

- Perform a preliminary skin prick test with each preparation at the 1.0 µg/ml concentration, with the diluent as a negative control, and with histamine base at 1 mg/ml as a positive control. For most patients, all tests but the positive control should be negative. Patients reacting to the prick test at 1.0 of venom should be considered highly sensitive to the venom, and suitable precautions should be taken. If the positive control is negative, the possibility of skin non-reactivity must be considered.
- Begin intradermal testing with all venoms, starting at the 0.001 µg/ml dilution for all patients who did **not** react to the skin prick test, and at the 0.0001 µg/ml for highly sensitive patients.
- Read the test response after 15 minutes, and determine the degree of response to the injection, in comparison to the negative control. A suggested grading system appears in Table 2.

Table 2  
Skin Test Grading System

... Mean Diameters (cm) ...		
Grade	Wheal	Erythema
0	<0.5	<0.5
±	0.5-1.0	0.5-1.0
1+	0.5-1.0	1.1-2.0
2+	0.5-1.0	2.1-3.0
3+	1.0-1.5, pseudopodia	3.1-4.0
4+	>1.5, many pseudopodia	>4.0

- If the intradermal reaction is negative at the initial concentration, continue intradermal testing with tenfold increments in the concentration until a clearly positive response has been obtained or a concentration of 1 µg/ml has been tested, whichever occurs first. The use of venom concentrations greater than 1 µg/ml for intradermal testing is not recommended because of the risk of false-positive reactions<sup>4</sup>. If there is a positive response at concentrations of 0.01 µg/ml or less, the patient should be considered highly sensitive to the venom.

The interpretation of the skin response is based on the size of the wheal, the size of the erythema, and the appearance of irregular, spreading, pseudopod-like projections from the test area. The presence of the latter indicates marked hypersensitivity.

A patient is considered sensitive to the test extract if there is a reaction of 1 + or greater at a concentration of 1 µg/ml or less, providing that the 1 + reaction is in relation to the negative control.

If skin tests are negative in a recently stung patient, the skin testing should be repeated after two weeks have elapsed. For patients with negligible response to the histamine control, skin testing should be repeated after 72 hours.

**Treatment:**  
An allergic individual should be treated with each venom that provokes a positive skin test. If more than one Hymenoptera venom preparation is indicated, the different preparations should be given by separate injections. The mixed vespid preparation should not be substituted for single-venom treatments unless the patient is allergic to all three of the constituent venoms: yellow jacket, yellow hornet, and white faced hornet.

Administer the venom solution **subcutaneously**, using a suitable sterile syringe with 0.1 ml graduations and a 25-27 gauge 1/4 to 5/8 inch needle. The injections are typically given in the lateral aspect of the upper arm.

**Dosage Schedule:**  
Dosage of allergenic extracts is a highly individualized matter, and varies according to the degree of sensitivity of the patient, the clinical response, and tolerance of the extract administered previously.

The dosage schedule in Table 3 is based on the results of a clinical trial involving 103 patients, and is suitable for most patients. It should be noted, however, that the clinical trial incorporated a flexible dosage schedule that utilized

guidelines that were somewhat more aggressive in the starting dose and in the dosage increments in the early phases of immunotherapy than those recommended in Table 3 and that no single dosage schedule can be recommended for all patients. See Precautions above.

The safe administration of venom preparations does not differ in principle from the safe administration of other allergenic extracts. Increasing doses of venom are given at increments dependent on the patient's ability to tolerate the venoms, until a maintenance dosage is reached and maintained. The prescribed maintenance dosage is 100 µg per venom, and, since the efficacy of lower doses has not been established, it is considered extremely important that the patient be able to reach this dosage.

During the initial phases of immunotherapy, the patient may receive two or three injections of each venom per visit, spaced at 1/2 hour intervals, with dosage increments no greater than those shown in Table 3.

After each injection, the patient's skin reaction and overall response are evaluated to determine whether the next scheduled dose can be given. The conditions for proceeding to the next dose are as follows:

- If a single dose results in more than a moderate local reaction (>5.0 cm wheal) within 1/2 hour, no additional dose of the venom should be given during that visit, and the same dose should be repeated at the next visit – or visits – until the patient has tolerated it.
- If any systemic manifestation of sensitivity occurs during or following a visit, or if a single dose results in an excessive local reaction (>10 cm wheal) within 1/2 hour, no additional dose should be administered during the visit and the total dosage for the next visit should be reduced to half of the dose that caused the reaction.
- Delayed local reactions (occurring 24-48 hours after injection) are relatively common, and do not appear to predict difficulties with future doses. As a rule, therefore, dosage adjustment is not required in most instances. However, at the physician's discretion and for the comfort of the patient, if delayed large local reactions over 10 cm are reported, the subsequent dose should be held at the same level as the one causing the reaction.

The figures in Table 3 refer to treatment with a single venom. If a patient requires more than one venom preparation, the number of injections

per visit are increased to include the additional venom preparations.

Weekly visits are continued until the patient has received and tolerated two consecutive maintenance doses of 100 µg. Thereafter, the interval between doses can be increased by increments of one week, to a maximum of four weeks. Thereafter, monthly injections of 100 µg are to be continued indefinitely.

The use of the Table 3 regimen or a slightly modified dosage schedule may result in some form of mild to moderate allergic reaction in approximately 1/4 of the patients, but such reactions are typically not severe enough to warrant stopping the treatment.

The maintenance dose of 100 µg is recommended for both children and adults, and there is no evidence that any lower maintenance dose provides adequate protection. If a patient on maintenance therapy is stung and still has a systemic manifestation of sensitivity, the maintenance dosage of the relevant venom should be increased to 200 µg at no more than 50 µg increments.

**Duration of Treatment:** At the present time it appears necessary to continue maintenance injections indefinitely.

**Storage:** The freeze-dried venom preparations, the diluent, the reconstituted extract, and all dilutions should be kept refrigerated at 2-8°C. The maximal storage times for these materials are as shown in Table 4.

Table 4  
Recommended Shelf Life

Venom dosage Form	Recommended Shelf Life
Unreconstituted Freeze-Dried Powder	As shown on label
Reconstituted in HSA Diluent to a concentration of:	
100 µg/ml	Twelve months from date of reconstitution*
1.0-10 µg/ml	One month from the date of dilution*
0.1 µg/ml	Two weeks from the date of dilution*
<0.1 µg/ml	Prepare fresh daily.

\* But not to exceed the expiration date of the freeze-dried extract or of the source dilution.

Table 3  
Representative Treatment Schedule Using a Single Venom Preparation\*

Week No.	Day No.	Dose No. Per Day at 1/2 Hr. Interval	Concentration of Venom to be Used (µg/ml)	Volume to be Injected (ml)	Amount of Venom Injected (µg)	Conditions for Proceeding to Next Dose:
1	1	1	0.01	0.1	0.001	1. If a single dose results in more than a moderate local reaction (>5.0 cm wheal) within 1/2 hour, an additional dose should not be given during that visit. Repeat the same dose at the next visit - or visits - until tolerated.
		2	0.1	0.1	0.01	
		3	1.0	0.1	0.1	
2	8	1	1.0	0.1	0.1	
		2	1.0	0.5	0.5	
		3	10	0.1	1.0	
3	15	1	10	0.1	1	
		2	10	0.5	5	
		3	10	1.0	10	
4	22	1	100	0.1	10	
		2	100	0.2	20	
5	29	1	100	0.2	20	
		2	100	0.3	30	
6	36	1	100	0.3	30	
		2	100	0.3	30	
7	43	1	100	0.4	40	
		2	100	0.4	40	
8	50	1	100	0.5	50	
		2	100	0.5	50	
9	57	1	100	1.0	100	
Monthly		1	100	1.0	100**	

\* For the mixed vespid preparation, the total venom protein concentration and the total amount of venom protein injected will be triple the amounts shown, with no changes in injection volumes.

\*\* If a patient on maintenance therapy is stung and has any systemic manifestations of sensitivity, his maintenance dosage should be increased to 200 µg for the relevant venom, increasing at no greater than 50 µg increments.

The expiration date of thirty months for the unreconstituted, freeze-dried extract is based on stability data demonstrating that no significant loss of potency occurs after storage at 2-8°C for at least that period of time.

**How supplied**  
**Diagnostic Kit:** The diagnostic kit contains 5 vials of freeze-dried venom/venom protein extracts, one vial each of honey bee, yellow jacket, yellow hornet, white faced hornet, and wasp. When reconstituted with 1.2 ml of diluent, each vial contains 100 µg/ml of venom/venom protein.

**Treatment Kits:** The treatment kits contain 6 unit-dose vials of freeze-dried, venom/venom protein from either honey bee, yellow jacket, yellow hornet, white faced hornet, wasp, or mixed vespid. When reconstituted with 1.2 ml of diluent, each vial of single-venom preparations will contain 100 µg/ml of venom/venom protein, and the mixed vespid products will contain 300 µg/ml of venom/venom protein.

**Multi-dose Vials:** Multi-dose vials are single vials that contain enough venom/venom protein so that, when reconstituted as directed with 11 ml of diluent, will produce ten full maintenance doses. When reconstituted as directed with 11 ml of diluent, the multi-dose vials contain 100 µg/ml of venom protein for single-venom products, and 300 µg/ml for the mixed vespid product.

**HSA Diluent:** A diluent containing 0.03% human serum albumin (HSA), 0.9% sodium chloride, and 0.4% phenol should be used for reconstituting and diluting these preparations. This diluent is available in the US from ALK in vials containing 1.8 ml (packages of 100), or 30 ml (packages of 1 or 5) of diluent.

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**Warranty Statement**  
We warrant that this product was prepared according to the applicable regulations of the appropriate regulatory agency; that it is true to label; and that the contents of each unopened, undamaged container are sterile. We have no control over the conditions under which this product is used, the diagnosis of the patient, the dosage, the methods of administration or the handling of the product after it leaves our possession, and we do not warrant either a good effect or against an ill effect following use of this product.

The user of this product should be aware of the inherent danger of injecting any biological product and accept the risk of a serious anaphylactic reaction.  
The foregoing warranty is exclusive of all other warranties whether written, oral or implied (including any warranty of merchantability or fitness for use.)  
No representative of the company may change any of the foregoing, and the buyer hereby accepts the product subject to all the terms hereof.

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4/2006

## PRESCRIBING INFORMATION

### ALLERGENIC EXTRACTS HYMENOPTERA VENOM/VENOM PROTEIN

**Pharmalgen®**

- Honey Bee (*Apis mellifera*)
- Yellow Jacket (*Vespa* spp.)
- Yellow Hornet (*Dolichovespula arenaria*)
- White Faced Hornet (*Dolichovespula maculata*)
- Wasp (*Polistes* spp.)
- Mixed Vespid (Yellow Jacket, Yellow Hornet & White Faced Hornet)



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#### WARNING

**Hymenoptera venom preparations should be used only by or under the direction of physicians experienced in administering allergens to the maximum tolerated dose and only where adequate means for treating severe systemic reactions are immediately available.**

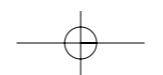
**Allergenic extracts may potentially elicit a severe life-threatening systemic reaction, rarely resulting in death<sup>1</sup>. Because of the possibility of severe systemic reactions, the patient should be instructed in the recognition of anaphylactic symptoms, observed in the office for at least 30 minutes after each injection, and warned to return to the office if symptoms of an allergic reaction occur.**

**Patients receiving beta-blockers may not be responsive to epinephrine or inhaled bronchodilators, and the risk of severely complicating the treatment of systemic reactions should be carefully considered before a decision to treat is reached.**

**Treatment with ACE-Inhibitors should be Stopped at least 24 hours Prior to injection due to An increased risk of anaphylactic reaction based on inhibition of the angiotensin metabolism.**

**All patients receiving venom immunotherapy should be instructed in the procedure for emergency self-injection of subcutaneous epinephrine. This self treatment might be necessary before patients have reached a maintenance dose of venom, and partially treated patients should be advised to carry an emergency epinephrine kit during the Hymenoptera season.**

**Before administering these venom preparations, physicians should be thoroughly familiar with the information in this insert, especially the Warnings, Precautions, and Adverse Reactions sections.**



### Description

Six sterile freeze-dried Hymenoptera preparations are available: honey bee venom, and yellow jacket, yellow hornet, white faced (bald faced) hornet, wasp, and mixed vespid venom protein. The mixed vespid preparation consists of equal amounts of yellow jacket, yellow hornet, and white faced hornet venom proteins.

Honey bees, yellow hornets, and white faced hornets are present primarily as the single species designated above, and the source material for those extracts is collected only from those species. There are a number of common species of yellow jackets and wasps in the environment, and those extracts reflect that variety and contain venom protein from a number of species. Information concerning the species included in the yellow jacket and wasp preparations is available on request from ALK customer service (1-800-252-9778; in TX and Canada, 203-877-4782).

Honey bee venom is obtained from live insects by an electric shock method. The other venoms are obtained from dissected venom sacs, which are crushed in a  $\beta$ -alanine/acetic acid buffer to release the venom. The sac residue is then removed by centrifugation and filtration. Allergenic components in the raw honey bee and yellow jacket venom materials have been described<sup>2, 3</sup>.

These extracts are available in freeze-dried form, and just prior to use, the contents of each vial should be reconstituted with HSA diluent (see How Supplied), using the volume specified on the vial label. When reconstituted as directed, the single-venom preparations will contain 100  $\mu\text{g/ml}$  of venom or venom protein, and the mixed vespid preparation will contain 300  $\mu\text{g/ml}$  of venom protein. This is the concentration from which full maintenance doses are typically drawn. Other ingredients in the solution reconstituted as directed with HSA diluent are 0.06% albumin human USP, 3.0% mannitol 0.9% sodium chloride, and 0.4% phenol. **All these preparations must be diluted before use in diagnosis or in the initial stages of treatment.**

### Clinical Pharmacology<sup>1</sup>

The mode of action of allergenic extracts is under investigation.

The skin test reaction occurring in previously sensitized individuals is probably related to the interaction of antigen with IgE antibody and the subsequent release of histamine from mast cells. The therapeutic action of allergenic extracts may be related to the production of IgG (blocking) antibodies. Effective immunotherapy with allergenic extracts is usually associated with a rise in serum levels of specific IgG. Immunotherapy also produces an initial rise in specific IgE levels, which then decrease as therapy continues.

### Indications and Usage

The Pharmedgen venom preparations are indicated for use in the diagnosis and treatment of Hymenoptera sting allergy. The following general considerations should be applied in determining the proper use of these preparations:

- Approximately two-thirds of adult patients with a history of sting anaphylaxis and a positive venom skin test but who do not receive immunotherapy will experience a systemic reaction if stung by the implicated insect again. These patients should receive therapy<sup>4</sup>. Children whose reactions have been limited to the skin have an approximately 10% risk of future reactions if stung and not immunized. The nature and severity of these reactions is in general similar to the original reaction and therefore children with this kind of history may not need venom therapy<sup>5</sup>.
- The risk of anaphylaxis following a future sting is unknown in patients who have been stung without experiencing a systemic reaction but who are currently venom skin test positive. At this time, no recommendation can be made that such patients receive venom immunotherapy, but they should be counseled on their condition and may benefit from instruction in the self administration of subcutaneously injected epinephrine. There is an approximately 10% risk of future systemic reactions if prior reactions have consisted of large delayed local reactions<sup>6</sup>. This risk must be considered in deciding

whether or not to recommend venom therapy.

- Patients with a history of serious systemic reaction to a sting but who are skin test negative to all five venoms are not candidates for therapy. It is not known whether such patients may be resensitized by future stings, and such patients should be retested after any subsequent sting.
- A small percentage of patients who have reached the maintenance dose suggested below, may still experience some degree of allergic response upon being stung by the implicated insect.

**Diagnosis:** The five individual Hymenoptera venom extracts present in the diagnostic kit (see How Supplied) are indicated for diagnostic skin testing of patients with a history of systemic reactions consistent with insect sting allergy<sup>7</sup>.

**Treatment:** The Hymenoptera venom extracts are indicated for immunotherapy in patients who have a history of a systemic reaction of any severity to a Hymenoptera sting and a positive skin test to one or more of the venoms. Therapy cannot be recommended in the absence of either of those conditions.

The single-venom extracts are intended for both diagnosis and immunotherapy; the mixed vespid product is intended for immunotherapy only.

Multiple venom preparations are indicated in patients with multiple skin test sensitivities.

### Contraindications

No absolute contraindications to venom immunotherapy are known.

However, the risk of serious systemic anaphylactic reactions to venom or any potent allergenic extract suggests a number of preexisting conditions that should be considered relative contraindications. Among those conditions are acute infections, immune disease, severe cardiac disease, and treatment with  $\beta$ -adrenergic antagonist drugs (beta-blockers) and angiotensin inhibitors (ACE-inhibitors). See also Warnings, Precautions, and Adverse Reactions.

### Warnings

See additional warnings given in the box at the beginning of this insert.

Some patients are highly sensitive to Hymenoptera venoms and, for such patients, it must be anticipated that even a small skin test dose could result in a serious systemic reaction. Adequate means to treat such reactions must be immediately available, including the following equipment<sup>8</sup>: stethoscope and sphygmomanometer; tourniquets, syringes, hypodermic needles, and large-bore (14 gauge) needles; aqueous epinephrine HCl, 1:1000; oxygen, intravenous fluids, and the equipment for administering them; oral airway; diphenhydramine or similar antihistamine; aminophylline and corticosteroids for intravenous injection; vasopressor.

Patients are most at risk of serious systemic reactions:

- During skin testing and the build-up to maintenance dose, before tolerance of the extract is established. Do not begin immunotherapy without establishing the appropriate initial dose by skin testing (see Dosage and Administration), and do not inject the undiluted extract concentrate at any time unless tolerance has been demonstrated.
- When changing to a freshly-reconstituted extract; all extracts lose potency over time, and a fresh extract could have an effective potency that is substantially greater than that of the old extract. Reduce the dose by at least 50% when switching a patient to a freshly-reconstituted extract; this is particularly important when the previous extract was near its expiration date.
- When changing to an extract from a different manufacturer. Processing and source materials may differ markedly among manufacturers, and extracts from different manufacturers should not be considered interchangeable. Such changes should not be made without establishing the proper dosage by skin testing.
- If an error in dosage occurs. Take care to properly prepare, label, store, and control all dilutions.

Observe the patient for at least 30 minutes after injection, and be alert for the signs of impending reaction. Make sure the patient understands that serious delayed reactions can occur later on, how to recognize them, and what to do if they occur.

Patients who are receiving beta-blocking medication are high-risk patients for immunotherapy, because systemic reactions to the extract may be more severe in such patients<sup>9</sup>, and because the beta-blocker may impair the ability to reverse the reaction<sup>10</sup>. In such patients, this risk should be carefully weighed before a decision to treat is reached.

Treatment with ACE-Inhibitors should be Stopped at least 24 hours Prior to injection due to An increased risk of anaphylactic reaction based on inhibition of the angiotensin metabolism<sup>12, 13, 14</sup>.

Do not inject this or any allergenic extract intravenously. Before injecting the extract subcutaneously, retract the plunger on the syringe slightly and verify that no blood enters the syringe. If it does, remove the syringe and repeat the procedure at a different site.

This and any allergenic extract should be temporarily withheld or its dosage reduced under any of these conditions<sup>11</sup>.

- When the patient has an unexpectedly severe local or any systemic reaction to the previous dose.
- If the patient is experiencing allergic symptoms such as rhinitis or asthma, or is ill with flu or infection accompanied by fever.
- If an unusually long time has passed since the previous injection.

Allergic patients differ widely in their sensitivity to this or any allergenic extract, and no single dosage regimen can be recommended for all patients. The treatment schedule described under Dosage and Administration, below, is suitable for the majority of patients, but is based on a rather rapid build-up to the maintenance dosage and will have to be adjusted for sensitive patients. Progression to the next higher dose requires tolerance of the previous one, and the regimen must be modified if any of the conditions described above occur. Such modifications should include weaker dilutions and smaller dosage increments.

### Precautions

**General:** It is not unusual for patients to be treated with multiple venom preparations simultaneously. Although the majority of patients receiving multiple venoms tolerate treatments as well as patients receiving a single venom, the theoretically greater risk of systemic reactions in patients receiving multiple venoms should be kept in mind.

Do not use the mixed vespid preparations for diagnosis; even though cross-reactivity among those three venoms is common, it is not universal and patients should not be treated with any venom to which they are not demonstrably sensitive.

Patient compliance is an important consideration in the decision to initiate immunotherapy with any potent allergenic extract. Therapy should not be initiated if in the judgement of the physician the patient cannot be depended upon to respond promptly and properly to an impending adverse reaction, or to report such reactions.

Care must be taken to control the preparation, labeling, storage, and use of dilutions. The ramifications of inadvertent overdosage are severe (see Warnings and Adverse Reactions), and so procedural safeguards such as training programs, color-coded labeling, storage controls, and auditing are recommended<sup>11</sup>.

As with the administration of any parenteral drug, observe all aspects of good sterile technique. In both testing and treatment, use a separate sterilized needle and syringe for each individual patient, to prevent transmission of hepatitis and other infectious agents from one person to another.

**Drug Interaction:** Patients who are receiving beta-blocking medication are high-risk patients for immunotherapy, because systemic reactions to the extract may be more severe in such patients<sup>9</sup>, and because the beta-blocker may

impair the ability to reverse the reaction<sup>10</sup>. The patient should not take antihistamines in the 72-hour period prior to skin testing, since the pharmacological actions of such drugs might interfere with the skin test response. Also, the concurrent use of an antihistamine might mask an otherwise observable reaction to an injection in patients who are on venom treatment.

**Carcinogenesis, mutagenesis, impairment of fertility:** No long term studies with this or any allergenic extract have been carried out to determine their effect on carcinogenesis, mutagenesis, or impairment of fertility.

**Pregnancy:** Pregnancy Category C. Animal reproduction studies have not been conducted with allergenic extracts. It is also not known whether allergenic extracts can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Allergenic extracts should be given to a pregnant woman only if clearly needed.

**Nursing mothers:** It is not known whether this drug is 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:** The Hymenoptera venom extracts are indicated for immunotherapy in children who have a history of a systemic reaction not confined to the skin, and a positive skin test to one or more of the venoms. The maintenance dose of 100  $\mu\text{g}$  is recommended for both children and adults. If the injection volume is too large for a small child to tolerate comfortably, then the injection volume may be split into multiple injections.

**Geriatric Use:** Clinical studies of venom extracts did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

### Adverse Reactions

**Severe anaphylactic reactions to this extract can occur in extremely allergic patients and at any dosage level. Do not use this extract unless you are prepared to deal with these reactions, and until you have read and understood the Warnings, Precautions, and Dosage and Administration sections of this insert.**

The most serious systemic reaction that can occur is anaphylactic shock, which, while rare, is life threatening and must be treated immediately. Among other systemic reactions that have occurred are laryngeal edema, fainting, pallor, bradycardia, hypotension, bronchospasm, angioedema, cough, sneezing, conjunctivitis, rhinitis, and urticaria.

Should a serious systemic reaction occur:

- Inject 0.3-0.5 ml of 1:1000 epinephrine into the opposite arm; this may be repeated every 5 to 10 minutes, as a succession of smaller doses is more effective and less dangerous than a single larger one. Use a smaller dose for infants and children, in the range of 0.01 ml/kg of body weight.
- Apply a tourniquet proximal to the injection site; loosen it at least every 10 minutes.
- Inject no more than 0.1 ml of 1:1000 epinephrine at the injection site, to delay the absorption of the remaining extract.

These measures will almost always reverse the reaction, but in the rare instances when they do not, then the full armamentarium of emergency medicine may be required, among them: direct laryngoscopy, direct current cardioversion, tracheotomy, and intracardiac injection of drugs<sup>8</sup>.

The occurrence of a severe systemic reaction to an injection of this extract does not contraindicate further therapy, but the next dose given should be reduced by at least 90%, and raised

very slowly thereafter. If a pattern of systemic reactions – even very mild ones – appears, then the benefits of continued treatment must be carefully weighed against the substantial demonstrated risk.

Local reactions, even relatively severe but transient redness, swelling and discomfort, are the normal physiologic response to the allergens and to the volume of the fluid injected, and in their milder form are evidence of the effectiveness of the therapy. Local reactions generally subside quickly and do not require treatment, but application of cold to the injection site or other symptomatic measures may be useful.

However, severe local reactions should be considered a warning of potential systemic reaction if that dosage is continued. Always reduce the dose substantially if such a local reaction occurs.

**Overdosage:** See Adverse Reactions section.

### Dosage and Administration

#### Reconstitution and Dilution:

A diluent containing 0.03% human serum albumin (HSA), 0.9% sodium chloride, and 0.4% phenol should be used for reconstituting and diluting these preparations.

Reconstitute each vial of freeze-dried venom material by drawing the amount of diluent specified on the label into a syringe, and transferring it to the vial of extract using aseptic technique. Swirl or rock the vial gently until all the material has gone into solution. Do not shake the vial or agitate it violently enough to cause the fluid to foam. **Note that a needle that has been inserted into a vial of venom must not be inserted into a stock bottle of diluent, or into a vial containing another type of extract.**

When reconstituted as directed on the label, the vial will contain 100  $\mu\text{g}$  of venom per ml (300  $\mu\text{g/ml}$  in the case of the mixed vespid preparation). This is the concentration from which the typical maintenance dose is drawn, but it is not suitable for testing or for the initial stages of immunotherapy.

To obtain the concentrations required for testing or the initial stages of immunotherapy, prepare serial ten-fold dilutions of the concentrate to achieve the concentrations specified in Table 1.

Take This Much Venom	At This Concentration	Add It To This Much Diluent	To Get This Much Venom	At This Concentration
0.2 ml	100 $\mu\text{g/ml}$	1.8 ml	2.0 ml	10 $\mu\text{g/ml}$
0.2 ml	10 $\mu\text{g/ml}$	1.8 ml	2.0 ml	1 $\mu\text{g/ml}$
0.2 ml	1 $\mu\text{g/ml}$	1.8 ml	2.0 ml	0.1 $\mu\text{g/ml}$
0.2 ml	0.1 $\mu\text{g/ml}$	1.8 ml	2.0 ml	0.01 $\mu\text{g/ml}$
0.2 ml	0.01 $\mu\text{g/ml}$	1.8 ml	2.0 ml	0.001 $\mu\text{g/ml}$
0.2 ml	0.001 $\mu\text{g/ml}$	1.8 ml	2.0 ml	0.0001 $\mu\text{g/ml}$

\*Note: For mixed vespid, the concentrations will be 3 times those shown.

The relatively small 0.2 ml volume conserves the original concentrate, and is convenient because sterile diluent is readily available in prefilled 1.8 ml volumes.

For each vial, record the date of reconstitution or dilution on the label. Then calculate the appropriate shelf life based on the information in Table 4, and write that on the label as well. Note that the calculated shelf life of a dilution must not exceed that of the concentrate from which it was made.

### Skin Testing:

Patients with relevant sting histories should be skin tested with appropriate concentrations of each of the five single Hymenoptera venom preparations (honey bee, yellow jacket, yellow hornet, white faced hornet, wasp).

The location for testing is usually the flexor surface of the forearm. Use aseptic technique and a separate, sterilized syringe and needle for each extract and each patient. For intradermal testing, introduce the needle into the superficial skin layers until the bevel is completely buried. Slowly inject approximately 0.05 ml.

The following skin testing protocol can be recommended:

- Reconstitute each of the five vials of a diagnostic kit using HSA diluent, and prepare serial dilutions such as those in Table 1.