INSTRUCTIONS AND DOSAGE SCHEDULE FOR ALLERGENIC EXTRACTS

HYMENOPTERA VENOM PRODUCTS

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

DESCRIPTION

Hymenoptera Venom products are sterile freeze-dried venom of Honey Bee (Apis mellifera) and venom protein of Yellow Jacket (Vespula sp.), Yellow Hornet (Dolichovespula arenaria), White-Faced Hornet (Vespa crabro), Yellow Wasp (Vespula maculata), and Mixed Vespid. The product is reconstituted with 5.5 mL of fluid, the resulting solution contains 100 micrograms of venom protein (100 μg/mL) plus 7.7 milligrams of mannitol per mL when reconstituted with Neutral Albumin Saline (containing 0.6% NaCl and 1.8% mannitol human serum albumin) at a concentration of 100 μg/mL (300 μg/mL for Mixed Vespid Venom Protein). Dilutions of this concentration should be made only with sterile Albumin Saline with Phenol (0.4%). See DOSAGE AND ADMINISTRATION for specific dilutions of venom for treatment and storage. Space is provided on the container label to record the date (month, day, year) venom is reconstituted. Refer to dating period shown under PRECAUTIONS. At the time of reconstitution, write the date of the reconstituted product expiration date (month, day year) on the vial label in the space provided.

CLINICAL PHARMACOLOGY

Diagnosis

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

Treatment

Repeated injections of increasing doses of insect venom extracts have been shown to ameliorate the intensity of allergic reactions to insect stings. The mechanism by which hypo-sensitization is achieved is not known completely. IgE antibodies (blocking antibodies) appear in the serum of patients treated with injected venom (or direct relationship has been identified between the level of blocking antibodies (or the ratio of blocking antibody to IgE antibody directed to the same venom antigens) and the degree of hypo-sensitization. However, patients who show protection from symptoms after stings have been found to have significant levels of specific blocking antibody.

Initially, after a period of immunotherapy with specific venom antigens, levels of IgE antibody may increase. However, from studies carried out with other venom preparations, these levels are reported to decline after a time. After maintenance level has been reached and maintained, symptoms after stings have been shown to decrease considerably. (5, 14)

It is not known if skin-sensitizing antibody can be eradicated or if the patient can be entirely cured, nor is it known how long immunotherapy must be continued. In a clinical study with Honey Bee, patients were injected with venom protein (100 μg) every 2-3 weeks after beginning therapy. Whether efficacy of therapy is influenced by the time required to reach maintenance has not yet been determined.

Large local reactions occurred in approximately 60% of the patients given immunotherapy. Some systemic response occurred, often repeatedly, in one-third of the patients treated in the clinical trial. Only one systemic reaction occurred on the first dose given. The others occurred at various times after beginning therapy. Some patients with large local reactions (or to skin tests) are diagnostic of clinical sensitivity. However, patients with a history of reactions to insect stings may also be more refractory to the normal allergy treatment regimen. Patients should be treated only if the benefit of treatment outweighs the risks. (5)

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.

Immunotherapy for insect sting allergy should be given to those patients who have experienced significant systemic reactions (for detailed description of symptoms see INDICATIONS AND USAGE and ADVERSE REACTIONS) from insect stings and who demonstrate hypersensitivity by skin testing with venom protein. (See section on Skin Testing under CLINICAL PHARMACOLOGY for approved method for diagnosing insect sting allergic patients for immunization by skin testing).

This product must never be injected intravenously.

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

CONTRAINDICATIONS

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

Patients showing negative intradermal tests to specific venom at 1:1,000,000 dose are not considered for venom immunotherapy.

CONTRAINDICATIONS FOR IMMUNOTHERAPY USING HYMENOPTERA VENOM PRODUCTS

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

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**WARNINGS**

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

Vaccine extract must be temporarily withheld from patients or the dose adjusted downward if any of the following conditions exist: (1) severe symptoms of rhinitis or asthma; (2) infection of flu exacerbated by fever; (3) any evidence of an excessively large local or systemic reaction following the initial stage of vaccination; or during maintenance therapy; and/or (4) insect sting prior to scheduled injection. Do not administer vaccine injections during a period of symptoms following an insect sting or on the day the patient received an insect sting, since this could result in an allergic load that exceeds the patient’s tolerance. The **CONCENTRATE MUST NOT BE INJECTED AT ANY TIME UNTIL TOLERANCE HAS BEEN DETERMINED.** DILUTED VENOM SOLUTIONS MUST NOT BE ADMINISTERED. ALBUMIN SALINE WITH PHENOL (0.4%) FOR SKIN TESTING AND IMMUNOTHERAPY.

**INJECTIONS MUST NEVER BE GIVEN INTRAVENTRICULARLY.** Subcutaneous injection is recommended. Intracutaneous injection of a large local reaction is not advisable, even if it is not excessively painful. AFTER INSERTING NEEDLE SUBCUTANEOUSLY, BUT BEFORE INJECTING, ALWAYS PULL OUT THE PLUGGER SLIGHTLY. IF BLOOD APPEARS IN THE SYRINGE, CHANGE NEEDLE AND GIVE THE INJECTION IN ANOTHER SITE. The presence of asthmatic signs and symptoms appear to be an indicator for severe respiratory reactions following allergy injections. An assessment of airway obstruction either by auscultation or by peak flow measurement may be used to determine the need for emergency treatment. Bronchoconstriction is characterized by wheezing or a persistent diminution in the peak flow measurement. If wheezing or peak flow measurement decreases greater than 20%, or if any other respiratory symptoms occur or if the patient becomes hypoxic, intravenous corticosteroids (e.g., methylprednisolone, 125 mg/day) should be administered immediately and should be continued for 3-5 days. TRICYCLIC ANTIDEPRESSANTS, SUCH AS DOXEPIN, SHOULD BE WITHHELD FOR AT LEAST 7 DAYS BEFORE INJECTIONS. **Local Reactions**

Patients with hypersensitivity to vaccine who undergo desensitization treatment while under concomitant therapy with ACE (angiotensin-converting enzyme) inhibitors, may have an increased risk of life-threatening anaphylactic reactions. Patients without vaccine hypersensitivity, who take ACE inhibitors, and are stung by insects such as bee or wasp, may have reactions following allergy injections. An assessment of airway obstruction either by auscultation or by peak flow measurement may be used to determine the need for emergency treatment. Bronchoconstriction is characterized by wheezing or a persistent diminution in the peak flow measurement. If wheezing or peak flow measurement decreases greater than 20%, or if any other respiratory symptoms occur or if the patient becomes hypoxic, intravenous corticosteroids (e.g., methylprednisolone, 125 mg/day) should be administered immediately and should be continued for 3-5 days. Tricyclic antidepressants, such as doxepin, should be withheld for at least 7 days before injections. **Drug Interactions**

Patients with cardiovascular diseases and/or pulmonary diseases such as symptomatic, arterial blood flow with the tourniquet. For the patient’s safety, the physician should be prepared in advance for such treatment measures. **ADVERSE REACTIONS** for such treatment measures.

Patients may lose tolerance for allergen injections during prolonged periods between injections. IF A PROLONGED PERIOD OF TIME HAS ELAPSED SINCE THE LAST INJECTION: IF THE VENOM EXTRACT PREVIOUSLY USED WAS FROM ANOTHER MANUFACTURER, the physician should be prepared in advance for such treatment measures. **ADVERSE REACTIONS** for such treatment measures.

It is also not known whether Hymenoptera Venom Products can cause fetal harm when administered to a pregnant woman only if clearly needed. Venom Products should be given to a pregnant woman only if clearly needed. On the basis of histamine’s known ability to contract uterine muscle, theoretically, a systemic reaction, while a sting from an insect sting or from venom skin testing or treatment dose, should be avoided. Therefore, the physician must carefully consider the benefit-risk ratio, to both patient and fetus, of continuing venom immunotherapy during pregnancy, or performing venom skin testing, and especially of initiating a venom immunotherapy program where there is a possibility that the patient may not be able to reach the recommended maintenance dose without significant risk of a systemic reaction.

**Nursing Mothers**

There are no adequate and well-controlled studies on the secretory of the allergenic extract components in human milk or effect on the nursing infant. Because many drugs are excreted in human milk, caution should be exercised when allergenic extracts are administered to a nursing woman.

**(7) Use**

Since dosage for the pediatric population is the same as for adults, the larger volumes of solution may produce excessive discomfort. Therefore, in order to achieve the total dose required, the solution may be divided into more than one injection per visit. A study done in children ages 4 to 17 showed no special problems with venom immunotherapy in this population.

**(8) Intranasal 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, and could be used to treat systemic reactions, or for the treatment of more sensitive to the cardiovascular side effect of epinephrine because of pre-existing cardiovascular disease.

**ADVERSE REACTIONS**

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

(1) Local Reactions

Some erythema, swelling or pruritis at the site of injection are common, the extent varying with the amount of allergen administered. Reactions of varying severity may occur from skin tests or immunotherapy. Frequent application of cold, wet dressings to the area and/or the use of oral antihistamines will ameliorate the discomfort. Reactions usually subside in 24-72 hours. Oxygen should be given by mask. Intravenous antihistamines, inhaled bronchodilators, and parenteral corticosteroids may be used if necessary after adequate epinephrine administration.

(2) Drug Interactions

Patients on beta blockers may be more reactive to allergens given for testing or treatment. Patients on beta blockers may be more reactive to allergens given for testing or treatment. Some erythema, swelling or pruritis at the site of injection are common, the extent varying with the amount of allergen administered. Reactions of varying severity may occur from skin tests or immunotherapy. Frequent application of cold, wet dressings to the area and/or the use of oral antihistamines will ameliorate the discomfort. Reactions usually subside in 24-72 hours. Oxygen should be given by mask. Intravenous antihistamines, inhaled bronchodilators, and parenteral corticosteroids may be used if necessary after adequate epinephrine administration.
of 0.05 mL for intradermal testing. Introduce the needle through the surface of the drop with a sterile 27 gauge needle. The prick is applying one drop of the 1 g/mL. Patients showing a positive reaction to the prick test at the 1 concentration for intradermal testing. See Intradermal Tests below. Skin testing (prick and intradermal) provides information to assist in identifying those patients who are to be classified as extremely sensitive, individuals reacting with a significant skin reaction at the 1 g/mL has been tested, whichever occurs first.

In identifying those patients to be classified as extremely sensitive, individuals reacting with a significant skin reaction at the 1 g/mL. Patients with multiple venom sensitivities should be given each specific venom concentration in a separate site. (Except, if the patient has sensitivities to Yellow Jacket, Yellow Hornet, and White-Faced Hornet venoms concurrently, s/he can be injected with Mixed Vespid venom protein, an equal mixture of these three vespid venoms.) Note which venom preparation is injected at a specific site, so that dosage of that venom preparation can be adjusted if an excessive local reaction occurs in patients receiving more than one venom, there is theoretically a greater risk of systemic reactions.

CAUTION: Sensitivity to venom differs from patient to patient. Thus, it is not possible to provide a dosage schedule that will be suitable for all patients. The Suggested Dosage Schedule shown below was used in clinical trials and should be suitable for a majority of patients. In EXTREMELY SENSITIVE PATIENTS, however, an individualized dosage schedule must be employed which will be dictated by the patient’s sensitivity. This individualized schedule will probably include smaller volumes and smaller increments between doses in progressing to the maintenance level (1 µg per µL per venom).

A 1 mL tuberculin syringe with a short 27-gauge needle should be used to deliver a volume of 0.05 mL. Start intradermal tests with the most dilute solution. If after 20 minutes no skin reaction is obtained, continue the intradermal testing using ten-fold increments in the concentration until a reaction of 5-10 mm wheal and 11-20 mm erythema is obtained, or until a concentration of 1 µg/mL has been tested, whichever occurs first.

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

(3) Immunotherapy

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

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

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

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

The optimum duration for immunotherapy is not known, so current recommendations are for ongoing maintenance.

Jubilant HollisterStier sterile freeze-dried Hymenoptera Venom Products are supplied in 10 mL vacuum-sealed vials containing 550 micrograms (550 µg) of freeze-dried venom product. Mixed Vespid Venom will contain three times the quantity of each single venoms, and 1650 micrograms (1650 µg) of the single venoms, and 1650 micrograms (1650 µg) of monomeric antigen. The dose for patients experiencing life-threatening anaphylaxis after insect stings.

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

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

LIMITED WARRANTY

A number of factors beyond our control could reduce the efficacy of this product or even result for analysis. For those included in 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


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**PLEASE NOTE:** Minor leakage of vial contents may occur after stopper is punctured several times if excessive amounts of air are injected into the vial. To prevent leakage, avoid buildup of air pressure, or store vial in upright position.

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

- [ ] Bulk-5 Dose
- [ ] Bulk-12 Dose
- [ ] Venomil®

**CAUTION:** See INDICATIONS AND USAGE, Treatment, and DOSAGE AND ADMINISTRATION in this INSTRUCTIONS Sheet.