PRODUCT MONOGRAPH

PHARMALGEN

Allergenic Extracts
Hymenoptera Venom/Venom Protein

Honey Bee (Apis mellifera)
Yellow Jacket (Vespula spp.)
Yellow Hornet (Dolichovespula arenaria)
White Faced Hornet (Dolichovespula maculate)
Wasp (Polistes spp.)
Mixed Vespid (Yellow Jacket, White Faced Hornet & Yellow Hornet)

Powder for solution, 100μg/mL for single-venom, 300μg/mL for the mixed vespid

Manufactured by:
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Table of Contents

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intradermal subcutaneous	Powder for solution/100 μg/mL for single-venom, 300 mg/μL for the mixed vespid	Mannitol, Human Serum Albumin, Phenol *For a complete listing see Dosage Forms, Composition and Packaging section.*

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

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 paper 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 1-800-663-0972 in Canada

Honey bee venom is obtained from live insects by an electric shock method. The other preparations are obtained from dissected venom sacs, which are crushed in a β-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 in the literature[2,3]

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 µg/mL of venom or venom protein, and the mixed vespid preparation will contain 300 µg/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 0.03% 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.

INDICATIONS AND CLINICAL USE

PHARMALGEN: Honey Bee (Apis mellifera), Yellow Jacket (Vespula spp.), Yellow Hornet (Dolichovespula arenaria), White Faced Hornet (Dolichovespula maculate), Wasp (Polistes spp.), Mixed Vespid (Yellow Jacket, White Faced Hornet & Yellow Hornet) is indicated for:

- Diagnosis and treatment of Hymenoptera sting allergy

The following general considerations should be applied in determining the proper use of these preparations:

1. 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[4]. Children whose reactions have been limited to the skin have approximately a 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[5].

2. 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 counselled on their condition and may benefit from instruction in the self-administration of intramuscularly injected epinephrine. There is an approximately 10% risk of future systemic reactions if prior

reactions have consisted of large delayed local reactions[6]. This risk must be considered in deciding whether or not to recommend venom therapy.

3. 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.

4. 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 are indicated for diagnostic skin testing of patients with a history of systemic reactions consistent with insect sting allergy[7].

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.

Geriatrics (> 65 years of age):

Allergenic extracts have not been studied systematically in various age groups (see WARNINGS AND PRECAUTIONS, Special Populations).

Pediatrics (> 5 years of age):

Allergenic extracts have been used in children greater than 5 years of age (see WARNINGS AND PRECAUTIONS, Special Populations).

CONTRAINDICATIONS

Hymenoptera venom is contraindicated in patients who have or are:

- Immune pathologic conditions such as immune complex and immunodeficiency diseases.
- Malignancy
- Unstable or severe chronic or severe seasonal asthma (FEV1 consistently under 70% of predicted value after adequate pharmacologic treatment)
- Diseases or conditions preventing the treatment of possible anaphylactic reactions, e.g. chronic heart and lung diseases, severe arterial hypertension and treatment with β-blockers
- Treated with tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs)
- Treated with ACE inhibitors

Also see **WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS.**

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Treatment should only be carried out by or under supervision of physicians experienced in specific immunotherapy and where full facilities for cardio-respiratory resuscitation are immediately available.
- Patients with asthma may be more susceptible to severe adverse reactions. (See **Contraindications**).
- The patient must be under observation for at least 30 minutes (longer in high risk patients) after having received an injection with PHARMALGEN.
- All patients receiving venom immunotherapy should be instructed in the procedure for emergency self-injection of epinephrine (See WARNINGS AND PRECAUTIONS).
- Severe fatal life-threatening systemic reactions including anaphylactic shock can occur with the use of PHARMALGEN (Ref. ADVERSE REACTIONS).
- Sterile technique should be ensured throughout. In order to avoid possible contamination it is advised that solutions, once made up, should be discarded after four hours.
- Avoid intra-vascular injection

Treatment with hymenoptera venom should be administered under the supervision of a physician experienced in specific immunotherapy.

Due to the risk of potentially fatal anaphylactic reactions, treatment with hymenoptera venom must be carried out in hospitals or clinics where full resuscitation equipment and drugs, including epinephrine for injection, are immediately available for use by adequately trained personnel.

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 (longer in the case of high risk patients or patients with a history of a previous systemic reaction) after each injection, and advised to seek immediate medical attention if symptoms of an allergic reaction occur.

The patient must be instructed that serious delayed reactions can occur later on, how to recognize them and to seek immediate medical attention if they occur.

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

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[8]: stethoscope and sphygmomanometer; tourniquets, syringes, hypodermic needles, and large-bore (14 gauge) needles; aqueous epinephrine 1:1000; oxygen, intravenous fluids, and the equipment for administering them; oral airway; diphenhydramine or similar antihistamine; aminophylline and corticosteroids for intravenous injection; vasopressor.

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 large dose. 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[8].

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 to 10% of the dose provoking the reaction, 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.

Patients who are receiving beta-blocking medication should not receive

immunotherapy, because systemic reactions to the extract may be more severe in such patients[9], and because the beta-blockers may impair the ability to reverse the reaction[10]. Patients receiving beta-blockers may not be responsive to epinephrine or inhaled bronchodilators. Concomitant use of PHARMALGEN and β-blockers is contraindicated.

ACE inhibitors may exacerbate the allergic response to insect venom, resulting in life threatening allergic reactions to insect stings or venom immunotherapy. Temporary discontinuation of ACE inhibitor treatment prior to venom immunotherapy (based on the half-life of the ACE inhibitor in question) may avoid this risk. ACE inhibitors that have prolonged half-lives require discontinuation for longer time periods. However, the risk of discontinuing treatment with an ACE inhibitor should be carefully balanced against the benefit of the allergy immunotherapy in patients with bee venom induced systemic reactions. Concomitant use of PHARMALGEN and ACE-inhibitors is contraindicated.

Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) potentiate epinephrine and increase the risk of cardiac arrhythmias (with possible fatal consequence). Use of tricyclic antidepressants and monoamine oxidase inhibitors may interfere with the treatment of anaphylaxis and therefore concomitant use of bee venom with these drugs is contraindicated.

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[11]:

- When the patient has and 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.

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 extract. The theoretically greater risk of systemic reactions in patients receiving multiple venom extracts should be kept in mind.

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

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 can be severe (see Warnings and Adverse Reactions). Procedural safeguards such as training programs, color-coded labeling, storage controls, and auditing are also recommended[11].

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.

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.

Carcinogenesis and Mutagenesis

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.

Immune

In patients with increased baseline serum tryptase levels and/or mastocytosis, the risk of systemic allergic reactions and the severity of these may be increased.

Patients suffering from mastocytosis may expect less efficacy compared with the general insect venom allergic population.

Special Populations

Pregnant Women:
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 Women:
It is not know 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.

Pediatrics (> 5 years of age):

The Hymenoptera venom extracts are indicated for immunotherapy in children (> 5 years of age) who have a history of a systemic reaction not confined to the skin, and a positive skin test to one or more of the venom extracts. The maintenance dose of 100 µg 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 (SEE DOSAGE AND ADMINISTRATION).

Geriatrics (> *65* years of age):

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.

Monitoring and Laboratory Tests

Patients receiving allergenic extracts should be kept under observation a minimum of 30 minutes so that any adverse reaction can be observed and properly handled. Airway obstruction in high risk patients can be monitored by peak flow measurements before and after administration of allergens.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Severe anaphylactic reactions to this extract can occur in extremely allergic patients and at any dosage level (see WARNINGS AND PRECAUTIONS).

The most severe systemic reaction that can occur is an anaphylactic shock, which is rarely observed in patients treated with venom immunotherapy. An anaphylactic shock is a life threatening reaction and must be treated immediately. Among other systemic reactions that can occur are laryngeal edema, fainting, pallor, bradycardia,

hypotension, bronchospasm, angioedema, cough, sneezing, conjunctivitis, rhinitis, and urticaria.

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 they 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.

Post-Market Adverse Drug Reactions

Adverse reactions are divided into groups according to the MedDRA-convention frequencies: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to ≤1/100), rare (≥1/10,000 to ≤1/1,000), very rare (≤1/10,000). Frequencies are based on clinical trials with immunotherapy products in general, and includes allergens from pollen, hymenoptera venom and animal hair and dander.

System Organ Class	Frequency[1]	Adverse Drug Reaction
Immune system disorders	Uncommon	Anaphylactic reaction
	Rare	Anaphylactic shock
Nervous system disorders	Very common	Headache
	Not known[2]	Dizziness, paraesthesia
Eye disorders	Common	Conjunctivitis
	Not known	Eyelid oedema
Ear and labyrinth disorders	Not known	Vertigo
Cardiac disorders	Not known	Palpitations, tachycardia, cyanosis
Vascular disorders	Common	Flushing
	Not known	Hypotension, pallor
Respiratory, thoracic and mediastinal disorders	Common	Wheezing, cough, dyspnoea
	Not known	Asthma, nasal congestion, allergic rhinitis, sneezing, broncospasms, throat irritation, throat thightness
Gastrointestinal disorders	Common	Diarrhea, vomiting, nausea, dyspepsia
	Not known	Abdominal pain
Skin and subcutaneous tissue disorders	Common	Urticaria, pruritus, rash
	Not known	Angioedema, erythema
Musculoskeletal and connective tissue disorders	Uncommon	Back pain
	Not known	Joint swelling, arthralgia
General disorders and administration site conditions	Very common	Injection site swelling
	Common	Injection site pruritus, injection site urticaria, discomfort, fatigue
	Not known	Pruritis, chest discomfort, chills, injections site erythema, injection site nodules, injection site pain, injection site discolouration, sensation of foreign body

[1] Not known: frequency cannot be estimated from the available data and is based on post marketing experience.

DRUG INTERACTIONS

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 and otherwise observable reaction to an injection in patients who are on venom treatment.

Concomitant treatment of beta-blocking drugs, tricyclic antidepressants and monoamine oxidase inhibitors (MAO-inhibitors) may interfere with treatment of an anaphylactic reaction. The effects of epinephrine may be potentiated by tricyclic antidepressants and monoamine oxidase inhibitors (MAO-inhibitors). The beta-stimulating effect of epinephrine can be inhibited by concomitant beta-blocking drugs.

Concomitant treatment with ACE inhibitors may aggravate an anaphylactic reaction.

Therefore, concomitant use of bee venom with these drugs is contraindicated.

DOSAGE AND ADMINISTRATION

Before administering these venom preparations, physicians should be thoroughly familiar with the information in this insert, especially the WARNINGS AND PRECAUTION and ADVERSE REACTION sections.

Dosing Considerations

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:

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

2. 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 µg/mL 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.

3. 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 the 0.0001 µg/mL for highly sensitive patients.

4. 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 1**.

Table 1
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

5. If the intradermal reaction is negative at the initial concentration, continue intradermal testing with ten-fold increments in the concentration until a clearly positive response has been obtained or a concentration of a 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[4]. If there is a positive response at concentrations of 0.01µg/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.

Recommended Dose and Dosage Adjustment

Treatment:
An allergic individual should be treated with each venom extract 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 a 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 2** 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 phase of immunotherapy than those recommended in **Table 2** and that no single dosage schedule can be recommended for all patients (See WARNINGS AND PRECAUTIONS).

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 extract, 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 product per visit, spaced at ½ hour intervals, with dosage increments no greater than those shown in **Table 2**.

After each injection, the patient's skin reaction and overall response are evaluated to determine whether the next scheduled dose can be given:

- If a single dose results in more than a moderate local reaction (>5.0 cm wheal) within ½ 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 ½ 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 reaction (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 2** refer to treatment with a single venom extract. If a patient requires more than one venom preparation, the numbers of injections per visit are increased to include the additional venom preparations.

Table 2

Representative Treatment Schedule Using a Single Venom Preparation*

Week No.	Day No.	Dose No. Per Day at ½ 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 2 3	0.01 0.1 1.0	0.1 0.1 0.1	0.001 0.01 0.1	1. If a single dose results in more than a moderate local reaction (>5.0 cm wheal) within ½ hour, an additional dose should not be give during that visit. Repeat the same dose at the next visit – or visits – until tolerated. 2. If systemic manifestations of sensitivity occur during or following a visit or a single dose results in an excessive local reaction (>10 cm wheal) within ½ hour, do not administer and additional dose during the visit and reduce the total dose for the next visit to half of the total that produced the reaction. 3. Delayed (24-48 hrs.) local reactions of <10 cm do not require adjusting the dose; for such reactions that are >10 cm, hold dose at previous level.
2	8	1 2 3	1.0 1.0 10	0.1 0.5 0.1	0.1 0.5 1.0	
3	15	1 2 3	10 10 10	0.1 0.5 1.0	1 5 10	
4	22	1 2	100 100	0.1 0.2	10 20	
5	29	1 2	100 100	0.2 0.3	20 30	
6	36	1 2	100 100	0.3 0.3	30 30	
7	43	1 2	100 100	0.4 0.4	40 40	
8	50	1 2	100 100	0.5 0.5	50 50	
9	57	1	100	1.00	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, the maintenance dosage should be increased to 200 µg for the relevant venom, increasing at no greater than 50 µg increments.

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 ¼ 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 has any systemic manifestations of sensitivity, the maintenance dosage should be increased to 200 µg for the relevant venom, increasing at no greater than 50 µg increments.

Administration

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.

Reconstitution and Dilutions:

		Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
Single Dose	Single venom	1 mL	1.2 mL	6 unit-dose	100 μg/mL
	Mixed Vespid	1 mL	1.2 mL	6 unit-dose	300 μg/mL
Multi Dose	Single venom	Multiple Dose Vial	11 mL	10 maintenance doses	100 μg/mL
	Mixed Vespid	Multiple Dose Vial	11 mL	10 maintenance doses	300 μg/mL

A special 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 re-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 μg of venom per mL (300 μg/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 for the initial stages of immunotherapy, prepare serial ten-fold dilutions of the concentrate to achieve the concentrations specified in **Table 3**.

Table 3: Dilution Chart for Single-Venom Preparations*				
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 µg/mL	1.8 mL	2.0 mL	10 µg/mL
0.2 mL	10 µg/mL	1.8 mL	2.0 mL	1 µg/mL
0.2 mL	1 µg/mL	1.8 mL	2.0 mL	0.1 µg/mL
0.2 mL	0.1 µg/mL	1.8 mL	2.0 mL	0.01 µg/mL
0.2 mL	0.01 µg/mL	1.8 mL	2.0 mL	0.001 µg/mL
0.2 mL	0.001 µg/mL	1.8 mL	2.0 mL	0.0001 µg/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 data 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.

Dose Reduction When Systemic Reactions Are Observed:

If a severe, systemic reaction occurs after injection, the treatment with PHARMALGEN should only be continued after careful consideration. If treatment is continued, it may be considered to reduce the following dose to 10% of the dose provoking the reaction.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre.

In case of overdose, the risk of systemic reactions increases. The patient must be observed and any reaction must be treated with the relevant symptomatic and supportive measures. Anaphylactic emergency kit must be immediately available.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

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[1]. 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 and initial rise in specific IgE levels, which then decrease as therapy continues.

Pharmacodynamics

Skin Test:
Superficial injection into the skin of a minute dose of specific allergen will produce a short-lived local reaction in subjects allergic to that allergen.

Treatment:
Escalating dosage according to the schedules described in the DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment section, encourages generation of blocking antibodies to such a level that protection from one or several sting may be developed. Resistance is sustained by maintenance doses.

Special Populations and Conditions

Pediatrics:

Refer to WARNINGS AND PRECAUTIONS Section.

Geriatrics:
Refer to WARNINGS AND PRECAUTIONS Section.

Duration of Effect

At the present time it appears necessary to continue maintenance injections indefinitely.

STORAGE AND STABILITY

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

Table 4
Maximal Recommended Shelf Life (2-8°C)

Venom dosage Form		Recommended Shelf Life
Unreconstituted Freeze-Dried Powder Reconstituted in HSA Diluent to a concentration of:		As shown on the label
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 of the source dilution.

SPECIAL HANDLING INSTRUCTIONS

Refer to **STORAGE AND STABILITY**.

DOSAGE FORMS, COMPOSITION AND PACKAGING

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 HSA 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 HSA 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 HSA 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 from ALK-Abelló in vials containing 1.8 mL (packages of 100), or 30 mL (packages of 1 or 5) of diluent.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Hymenoptera Venom/Venom Protein

Chemical name: Honey Bee (Apis mellifera)
Yellow Jacket (Vespula spp.)
Yellow Hornet (Dolichovespula arenaria)
White Faced Hornet (Dolichovespula maculate)
Wasp (Polistes spp.)

Product Characteristics

Freeze-dried Hymenoptera preparation of honey bees, yellow jacket, yellow hornets, white faced hornet, wasp, and mixed vespid venom protein. The mixed vespid preparations consist of equal amounts of yellow jacket, yellow hornet and white-faced hornet.

These extracts are available in diagnostic kit, treatment kits, and multi-dose vials. Just prior to use, the contents of each vial should be reconstituted with HSA diluent using the volume specified on the vial label.

DETAILED PHARMACOLOGY

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[1]. 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 and initial rise in specific IgE levels, which then decrease as therapy continues.

All contents of the previous Product Monograph for this section have been included in this revised (current) format.

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PART III: CONSUMER INFORMATION
PHARMALGEN
Allergenic Extracts
Hymenoptera Venom/Venom Protein

Honey Bee (Apis mellifera)
Yellow Jacket (Vespula spp.)
Yellow Hornet (Dolichovespula arenaria)
White Faced Hornet (Dolichovespula maculate)
Wasp (Polistes spp.)
Mixed Vespid (Yellow Jacket, White Faced Hornet & Yellow Hornet)

This leaflet is part III of a three-part "Product Monograph" published when PHARMALGEN was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PHARMALGEN. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
PHARMALGEN Allergenic Extracts are used for skin-test diagnosis of allergy and treatment of patients with history of allergy to specific bee, wasp, hornet and yellow jacket venom.

What it does:
Reduces symptoms associated with exposure to specific bee, wasp, hornet and yellow jacket venom.

When it should not be used:

- If you are allergic to any of its components (see "What the important nonmedicinal ingredients are").
- In persons with uncontrolled asthma
- In persons whose immune systems have a decreased ability to fight infection and disease, e.g. due to diseases such as leukemia, lymphoma, HIV infection or immunodeficiency syndromes
- In persons with severe infections
- In persons with severe or uncontrolled asthma
- In persons with chronic heart or lung disease or severe arterial hypertension
- In persons who are being treated with ACE inhibitors, β-blockers, tricyclic antidepressants or monoamine oxidase inhibitors (MAOIs)

What the medicinal ingredient is:
Allergenic Extracts, Hymenoptera Venom/Venom Protein

What the important nonmedicinal ingredients are:
Mannitol and Human Serum Albumin

What dosage forms it comes in:
Powder for injectable solution

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Intended for use only by physicians who are experienced in the administration of allergenic extracts and the emergency care of severe reactions (such as anaphylaxis), or for use under the guidance of an allergy specialist.
- Risk of severe reaction (including risk of potentially fatal anaphylactic reactions) in patients receiving beta blockers or ACE-inhibitors or tricyclic antidepressants or monoamine oxidase inhibitors; in those with uncontrolled asthma; or in patients with heart disease, mastocytosis (too many mast cells in your body) and/or increased tryptase levels prior to treatment.
- Patients should be monitored for at least 30 minutes after injection.
- Should not be injected into veins.

BEFORE you use PHARMALGEN talk to your doctor or pharmacist if:

- You have not been treated with venom allergenic extracts before.
- Emergency care of anaphylaxis is available at the treatment clinic.
- You are taking or have recently taken any medicines including medicines obtained without a prescription..
- You have any conditions mentioned above under Serious Warnings and Precautions.
- You have ever had a bad reaction to this injection or any medicines containing bee or wasp venom

INTERACTIONS WITH THIS MEDICATION

The following drugs may interfere with your allergy treatment: beta blockers, ACE inhibitors, tricyclic antidepressants, MAO inhibitors, antihistamines. Please inform your physician if you take any of these drugs. Before discontinuing any drugs you must consult your primary care physician to be placed on alternate medications prior to allergy treatment.

PROPER USE OF THIS MEDICATION

Usual dose:
When treatment with PHARMALGEN is initiated your physician will increase the dose of PHARMALGEN over time in order to find the appropriate dose.

Overdose:

For management of a suspected drug overdose, contact your regional Poison Control Centre.

Missed Dose:
Not applicable.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

You may have redness, swelling, or pain at the site after the injection. These symptoms usually start from 0 to 30 minutes after the injection and may not go away until the next day. To make you feel better, your doctor may ask you to put an ice pack on the injection site and take an antihistamine, like diphenhydramine (Benadryl is one brand name). Sometimes, the amount of your next dose may need to be changed.

A reaction that lasts longer than 24 hours also should be reported to the doctor.

Severe allergic reactions are less commonly observed. These reactions include:

- Sudden itching of the nose, eyes, throat, ears, or skin
- Shortness of breath or wheezing
- A lightheaded or dizzy feeling
- Tightness in the chest
- Hives or itchy palms

Systemic reactions can involve the entire body and most often occur within 30 minutes after the injection, but they may occur up to 24 hours after the injection. Should any of these symptoms occur, seek immediate medical attention.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical attention
		Only if severe	In all cases	
Common	Skin erythema (flushing of the skin)		✓	
	Urticaria (itchy rash)		✓	
	Pruritus (itchiness)		✓	
	Rhinitis (runny nose)		✓	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and seek immediate medical attention
		Only if severe	In all cases	
Uncommon	Swelling of the lips, face or tongue			✓
	Shortness of breath or wheezing			✓
	Extreme allergic reaction (anaphylaxis)			✓

This is not a complete list of side effects. For any unexpected effects while taking PHARMALGEN, contact your doctor or pharmacist.

HOW TO STORE IT

The freeze-dried venom preparations, the diluent, the reconstituted extract, and all diluents should be kept refrigerated at 2-8°C. Do not use after the expiration date shown on the vial label.

Reporting Suspected Side Effects

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

Report online at www.healthcanada.gc.ca/medeffect

Call toll-free at 1-866-234-2345

Complete a Canada Vigilance Reporting Form and:

Fax toll-free to 1-866-678-6789, or

Mail to:
Canada Vigilance Program
Health Canada
Postal Locator 0701D
Ottawa, Ontario
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting ALK-Abelló A/S at: 1-800-663-0972

This leaflet was prepared by ALK-Abelló A/S

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