1, Chapter 15, September 1988.
22. Allergy Principles and Practice,Third Edition, Vol. I and II, Edited by Middleton, Reed, Ellis, Adkinson, Yunginger, C.V. Mosby Co., 1988.
23. Allergy Principles and Practice, Third Edition, Vol. I, Chapt. 19, "In vivo methods for study of allergy: Skin tests", pg. 419-436, Middleton, Reed, Ellis, Adkinson, Yunginger, C.V. Mosby Co., 1988.
24. Reid, Michael J., Lockey, Richard F., Turkeltaub, Paul C., M.D., Platts-Mills, Thomas: "Survey of Fatalities from Skin Testing and Immunotherapy 1985-1989", Journal of Allergy and Clinical Immunology, Vol. 92, No. 1, pp. 6-15, 1993.

STANDARDIZED MITE, DERMATOPHAGOIDES PTERONYSSINUS

standardized mite, dermatophagoides pteronyssinus injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:49288-0172
Route of Administration	SUBCUTANEOUS, INTRADERMAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Dermatophagoides pteronyssinus (UNII: 57L1Z5378K) (Dermatophagoides pteronyssinus - UNII:57L1Z5378K)	Dermatophagoides pteronyssinus	10000 [AU] in 1 mL

Inactive Ingredients

Ingredient Name	Strength
Glycerin (UNII: PDC6A3C0OX)	0.525 mL in 1 mL
Water (UNII: 059QF0KO0R)	
Sodium Chloride (UNII: 451W47IQ8X)	0.0095 g in 1 mL
Sodium Bicarbonate (UNII: 8MDF5V39QO)	0.0024 g in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:49288-0172-2	5 mL in 1 VIAL, MULTI-DOSE		
2	NDC:49288-0172-3	10 mL in 1 VIAL, MULTI-DOSE		
3	NDC:49288-0172-4	30 mL in 1 VIAL, MULTI-DOSE		
4	NDC:49288-0172-5	50 mL in 1 VIAL, MULTI-DOSE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102225	10/22/1991	

STANDARDIZED MITE, DERMATOPHAGOIDES PTERONYSSINUS

standardized mite, dermatophagoides pteronyssinus injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:49288-0173
Route of Administration	SUBCUTANEOUS, INTRADERMAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Dermatophagoides pteronyssinus (UNII: 57L1Z5378K) (Dermatophagoides pteronyssinus - UNII:57L1Z5378K)	Dermatophagoides pteronyssinus	3000 [AU] in 1 mL

Inactive Ingredients

Ingredient Name	Strength
Glycerin (UNII: PDC6A3C0OX)	0.525 mL in 1 mL
Water (UNII: 059QF0KO0R)	
Sodium Chloride (UNII: 451W47IQ8X)	0.0095 g in 1 mL
Sodium Bicarbonate (UNII: 8MDF5V39QO)	0.0024 g in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:49288-0173-3	10 mL in 1 VIAL, MULTI-DOSE		
2	NDC:49288-0173-4	30 mL in 1 VIAL, MULTI-DOSE		
3	NDC:49288-0173-5	50 mL in 1 VIAL, MULTI-DOSE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102225	02/06/1992	

STANDARDIZED MITE, DERMATOPHAGOIDES PTERONYSSINUS

standardized mite, dermatophagoides pteronyssinus injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:49288-0174

Route of Administration	SUBCUTANEOUS, INTRADERMAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Dermatophagoides pteronyssinus (UNII: 57L1Z5378K) (Dermatophagoides pteronyssinus - UNII:57L1Z5378K)	Dermatophagoides pteronyssinus	5000 [AU] in 1 mL

Inactive Ingredients

Ingredient Name	Strength
Glycerin (UNII: PDC6A3C0OX)	0.525 mL in 1 mL
Water (UNII: 059QF0KO0R)	
Sodium Chloride (UNII: 451W47IQ8X)	0.0095 g in 1 mL
Sodium Bicarbonate (UNII: 8MDF5V39QO)	0.0024 g in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:49288-0174-3	10 mL in 1 VIAL, MULTI-DOSE		
2	NDC:49288-0174-4	30 mL in 1 VIAL, MULTI-DOSE		
3	NDC:49288-0174-5	50 mL in 1 VIAL, MULTI-DOSE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102225	10/22/1991	

STANDARDIZED MITE, DERMATOPHAGOIDES FARINAE

standardized mite, dermatophagoides farinae injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:49288-0175
Route of Administration	SUBCUTANEOUS, INTRADERMAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Dermatophagoides farinae (UNII: PR9U2YPF3Q) (Dermatophagoides farinae - UNII:PR9U2YPF3Q)	Dermatophagoides farinae	10000 [AU] in 1 mL

Inactive Ingredients

Ingredient Name	Strength
Glycerin (UNII: PDC6A3C0OX)	0.525 mL in 1 mL

Water (UNII: 059QF0KO0R)	
Sodium Chloride (UNII: 451W47IQ8X)	0.0095 g in 1 mL
Sodium Bicarbonate (UNII: 8MDF5V39QO)	0.0024 g in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:49288-0175-1	2 mL in 1 VIAL, MULTI-DOSE		
2	NDC:49288-0175-2	5 mL in 1 VIAL, MULTI-DOSE		
3	NDC:49288-0175-3	10 mL in 1 VIAL, MULTI-DOSE		
4	NDC:49288-0175-4	30 mL in 1 VIAL, MULTI-DOSE		
5	NDC:49288-0175-5	50 mL in 1 VIAL, MULTI-DOSE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102224	10/22/1991	

STANDARDIZED MITE, DERMATOPHAGOIDES FARINAE

standardized mite, dermatophagoides farinae injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:49288-0176
Route of Administration	SUBCUTANEOUS, INTRADERMAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Dermatophagoides farinae (UNII: PR9U2YPF3Q) (Dermatophagoides farinae - UNII:PR9U2YPF3Q)	Dermatophagoides farinae	3000 [AU] in 1 mL

Inactive Ingredients

Ingredient Name	Strength
Glycerin (UNII: PDC6A3C0OX)	0.525 mL in 1 mL
Water (UNII: 059QF0KO0R)	
Sodium Chloride (UNII: 451W47IQ8X)	0.0095 g in 1 mL
Sodium Bicarbonate (UNII: 8MDF5V39QO)	0.0024 g in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:49288-0176-3	10 mL in 1 VIAL, MULTI-DOSE		
2	NDC:49288-0176-4	30 mL in 1 VIAL, MULTI-DOSE		
3	NDC:49288-0176-5	50 mL in 1 VIAL, MULTI-DOSE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102224	02/06/1992	

STANDARDIZED MITE, DERMATOPHAGOIDES FARINAE

standardized mite, dermatophagoides farinae injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:49288-0177
Route of Administration	SUBCUTANEOUS, INTRADERMAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Dermatophagoides farinae (UNII: PR9U2YPF3Q) (Dermatophagoides farinae - UNII:PR9U2YPF3Q)	Dermatophagoides farinae	5000 [AU] in 1 mL

Inactive Ingredients

Ingredient Name	Strength
Glycerin (UNII: PDC6A3C0OX)	0.525 mL in 1 mL
Water (UNII: 059QF0KO0R)	
Sodium Chloride (UNII: 451W47IQ8X)	0.0095 g in 1 mL
Sodium Bicarbonate (UNII: 8MDF5V39QO)	0.0024 g in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:49288-0177-3	10 mL in 1 VIAL, MULTI-DOSE		
2	NDC:49288-0177-4	30 mL in 1 VIAL, MULTI-DOSE		
3	NDC:49288-0177-5	50 mL in 1 VIAL, MULTI-DOSE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102224	10/22/1991	

MIXTURE OF STANDARDIZED MITES

mixture of standardized mites injection, solution

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:49288-0182

Route of Administration	SUBCUTANEOUS, INTRADERMAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
Dermatophagoides pteronyssinus (UNII: 57L1Z5378K) (Dermatophagoides pteronyssinus - UNII:57L1Z5378K)	Dermatophagoides pteronyssinus	5000 [AU] in 1 mL
Dermatophagoides farinae (UNII: PR9U2YPF3Q) (Dermatophagoides farinae - UNII:PR9U2YPF3Q)	Dermatophagoides farinae	5000 [AU] in 1 mL

Inactive Ingredients

Ingredient Name	Strength
Glycerin (UNII: PDC6A3C0OX)	0.525 mL in 1 mL
Water (UNII: 059QF0KO0R)	
Sodium Chloride (UNII: 451W47IQ8X)	0.0095 g in 1 mL
Sodium Bicarbonate (UNII: 8MDF5V39QO)	0.0024 g in 1 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:49288-0182-2	5 mL in 1 VIAL, MULTI-DOSE		
2	NDC:49288-0182-3	10 mL in 1 VIAL, MULTI-DOSE		
3	NDC:49288-0182-4	30 mL in 1 VIAL, MULTI-DOSE		
4	NDC:49288-0182-5	50 mL in 1 VIAL, MULTI-DOSE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
BLA	BLA102225	10/22/1991	

Labeler - Antigen Laboratories, Inc. (030705628)

Establishment

Name	Address	ID/FEI	Business Operations
Antigen Laboratories, Inc.		030705628	manufacture

Revised: 9/2009 Antigen Laboratories, Inc.