INSTRUCTIONS AND DOSAGE SCHEDULE FOR ALLERGIC EXTRACTS
HYMENOPTERA VENOM PRODUCTS

Multidose 13.0 mL (Honey Bee, Yellow Jacket, Wasp, and Mixed Vespid)

INDICATIONS AND USAGE

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

The reconstituted single venom products are intended for subcutaneous injection for immunotherapy and percutaneous use for diagnosis. The Mixed Vespid venom protein is the immunotherapy only product available for use in percutaneous skin tests.

DESCRIPTION

Hymenoptera Venom Extracts may be used for treatment of patients with systemic allergies to insect stings, including severe reactions (anaphylaxis) and for the treatment of chronic urticaria and angioedema. The extracts are prepared for reconstitution and administration with the use of the diluting fluid provided. The extracts are reconstituted with Sehite Albumin Saline with Phenol which contains 0.9% NaCl, 0.4% phenol and 0.03% Normal Human Serum Albumin to a concentration of 100 µg/mL (300 µg/mL for Mixed Vespid venom protein).

The incidence of anaphylactic reactions after a single 13 µg dose was 0.006%.

DIAGNOSIS

Patients showing negative intradermal skin tests to specific venoms at 1 µg/mL are not considered for venom treatment. Patients with a history of reaction (any of the three reaction types described above) to insect stings, but who did not demonstrate a positive skin test reaction to venom, were considered in a previous study not to be clinically sensitive, and were not treated.

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

The best statement that can be made, at present, is that patients with significant positive history (reactions of the three types described above) following an insect sting, and who do not demonstrate a positive skin test reaction to a venom at a concentration of 1 µg/mL or less, are not recommended for treatment. Patients who have the history described above, but who do not react to a 1 µg/mL intradermal venom skin test, cannot be recommended for treatment. At present, venom skin tests may be used for diagnostic purposes. Tests at concentrations of 0.01, 0.1, and 1 µg/mL are available for venom skin tests.

The dosage schedule is based on the results of controlled clinical studies in which the venom products were shown to be safe and effective and the criteria established for treatment with insect venom extracts. The dosage schedule, based on the patient’s sensitivity to and tolerance of the injections, is designed to increase the patient’s degree of tolerance in a stepwise fashion and to establish antigen-specific blocking antibodies.

CONTRAINdications

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

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

Any injections, including immunotherapy, should be avoided in patients with a bleeding tendency. Patients with cardiovascular diseases and/or pulmonary diseases such as symptomatic unstable, steroid-dependent asthma, and/or those who are receiving cardiovascular drugs.
such as beta blockers, may be at higher risk for severe adverse reactions. These patients may also be more refractory to the normal allergy treatment regimen. Patients should be treated only if the benefit of treatment outweighs the risks. 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 severe systemic reactions. Since there are differences of opinion concerning the possibility of routine immunizations altering autoimmune disease, it should be given cautiously to patients with other immunologic diseases and only if the risk from insect stings is greater than the risk of exacerbating the underlying disorder.

**WARNINGS**

See WARNINGS box at the beginning of this Instruction Sheet. See also PRECAUTIONS. Venom extract must be temporarily withdrawn from patients or the dose adjusted downward if any of the following conditions exist: (1) severe symptoms of rhinitis and/or asthma; (2) any injection or flu accompanied by fever; (3) severe symptoms generally not limited to the local site of injection; (4) insect sting prior to a scheduled injection. Do not administer in patients undergoing maintenance therapy; and/or (4) insect sting prior to a scheduled injection. Do not administer in patients with bleeding disorders prior to a scheduled injection. Do not administer to patients with a history of anaphylaxis to insect venom, who have undergone a desensitization treatment while on maintenance therapy; and/or (4) insect sting prior to a scheduled injection.

Proper selection of the dose and careful injection should prevent most systemic reactions. Patients with hypersensitivity to insect venom who undergo desensitization treatment while on maintenance therapy; and/or (4) insect sting prior to a scheduled injection. Do not administer in patients with bleeding disorders prior to a scheduled injection. Do not administer to patients with a history of anaphylaxis to insect venom, who have undergone a desensitization treatment while on maintenance therapy; and/or (4) insect sting prior to a scheduled injection.

IF THE PREVIOUS EXTRACT WAS FROM ANOTHER MANUFACTURER: The dating period for allergenic extracts should be considered from the date of reconstitution. The time from reconstitution to the injection should not be greater than 3 months. The expiration date of any concentration or diluent should be considered as the date from which the extract should be considered to have expired. If a patient is changed to a new, and if any of the following conditions exist: (1) severe symptoms of rhinitis and/or asthma;

Concentration  Diluent  Recommended  Expiration Date*  
10 µg/mL  Albumin Saline with Phenol (0.4%)  12 months  
10 µg/mL  Albumin Saline with Phenol (0.4%)  1 month  
10 µg/mL  Albumin Saline with Phenol (0.4%)  14 days  
Less than 0.1 µg/mL  Albumin Saline with Phenol (0.4%)  Prepare fresh daily  

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

Stabilized vials, syringes, vials, etc., should be used and aseptic precautions observed in making dilutions. To avoid cross-contamination, do not use the same needle to withdraw materials from vials of more than one extract, or extract followed by diluent. A sterile tuberculin syringe, with a needle at least 5/8” long and graduated in 0.01 mL units, should be used to measure carefully each dose from the appropriate diluent. Aseptic techniques should always be employed when injections are being administered. A separate sterile syringe should be used for each patient to prevent transmission of hepatitis and other infectious agents from one person to another.

Patient reactions to previous injections should be reviewed before each new injection so that dose can be adjusted accordingly. See ADVERSE REACTIONS and WARNINGS. Risk of patient is encountered while developing systemic reactions to minutes of an-

lenger and does not demonstrate increasing tolerance to injections after several months of treatment. It is suggested that if systemic reactions or excessive local responses occur at very small doses of venom, a dose of 0.01 mg of venom may be used to determine a patient’s ability to reach the recommended maintenance dose without significant risk of a systemic reaction.

**ADVERSE REACTIONS**

Physicians administering Hyposens, 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).

**Local Reactions**

Some erythema, swelling or pruritis at the site of injection are common, the extent varying with the patient. Excessively large, painful or persistent local reactions can occur from skin tests or immunotherapy. Preference activity of cold, wet dressings or of the area or the use of oral antihistamines may be effective in local reactions usually occur in 24-36 hours. Local reactions occurred in approximately 60% of the patients given immunotherapy in a clinical study. None of the local reactions required specific treatment; however, subsequent injections in many instances were held to the previous dose or a reduced dose. Some patients had repeated local reactions that slowed the increase in the immunotherapy dosage. See also CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION Sections. A mild burning immediately after the injection is to be expected. This usually leaves in 10 to 20 seconds. See also WARNINGS and PRECAUTIONS regarding proper method and route of injection.

**Systemic Reactions**

Most severe systemic reactions usually will begin within a 30-minute time period, but systemic reactions may occur at any time after skin tests or immunotherapy. Symptoms may be related to life-threatening from anaphylaxis as described under INDICA-

TIONS AND USAGE. With careful attention to dosage and administration, severe systemic reactions occur infrequently, but it cannot be overemphasized that in sensitive individuals, any injection could be followed by a systemic reaction. Therefore, it is important that allergists understand systemic reactions and be prepared for the treatment of severe reactions. See CLINICAL PHARMACOLOGY for clinical incidence of systemic reactions and course of action following systemic reactions.

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

ADULTS: 0.015 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 0.005 mg (mL) per kg body weight, for children 2 to 6 years of age, 0.02 mg (mL) and for children 6 to 12 years, 0.2 mg (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 to treatment.

After administration of epinephrine, profound shock or vasomotor collapse should be treated with intravenous fluids, and possibly vasoactive drugs. Airway patency should be ensured. Oxygen should be given by mask. Intravenous, antihistaminic, inhaled bronchodilators (epinephrine and/or corticosteroids may be used if necessary after adequate epinephrine and circulatory support have been given. Emergency resuscitation measures and personnel trained in their use must be available immediately in the event of a serious systemic or anaphylactie reaction not responsive to the above measures [Ref. J. Allergy and Clinical Immunology, 77(2): p.271-273, 1986]. Rarely are all of the above measures necessary; epinephrine usually produces a prompt
Skin testing should be carried out with to a sting, patients should not be tested until 2 to 4 weeks after any sting. Since the level of insect venom specific IgE

(2) Diagnosis

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

0.2 mL of 0.001 µg/mL + 1.8 mL = 0.0001 µg/mL

0.2 mL of 1 µg/mL + 1.8 mL = 0.1 µg/mL

0.2 mL of 10 µg/mL + 1.8 mL = 1 µg/mL

0.2 mL of 100 µg/mL + 1.8 mL = 10 µg/mL

See ADVERSE REACTIONS Section.

They must be made accurately and aseptically, using sterile solutions, vials, syringes, etc., and thoroughly mixed by rocking or swirling. DO NOT SHAKE. Store freeze-dried and reconstituted venom product, and venom dilutions constant at 2° - 8°C.

In identifying those patients to be classified as extremely sensitive, individuals reacting to the maintenance level (100 µg per venom).

Intradermal Tests:

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

Intradermal testing to determine appropriate con -

ساسية للجثة وتدور على استجابة الجلد بعد وصول الفئران. كان الجلود المثلثةzikية والمثقالة المثلثية للفئران تظهر أن الجلد المثلثةzikية والمثقالة المثلثية للفئران تظهر أن الجلد المثلثةzikية والمثقالة المثلثية للفئران تظهر أن الجلد المثلثةzikية والمثقالة المثلثية للفئران تظهر أن الجلد المثلثةzikية والمثقالة المثلثية للفئران تظهر أن الجلد المثلثةzikية والمثقالة المثلثية للفئران تظهر أن الجلد المثلثةzikية والمثقالة المثلثية للفئران تظهر أن الجلد المثلثةzikية والمثقالة المثلثية للفئران تظهر أن الجلد المثلثةzikية والمثقالة المثلثية للفئران تظهر أن الجلد المثلثةzikية والمثقالة المثلثية للفئران تظهر أن الجلد المثلثةzikية والمثقالة المثلثية للفئران تظهر أن الجلد المثلثةzikية والمثقالة المثلثية للفئران تظهر أن الجلد المثلثةzikية والمثقالة المثلثية للفئران تظهر أن الجلد المثلثةzikية والمثقالة المثلثية للفئران تظهر أن الجلد المثلثةzikية والمثقالة المثلثية للفئران تظهر أن الجلد المثلثةzikية والمثقالة المثلثية للفئران تظهر أن الجلد المثلثةzikية والمثقالة المثلثية للفئران تظهر أنه يمكن أن يكون نتيجة لانعكاسات بين الفئران. يساعد الجلود المصغرة المثلثية في تفسير نتائج التجربة.

*See preceding CAUTION SECTION.

In proceeding with the Suggested Dose Schedule, or modified schedules (for highly sensi-
tive patients) it is recommended that injections be given at least once per week, as in the clinical situation. (See CLINICAL PHARMACOLOGY and INDICATIONS AND USAGE).

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

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

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

Prick Tests: Prick tests are accomplished by applying one drop of the 1 µg/mL venom protein solution to the forearm, and by pricking the skin through the surface of the drop with a sterile 27-gauge needle. The prick should be deep enough to raise a small bubble.

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

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

Intradermal Tests: Patients should receive a prick test at the 1 µg/mL concentration should begin intradermal tests at concentrations of not more than 0.0001 to 0.001 µg/mL. Patients with negative prick tests may begin intradermal tests at a concentration of 0.001 µg/mL. A 1 mL tuberculin syringe with a short 27-gauge needle should be used to deliver a volume of 0.05 mL for intradermal testing. Introduce the needle into the superficial skin layers, bevel down, until the bevel is completely buried, then slowly inject a 0.05 mL aliquot of this concentration, making as small bubble

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 concentra -
tion 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 venom when a skin response 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.

If the intradermal test reaction is greater than that of the diluent control, the patient is considered sensitive to the venom.

Prick testing should be done before intradermal testing to determine appropriate concentra-
tion for intradermal testing. Intradermal testing (prick and intradermal) provides information to assist in identifying those patients who are to be classified as extremely sensitive and who may not tolerate the Suggested Dose Schedule. See DOSAGE AND ADMINISTRATION. Intradermal testing should be done to a sting, patients should not be tested until 2 to 4 weeks after any sting.

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

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A patient should be considered sensitive to the venom when a skin response 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.

If the intradermal test reaction is greater than that of the diluent control, the patient is considered sensitive to the venom.

Suggested Dose Schedule for a Single Venom:

<table>
<thead>
<tr>
<th>Dose No.</th>
<th>*Volume of 1 µg/mL</th>
<th>Dose No.</th>
<th>Volume of 1 µg/mL</th>
<th>Dose No.</th>
<th>Volume of 100 µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.05 mL</td>
<td>5</td>
<td>0.05 mL</td>
<td>9</td>
<td>0.05 mL</td>
</tr>
<tr>
<td>2</td>
<td>0.10 mL</td>
<td>6</td>
<td>0.10 mL</td>
<td>10</td>
<td>0.10 mL</td>
</tr>
<tr>
<td>3</td>
<td>0.20 mL</td>
<td>7</td>
<td>0.20 mL</td>
<td>11</td>
<td>0.20 mL</td>
</tr>
<tr>
<td>4</td>
<td>0.40 mL</td>
<td>8</td>
<td>0.40 mL</td>
<td>12</td>
<td>0.40 mL</td>
</tr>
<tr>
<td>5</td>
<td>1.00 mL</td>
<td>9</td>
<td>1.00 mL</td>
<td>13</td>
<td>1.00 mL</td>
</tr>
<tr>
<td>6</td>
<td>3.00 mL</td>
<td>10</td>
<td>3.00 mL</td>
<td>14</td>
<td>3.00 mL</td>
</tr>
</tbody>
</table>

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

In proceeding with the Suggested Dose Schedule, or modified schedules (for highly sensi-
tive patients) it is recommended that injections be given at least once per week, as in the clinical situation. (See CLINICAL PHARMACOLOGY and INDICATIONS AND USAGE).

It is important that doses not exceed one week’s treatment, since some patients may develop adverse reactions to the venom.

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

Suggested Dose Schedule shown below was used in clinical trials (4) and should be suitable for a majority of patients.

For proper method and route of injection, see WARNINGS, PRECAUTIONS and DOSAGE AND ADMINISTRATION.

Intradermal Tests:


In most cases, injections should be given only after the first intradermal test reaction has subsided.

A number of factors beyond our control could reduce the efficacy of this product or even

See CLINICAL PHARMACOLOGY and INDICATIONS AND USAGE for further information

With respect to drug administration.

The most common site of injection is the lateral aspect of the upper arm. For proper method and route of injection, see WARNINGS, PRECAUTIONS and ADVERSE REACTIONS.

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

In Vivo allergen testing. Allergy.


In Vivo allergen testing. Allergy.
Schedule for Immunotherapy

Dr. *Patient* Venom Product Lot No.

<table>
<thead>
<tr>
<th>Dose No.</th>
<th>1 µg/mL</th>
<th>10 µg/mL</th>
<th>100 µg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.05 mL</td>
<td>0.10 mL</td>
<td>0.50 mL</td>
</tr>
<tr>
<td>2</td>
<td>0.10 mL</td>
<td>0.20 mL</td>
<td>1.00 mL</td>
</tr>
<tr>
<td>3</td>
<td>0.20 mL</td>
<td>0.40 mL</td>
<td>2.00 mL</td>
</tr>
<tr>
<td>4</td>
<td>0.40 mL</td>
<td>0.80 mL</td>
<td>4.00 mL</td>
</tr>
</tbody>
</table>

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

*See CAUTION Section in DOSAGE AND ADMINISTRATION: Immunotherapy.

Dilution Mixes:

1 part of 0.01 µg/mL + 9 parts = 0.001 µg/mL
1 part of 10 µg/mL + 9 parts = 1 µg/mL
0.2 mL of 10 µg/mL + 1.8 mL = 1 µg/mL

**CAUTION**

Skin testing should be carried out with all five individual venoms, since many patients react to a sting, patients should not be tested until 2 to 4 weeks after any sting.

Since the level of insect venom specific IgE is very low, skin testing is mandatory in all patients. Concentrations of 0.01 µg/mL or less are recommended to indicate a high level of sensitivity to the test venom.

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

In identifying those patients to be classified as extremely sensitive, individuals reacting to the prick test at the 1 µg/mL concentration should begin intradermal tests at concentrations of not more than 0.0001 µg/mL and proceed with weaker dilutions and smaller increments between doses in progressing to higher concentrations. The dose for the pediatric population is the same as for adults. (See PRECAUTIONS).

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

HollisterStier

Dr. Signature

(continued)

**REFERENCES**

6. Theophylline and/or corticosteroids may be used if necessary after adequate epinephrine therapy. Oxygen should be given by mask. Intravenous antihistamines, inhaled bronchodilators, steroids, and circulatory support have been given.