1. NAME OF THE MEDICINAL PRODUCT

Diater Hymenoptera Venom 100 µg/ml powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Diater Hymenoptera Venom is a sterile lyophilised treatment of allergenic extracts of hymenoptera venoms to which the patient is sensitized, together with a reconstitution solvent (physiological saline solution with phenol).

The active substance consists of the allergen extract *Polistes spp.*:

Diater Hymenoptera Venom consists of three vials with different amounts of freeze-dried product:

	Vial 1 Green label	Vial 2 Yellow label	Vial 3 Red label
Hymenoptera Venom (Polistes spp.)	1.2 micrograms	12 micrograms	120 micrograms

After reconstitution with 1.2 ml of solvent the concentrations of the three vials are 1, 10 and 100 micrograms per ml, respectively.

Excipient(s) with known effect
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diater Hymenoptera Venom is indicated for the treatment of IgE-mediated hypersensivity in patients diagnosed with allergy to hymenoptera venom *(Polistes spp.*).

4.2 Posology and method of administration

Diater Hymenoptera Venom should always be prescribed by an allergy specialist.

General recommendation for dosage is (although the doctor could modify it):

1. **Initiation**: the aim is to increase the dose stepwise until the maximum recommended dose (100 µg), the maintenance dose, has been attained. Due to differing sensitivity towards allergens, the treatment of each patient must be monitored closely. The dosage must only be increased if the previous dose was full tolerated.

2. **Continuation**: it consists of the administration of the maximum recommended dose (100 µg) for a period of 3 to 5 years, as determined by the physician. It is important that Diater Hymenoptera Venom be used regularly throughout the treatment period for it to be effective.

Diater Hymenoptera Venom is a subcutaneous treatment.

For instructions on reconstitution prior to administration, see section 6.6.
Do not reconstitute subsequent vials until administration is complete.

This dosage should always be followed except when otherwise indicated by the physician:

InitiationTreatment

Check the package consists of eight vials of lyophilised and eight vials of reconstitution solvent. Always start treatment administration with the lowest numbered vial corresponding to the lowest concentration of lyophilised.

Conventional schedule

Injections will be administered at weekly intervals.

It is recommended that these doses be divided into two equal parts, administered 30 minutes apart, to avoid the possibility of adverse reactions.

DAY	VIAL	VOLUME TO INJECT	RECOMMENDED DOSE	ADMINISTRATION INTERVAL BETWEEN DOSES	ADMINISTRATION INTERVAL	DATE
Day 1	**No.1 Vial**	0.1 ml	0.1 µg	weekly		
Day 8	**No.2 Vial**	0.1 ml	1 µg	weekly		
Day 15	**No.2 Vial**	0.5 ml	5 µg	weekly		
Day 22	**No.3 Vial**	0.1 ml	10 µg	weekly		
Day 29		0.2 ml	20 µg	weekly		
Day 36		0.3 ml	30 µg	weekly		
Day 43	**No.3 Vial**	0.4 ml	40 µg	weekly		
Day 50		0.5 ml	50 µg	weekly		
Day 57	**No.3 Vial**	0.6 ml	60 µg	weekly		
Day 64	**No.3 Vial**	0.8 ml	80 µg	weekly		
Day 71	**No.3 Vial**	1 ml	100 µg	weekly		

The same No.3 vial reconstituted in Day 22 will also be used for the administration of the doses in Day 29 and 36; similarly the vial reconstituted in Day 43 will be used for the administration of the dose in Day 50 (see storage conditions after reconstitution and expiry in section 6.3).

Rapid schedule (grouped or cluster): 4 weeks to maximum dose

DAY	VIAL	VOLUME TO INJECT	RECOMMENDED DOSE	ADMINISTRATION INTERVAL BETWEEN DOSES	ADMINISTRATION INTERVAL	DATE
Day 1	**No.2 Vial**	1st Dose: 0.5 ml	5 µg	30 minutes	weekly	
	No.3 Vial	2nd Dose: 0.1 ml	10 µg			
Day 8		1st Dose: 0.2 ml	20 µg	30 minutes	weekly	
		2nd Dose: 0.3 ml	30 µg			
Day 15	**No.3 Vial**	1st Dose: 0.5 ml	50 µg	30 minutes	2 weeks	
		2nd Dose: 0.5 ml	50 µg			
Day 29	**No.3 Vial**	1 ml	100 µg	monthly		
Day 59	**No.3 Vial**	1 ml	100 µg	monthly		

This schedule is intended to be exclusively administered in hospitals.

The same No.3 vial reconstituted in Day 1 used for the administration of the second dose of that day should also be used for the administration of the two doses in Day 8 (see storage conditions after reconstitution and expiry in section 6.3).

Rapid schedule (grouped or cluster): 3 weeks to maximum dose

DAY	VIAL	VOLUME TO INJECT	RECOMMENDED DOSE	ADMINISTRATION INTERVAL BETWEEN DOSES	ADMINISTRATION INTERVAL	DATE
Day 1	**1 No.2 Vial**	1st Dose: 0.5 ml	5 µg	30 minutes	weekly	
	1 No.3 Vial	2nd Dose: 0.1 ml	10 µg			
		3rd Dose: 0.2 ml	20 µg			
		4th Dose: 0.2 ml	20 µg			
Day 8	**1 No.3 Vial**	1st Dose: 0.5 ml	50 µg	30 minutes	2 weeks	
		2nd Dose: 0.5 ml	50 µg			
Day 22	**1 No.3 Vial**	1 ml	100 µg	monthly		
Day 52	**1 No.3 Vial**	1 ml	100 µg	monthly		

This schedule is intended to be exclusively administered in hospitals.

The same No.3 vial reconstituted in Day 1 should be used for the administration of the second, third and fourth doses of that day (see storage conditions after reconstitution and expiry in section 6.3).

Continuation Treatment

Check the package consists of five vials of lyophilised No. 3 and five vials of reconstitution solvent.

Once the maintenance dose is reached with any type of dosage (100 µg or the maximum concentration tolerated by the patient), the interval between administrations will be gradually increased to 2, 3 and 4 weeks, and this monthly interval will be maintained until the end of treatment for 3-5 years.

DAY	VIAL	VOLUME TO INJECT	RECOMMENDED DOSE	ADMINISTRATION INTERVAL BETWEEN DOSES	ADMINISTRATION INTERVAL	DATE
Day 85	**No.3 Vial**	1 ml	100 µg	3 weeks		
Day 106	**No.3 Vial**	1 ml	100 µg	monthly		
Day 134	**No.3 Vial**	1 ml	100 µg	monhly		
Day 162	**No.3 Vial**	1 ml	100 µg	monthly until the end of treatment		

The length of the treatment will be determined by the physician.

Discontinuation of treatment with increase of the recommended interval between doses

In the event that the interval between doses recommended by your specialist doctor is exceeded during treatment, it is important that you consult you doctor before continuing with the treatment, so that he/she can consider reducing the dose compared to the previous dose administered.
The steps to be taken when the recommended dosing interval is exceeded are given below as a guideline, although the decision to modify the schedule should be taken by the specialist doctor.

Exceeded interval	Recommended dose reduction
Up to 8 weeks	Continue with the same dose

Paediatric population

The safety and efficacy of Diater Hymenoptera Venom in paediatric population has not been stablished.

In this case, the doctor should have experience in treatment of allergic diseases in children. However, treatment with subcutaneous immunotherapy in children is widely supported by scientific publications. Patient selection should be made carefully considering the expected level of efficacy in this age group (see section 5.1).

Method of administration

Diater Hymenoptera Venom is intended for subcutaneous administration.

It is very important to follow the instructions before using Diater Hymenoptera Venom:

- Always begin the administration of the treatment with the lowest numbered vial corresponding to the one with the lowest concentration.
- Shake the vial gently before each extraction.
- Proceed to extract the treatment doses.
- Ensure that the route of administration is subcutaneous. The injections will be made in the upper dorsal part of the arm, 20 cm above the elbow, alternating between the arms for each administration, making sure not to administer intravenously.
- Proceed in the same way as appropriate with the following vials, always in increasing order (numbering).

After each dose is applied, the patient must remain at least 30 minutes in the centre where the extract has been administered.

For the treatment to be effective it is important that Diater Hymenoptera Venom is administered regularly throughout the treatment period. Do not administer a double dose to compensate missed doses.

Diater Hymenoptera Venom must be reconstituted before administration. For instructions on reconstitution the medicinal product before administration, see section 6.6.

4.3 Contraindications

The use of subcutaneous immunotherapy with Diater Hymenoptera Venom is contraindicated in the following cases:

- Hypersensitivity to any of the excipients listed in section 6.1.
- Severe or non-controlled asthma.
- Active autoimmune disorders (without response to treatment).
- Active malignant neoplasias.
- Children (<5 years old).
- Pyrexia.
- HIV infection in the case of being in the AIDS stage.
- Immunotherapy treatment should not be started during pregnancy.

An exception to these contraindications is made for patients who suffered life-threatening reactions after an insect sting, where the risk-benefit ratio of the treatment must be assessed, and precautions taken (Kosnik & Korosec 2015).

Literature references

- Mitja Kosnik & Peter Korosec (2015) Venom immunotherapy: clinical efficacy, safety and contraindications, Expert Review of Clinical Immunology, 11:8, 877-884.
- Pitsios C et al. (2015) Clinical contraindication to Allergen immunotherapy: an EAACI Position Paper. Allergy; 70: 897-909.
- Sturn G.J. et al. (2017) EAACI Guidelines on allergen immunotherapy: Hymenoptera venom allergy. Allergy, 73(4): 744-764.

4.4 Special warnings and precautions for use

Diater Hymenoptera Venom should be used with caution, after appraisal of the individual benefit/risk in the following cases:

- Patients with partially controlled asthma. In patients with partially controlled asthma, stabilization is recommended prior the onset of the immunotherapy.
- Children from 2 to 5 years old, given the limited cooperation and the less clinical experience with this age group.
- Patients being treated with beta-blockers (see section 4.5).
- Patients with any pre-existence cardiovascular disease (i.e., ischemic cardiopathy or heart arrhythmia). The cardiac status and the patient tolerability should be assessed in the face of an anaphylactic episode and the use of adrenaline.
- Patients with elevated serum levels of basal tryptase and/or mastocytosis.
- Autoimmune or organ-specific disease in remission. The effect of immunotherapy on the underlying disease is unknown.
- Primary/secondary acquired immunodeficiencies or immunosuppressors use (other than anti-IgE treatments). Its impact on the effectiveness of immunotherapy is unknown.
- Chronic infectious diseases (i.e., Hepatitis B or C).

- Anamnesis of severe systemic reactions to immunotherapy due to the increased risk to the development of new systematic reactions.
- Low adherence.
- Psychiatric/mental disorders that prevents adequate treatment compliance. The patient should be in any case well controlled on the onset of the immunotherapy.

In general, clinical experience with immunotherapy in patients over 65 years of age is limited. In these patients, the presence of comorbidities and concomitant medications as described above should be taken into account.

In children with concomitant asthma and acute upper respiratory tract infection, treatment with Diater Hymenoptera Venom should be temporarily discontinued until the infection has cleared.

The recommended rapid schedules (cluster) are exclusively for hospital use (Gutiérrez Fernández 2013).

In exceptional cases, this treatment may involve a risk of generalised reactions that are sometimes serious (urticaria, asthma, anaphylactic shock, etc.). Therefore, the following recommendations should be followed throughout the duration of the treatment:

- It is of the utmost importance that healthcare personnel should read the administrations requirements carefully before administrating this medicine.
- The allergenic extract should always be administered under medical supervision.
- The allergenic extracts should only be applied if there are immediately accessible resources to treat a patient that may suffer a generalised reaction (urticaria, asthma, anaphylactic shock, etc.) such as intramuscular adrenalin or other resources. This is the reason why these treatments must be carried out in adequately equipped physician's surgeries, primary care centres, clinics, or hospitals. They should not under any circumstances be administered in the patient´s home.
- After all, and each dose is applied, the patient should stay at the health centre where the allergenic extract is administered for at least 30 minutes.
- If any adverse reaction appears, the risk should be appraised by a physician before continuing the treatment.
- It is essential for the patient to be monitored on a regular basis by the physician issuing the prescription, who is responsible for any necessary dilutions of the extract or other alteration in the treatment.

Diater Hymenoptera Venom is a treatment for subcutaneous administration, It is necessary to ensure that it is not administered intramuscularly or intravenously.

It is recommended that doses are divided into two equal parts, administered with an interval of 30 minutes, to avoid the possibility of adverse reactions.

A mild-moderate local reaction is considered when the papule (redness/swelling) at the injection site is less than 10 cm in diameter. In this case, no dose adjustment would be necessary and the specialist physician should assess the need for symptomatic treatment.
If the size is >10 cm, it is considered to be an extensive local reaction and the specialist physician should establish the symptomatic treatment considered, and should consider possible treatment modifications (e.g., splitting the dose between both arms). (EAACI Allergen Immunotherapy Alvaro-Lozano, et al. User's Guide 2020).

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially "sodium free".

It is advised not to make violent movements or exercise the first few hours after administration of the dose.

Litrerature references

- Pitsios C. *et al*. (2015) Clinical contraindications to allergen immunotherapy: an EAACI position paper. Allergy; 70: 897–909.
- Roberts G. *et al.* (2017) EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. Allergy; 1-34
- Alvaro-Lozano M. et al. EAACI Allergen Immunotherapy User's Guide. Pediatr Allergy Immunol. 2020;31 Suppl 25(Suppl 25):1-101. doi:10.1111/pai.13189.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

The concomitant use with symptomatic anti-allergic medicaments (e.g., antihistamines, corticosteroids) may increase tolerance of the patient to immunotherapy.

The use of beta-blockers should be considered, as in case of anaphylaxis it would interact with the emergency medication and would increase the risk of more severe systemic reactions. When feasible, beta-blockers should be substituted with an alternative (Pitsios *et al.*, 2015).

There are no clinical experience data regarding treatment with Diater Hymenoptera Venom and administration of prophylactic vaccines for infectious diseases (e.g., influenza, tetanus...). It is recommended as a precaution that prophylactic vaccines are administered in the maintenance phase and at least 7 days after the last dose of Diater Hymenoptera Venom, with the next maintenance dose administered at least 2 weeks later (Pfaar O. Allergol Select., 2022).

Literature references

- Pitsios C. *et al*. (2015) Clinical contraindications to allergen immunotherapy: an EAACI position paper. Allergy; 70: 897–909.
- Alvaro-Lozano M, Akdis CA, Akdis M, et al. EAACI Allergen Immunotherapy User's Guide. Pediatr Allergy Immunol. 2020
- Pfaar O. Allergol Select. 2022.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of these allergenic extracts/matabolites in pregnant women. Starting an allergen immunotherapy treatment, including Diater Hymenoptera Venom, should not be indicated during pregnancy.

Lactation

It is unknown whether these allergenic extracts/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded.

Fertility

There is not information concerning the safety of the medicine in fertility.

4.7 Effects on ability to drive and use machines

Diater Hymenoptera Venom has no or negligible influence on the ability to drive and use machines.

Undesirable effects

Summary of the safety profile

Reactions occurring in association with Diater Hymenoptera Venom treatment are usually due to an immunological reaction (local and/or systemic) to the wasp venom. Local reactions consist of the appearance of pruritus, urticaria, warmth, pain, oedema or inflammation at the injection site.

Symptoms of an immediate reaction appear during the first 30 minutes after injection. Symptoms of a delayed reaction appear during the first 24 hours after injection.

The swelling/erythema of the injection site is normal, it is considered mild-moderate if it does not exceed 10 cm in diameter and the treatment decision is left to clinical judgement. In case of a local reaction larger than 10 cm, a local reaction is considered extensive and the use of oral antihistamines and/or topical corticosteroids is advised. The measures and/or medicines indicated by the physician should be followed.

In general, systemic reactions consist of rhinitis, (rhino-)conjunctivitis, nasal obstruction or nasal congestion, rhinorrhea, sneeze, erythema, pruritus, paresthesia, angioedema, lip oedema or palpebral oedema, wheezing, dyspnoea, cough, hypoventilation or breathing difficulty, dysphagia, chest discomfort, hypotension, dizziness, pyrexia, headache and general malaise, which usually appear between 15 minutes and 4-6 hours after the subcutaneous injection.

In case of bronchospasm, it is recommended the use of bronchodilators. Exceptionally, this product could produce asthma, general urticaria, anaphylaxis, anaphylactic reaction.

Tabulated list of adverse reactions

Within the classification by organs and systems, adverse reactions identified during the marketing period are listed by frequency (number of patients who it is expected will experience the reaction), using the following category: frequency not known (cannot be estimated from available data).

Classification by organs and systems	Frequency	Adverse Reaction
Immune system disorders	Not known	Anaphylaxis, anaphylactic reaction, anaphylactic shock
Nervous system disorders	Not known	Paraesthesia, dizziness, headache
Eye disorders	Not known	Palpebral oedema, allergic rhinoconjunctivitis, allergic conjunctivitis
Vascular disorders	Not known	Hypotension
Respiratory, thoracic and mediastinal disorders	Not known	Dyspnoea, cough, bronchospasm, asthma, wheezing, allergic rhinitis, rhinorrhoea, nasal obstruction or congestion, sneezing, hypoventilation, or shortness of breath
Gastrointestinal disorders	Not known	Lip oedema, dysphagia
Skin and subcutaneous tissue disorders	Not known	Urticaria, pruritus, angioedema, erythema (including generalized)

Classification by organs and systems	Frequency	Adverse Reaction
General disorders and administration site conditions	Not known	Reactions at the injection/vaccination site (including erythema, urticaria, pruritus, papule, warmth, pain, oedema or swelling); peripheral oedema or swelling, chest discomfort, malaise, pyrexia

Description of adverse reactions

If the patient experiences significant adverse reactions from treatment, allergy medication should be prescribed at the discretion of the specialist.

This medicine may produce severe anaphylactic reactions, including anaphylactic shock, which is considered a class effect of immunotherapy. Therefore, as an important precautionary measure, treatment should be supervised by a physician and in a suitable environment (see sections 4.2 and 4.4).

A doctor should be contacted immediately in case of severe systemic reactions (e.g., difficulty in swallowing or breathing). In some cases, severe anaphylactic reactions (e.g., anaphylactic shock including hypotension, tachycardia and even unconsciousness) may occur.
In these cases, treatment should be stopped permanently, or until recommended by the physician.

Paediatric population

In general, the undesirable effects observed in children and adolescents treated with Diater Hymenoptera Venom is similar to that observed in adults.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

Literature references

- Pfaar O, Bachert C, Bufe A,. *et al*. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases Allergo J Int. 2014;23(8):282-319.
- Alvaro-Lozano M. et al. EAACI Allergen Immunotherapy User's Guide. Pediatr Allergy Immunol. 2020;31 Suppl 25 (Suppl 25): 1-101. doi:10.1111/pai.13189.
- Roberts G. et al. (2017) EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. Allergy; 1-34.

4.9 Overdose

If the delivered dose is higher than recommended daily dose, it may increase the risk of adverse reactions, including the risk of systemic reactions or severe local reactions. In these cases, treatment should be permanently suspended or until the physician’s recommendation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Group V (Various), ATC code: V01AA07. Insects

Mechanism of action

Recent evidence has provided a plausible explanation for the multiple mechanisms of specific immunotherapy (SIT), which induces rapid desensitisation and long-term allergen-specific immune tolerance, as well as suppression of allergic inflammation in affected tissue. The described mechanism includes the modification of the presentation of the allergen by dendritic cells, that in turn modify the phenotype of allergen-specific T lymphocytes, switching from a Th2 type response, typical of allergic inflammation, to a Th1 type response. An important role is played by allergen-specific T regulatory (Treg), which produce suppressive cytokines such as IL-10 and TGF-beta (Incorvaia, 2013). The induction and increase in the secretion of IL-10 by SIT apparently regulates against allergen specific IgE and this simultaneously increases the production of IgG4. Consequently, IL-10 not only generates tolerance in T lymphocytes but regulates the formation of specific isotypes and influences the IgE-specific response to a dominant IgG4 production (Akdis & Akdis, 2007). Evidence suggests important biological effects of allergen specific IgG4. These effects include the post-immunotherapy serum IgG-dependent ability to inhibit the binding of IgE-allergen complexes to B-cells, the blocking of subsequent IgE-facilitated allergen presentation and the activation of allergen-specific T lymphocytes, and the prevention of allergen-IgE activation of peripheral basophils.

Clinical efficacy and safety

Studies on the clinical efficacy of immunotherapy against hymenopteran venom show a decrease in the severity of allergic reactions after re-exposure to the venom. In some cases, no systemic reaction was triggered, but even in those patients who did react, the symptoms were mostly mild and much less severe than before the immunotherapy, indicating at least a partial efficacy of the treatment. Of patients treated with immunotherapy, only 0-9% of individuals allergic to wasps reacted after a sting, but the percentage rises to around 20% in those allergic to bee venom (Bonifazi *et al.*, 2005). This protection is maintained in most patients until years after the end of treatment, with only 5-15% of systemic reactions after 5-13 years (Krishna *et al.*, 2011).

With the commonly used schedules, weeks or months are required to reach the maximum dose (100 µg normally) with the conventional schedule, while the rapid schedule only needs a few days and the ultrafast schedule a few hours. The risk of systemic reactions usually increases with the speed of the schedule, although some trials suggest that the rapid schedule is as safe as the conventional schedule (Krishna *et al.*, 2011). The severity and number of systemic reactions is more related to the type of venom than to the type of schedule used in immunotherapy. Bee venom treatment has more systemic reactions than wasp venom. In the literature there is a wide range (0-46%) in the incidence of adverse reactions attributable to immunotherapy treatment with hymenopteran poisons (Bonifazi *et al.*, 2005).

In a multicentre study conducted with 840 patients (Mosbech *et al.*, 2000), 20% of the patients had adverse reactions (1.9% of injections during the initiation phase and 0.5% during the continuation phase). The vast majority of reported reactions were mild and only one third required medical treatment.

Paediatric population

Children can be given immunotherapy treatment with hymenoptera venom, as the safety of this is equal to or even better than in adults. The efficacy of immunotherapy against hymenoptera venom in children is similar to or better than that found in adults, with 2.8-9% of patients not responding to treatment (Bonifazi *et al.*, 2005), as is the duration of protection after treatment with only 5% of systemic reactions after 10-15 years in children (Krishna *et al.*, 2011).

Treatment is only recommended for children who have suffered severe systemic reactions to an insect sting, because they are likely to suffer the same reaction on subsequent occasions and are therefore at risk, but not for those with non-severe systemic reactions.

Literature references

- Incorvaia, C. (2013). "Preventive capacity of allergen immunotherapy on the natural history of allergy." J Prev Med Hyg 54(2): 71-74.
- Akdis, M. and C. A. Akdis (2007). "Mechanisms of allergen-specific immunotherapy." J Allergy Clin Immunol 119(4): 780-791.
- Bonifazi, F., Jutel, M., Biló, B. M., Birnbaum, J., Muller, U. and the EAACI Interest Group on Insect Venom Hypersensitivity (2005), Prevention and treatment of hymenoptera venom allergy: guidelines for clinical practice. Allergy, 60: 1459–1470.
- Krishna, M. T., Ewan, P. W., Diwakar, L., Durham, S. R., Frew, A. J., Leech, S. C. and Nasser, S. M. (2011), Diagnosis and management of hymenoptera venom allergy: British Society for Allergy and Clinical Immunology (BSACI) guidelines. Clinical & Experimental Allergy, 41: 1201–1220.
- Mosbech H, Müller U. Side-effects of insect venom immunotherapy: results from an EAACI multicenter study. Allergy 2000; 55: 1005-1010.

5.2 Pharmacokinetic properties

No information is available on the pharmacokinetic properties of Diater Hymenoptera Venom. Pharmacokinetic studies of immunotherapy products with specific immunotherapy are not possible because the concentration of active substance in the plasma is too low to be determined due to the nature of the product (CHMP/EWP/18504/2006).

Literature references

- Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases. CHMP/EWP/18504/2006.

5.3 Preclinical safety data

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Reconstitution solvent
Phenol
Sodium chloride
Water for inyection

6.2 Incompatibilities

Compatibility studies have not been performed. In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Do not use after the expiry date stated on the label.

After reconstitution
Store in a refrigerator (2°C-8°C). Do not freeze.

Shelf life after reconstitution is as follows:

- Vial 1 (1 µg/ml): 1 day
- Vial 2 (10 µg/ml): 1 day
- Vial 3 (100 µg/ml): 3 months

Keep the original package. Avoid prolonged exposure to high temperatures.

6.4 Special precautions for storage

Do not store above 25ºC. Do not freeze.

Store in original packaging.

Do not use Diater Hymenoptera Venom if you notice loss of contents of the vials or deterioration in the container.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Glass vial (Type I), with rubber stopper (Type I) and aluminium flip-off.

Diater Hymenoptera Venom consists of two presentations which are the initiation treatment and continuation treatment.

Initiation Treatment

Pack containing eight vials with the active substance (1-2-2-3-3-3-3-3) and eight vials with the reconstitution solvent.

	Vial	**No. vials**	**Strength of active substance**	**Volume**
Active substance *Polistes spp*	No. 1 Green label	1 vial	1.2 µg	-
	No. 2 Yellow label	2 vials	12 µg	-
	No. 3 Red label	5 vials	120 µg	-
Solvent for reconstitution	Grey label	8 vials	-	1.7 ml

Continuation treatment

Pack containing five vials with the active substance (3-3-3-3-3-3) and five vials with the reconstitution solvent.

	Vial	**No. vials**	**Strength of active substance**	**Volume**
Active substance *Polistes spp*	No. 3 Red label	5 vials	120 µg	-
Solvent for reconstitution	Grey label	5 vials	-	1.7 ml

5 ml syringes for reconstitution and 1 ml single-use syringe are included to ensure sterile conditions for administration and to facilitate dosing.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Do not use this medicine if you notice any visible sign of deterioration.

Reconstitution of the medicinal product

The product must be reconstituted prior to use. Withdrawn 1.2 ml from one of the reconstitution solutions and slowly added to the corresponding vial containing lyophilised extract according to the indicated administration schedule.

5 ml syringes for reconstitution and 1 ml syringe for single use are included to ensure sterile conditions during administration and to facilitate dosage. In their absence, 1 ml insulin or tuberculin syringes must be used, perfectly balanced, and graduated in tenths of a millilitre. The needles must be subcutaneous, 4/10 mm gauge.

Shake gently until a homogeneous solution is observed.

Shake the vial gently before each extraction.

Once the vials have been reconstituted, they must be used within the validity period indicated for each vial. Do not reconstitute the following vials until appropriate.

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

November 2023