1. NAME OF THE MEDICINAL PRODUCT

Diater Polymerized solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Diater Polymerized is an immunotherapy treatment (vaccine), consisting of allergenic extracts to which the patient is sensitized, for subcutaneous administration for the treatment of allergic conditions.

Diater Polymerized is prepared individually for each patient because each person manifests a different sensitivity to certain substance called allergens. The doctor is responsible for assessing the composition of Diater Polymerized in each case.

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

3. PHARMACEUTICAL FORM

Solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diater Polymerized is used for the treatment of allergic conditions such as rhinitis, rhino-conjunctivitis or seasonal or perennial bronchial asthma.

4.2 Posology and method of administration

Posology

Diater Polymerized is intended for subcutaneous use.

Treatment consists of two phases: initial phase and continuation phase. The general recommended schedule is (although the physician can modify it according to its therapeutic criterion):

1. **Initiation:** the aim is to gradually increase the allergen dose until the maximum recommended dose (0.5 ml) is reached, which will be considered the maintenance or continuation dose. Due to differing sensitivity towards allergens, the treatment of each patient should be monitored by his/her physician who may consider adjustments in the treatment. The dose should be increased only if the previous dose was well tolerated. There are different starting schedules for immunotherapy.

2. **Continuation:** in which the maximum recommended dose (0.5 ml) is injected monthly, usually for a period of 3 to 5 years, as determined by the physician.

The blank spaces in the administration booklet (tables in leaflet and summary of product characteristics) are intended for a dosage repetition or other modifications in the dosage or the schedule prescribed by the physician.

Two administration schedules are recommended: the conventional schedule, in which the allergen concentration is progressively increased, and the cluster schedule, in which the treatment begins with the maximum allergen concentration.

The following schedules should be followed except in case the physician indicates otherwise:

Starting phase

Outpatient schedule:

Check first that the package consists of two or three vials of Diater Polymerized (depending on physician criteria). Always start the administration by the lower numbered vial which corresponds to the lower concentration of polymerized.

Schedule 1:
Injections will be administered at weekly intervals, except once the maximum recommended dose is reached, in which the treatment will be administered monthly.

DAY	VIAL	RECOMMENDED DOSE	ADMINISTRATION INTERVAL	DATE
Day1				
	3 Red label	0.2 mL	weekly	
Day 8				
	3 Red label	0.5 mL	weekly	
Day 38				
	3 Red label	0.5 mL	weekly	

Schedule 2:
Always start treatment with the lowest numbered vial corresponding with the lowest polymerised concentration.

Injections will be administered at weekly intervals, except once the maximum recommended dose with the vial number 3 is reached, in which the treatment will be administered monthly.

DAY	VIAL	RECOMMENDED DOSE	ADMINISTRATION INTERVAL	DATE
Day 1				
	1 Green label	0.5 mL	weekly	
Day 8				
	2 Yellow label	0.5 mL	weekly	
Day 15				
	3 Red label	0.5 mL	weekly	
Day 45				
	3 Red label	0.5 mL	monthly	
Day 75				
	3 Red label	0.5 mL	monthly	

Rapid schedule (grouped or cluster):

DAY	VIAL	RECOMMENDED DOSE	ADMINISTRATION INTERVAL	DATE
Day 1	**3 Red label**	0.2 + 0.3 mL	30 - 45 minutes	
Day 31	**3 Red label**	0.5 mL	monthly	
Day 61	**3 Red label**	0.5 mL	monthly	
Day 91	**3 Red label**	0.5 mL	Monthly until finishing the content of the vial	

Continuation phase

Check first that the package consists of one or two vials number 3, according to the physician's prescription.

Injections will be administered monthly for 3-5 years.

DAY	VIAL	RECOMMENDED DOSE	ADMINISTRATION INTERVAL	DATE
Day 121				
	3 Red label	0.5 mL	monthly	
Day 151				
	3 Red label	0.5 mL	monthly	
Day 181				
	3 Red label	0.5 mL	monthly	
Day 211				
	3 Red label	0.5 mL	monthly	

The vials may be cloudy after shaking. This cloudy will be increased with the concentration of the vial.

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 your 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 Polymerized in paediatric population have not been established. Nonetheless, the use of subcutaneous immunotherapy in children is extensively supported by scientific publications (see section 5.1), although following the recommendations in force on the management of the subcutaneous immunotherapy, Diater Polymerized should not be used in children under 2 years of age and it should be used with caution in children aged 2-5 years, always after a risk-benefit assessment on a case-by-case basis.

Elderly population

The safety and efficacy of Diater Polymerized in elderly population (over 65 years of age) have not been established. The posology for this patient group is the same as recommended for adults. The risk-benefit balance should be carefully assessed, as well as any co-morbidities (e.g., cardiovascular or cerebrovascular diseases) that may increase the risk of using this treatment.

Method of administration

Diater Polymerized is intended for subcutaneous administration.

It is very important to follow the instructions before the use of Diater Polymerized:

- Desinfect the skin of the arm to be injected.
- Shake the vial gently before each extraction.
- Always begin the administration of the treatment with the lowest numbered vial (corresponding to the vial with the lowest concentration).
- Extract the dosage of the treatment.
- Ensure that the administration route is subcutaneous. The injection will be administered in the dorsal upper arm, 20 cm above the elbow, alternating arms in each administration, making sure it is not administered intravenously.
- Proceed in the same way as appropriate for the following vials.

After each dose is applied, the patient should stay at the health centre where the administration is administered for at least 30 minutes.

4.3 Contraindications

Hypersensitivity to any of the excipients listed in section 6.1.

According to current recommendations, the use of subcutaneous immunotherapy with aeroallergens, including Diater Polymerized, is additionally contraindicated in the following cases:

- Severe or poorly controlled asthma
- Active autoimmune disorders (without response to treatment)
- Malignant neoplasias
- Children under 2 years old
- Immunotherapy treatment should not be initiated during pregnancy
- AIDS

Literature references

- Pitsios C, et al. (2015) Clinical contraindications to allergen immunotherapy: an EAACI position paper. Allergy; 70: 897–909.

4.4 Special warnings and precautions for use

Following current recommendations, the use of subcutaneous aeroallergen immunotherapy, including Diater Polymerized, is additionally contraindicated in the following cases:

- Patients with partially controlled asthma. In a patient with partially controlled asthma, stabilization prior starting the treatment is recommended.
- Children aged 2-5 years due to limited cooperation and less clinical experience in 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 arrhytmia). The cardiac status and the patient tolerability should be assessed in the face of an anaphylactic episode and the use of adrenaline.
- Autoimmune or organ-specific disease in remission. The effect of immunotherapy on the underlying disease is unknown.
- Acquired immunodeficiencies or immunosupressors use (other than anti-IgE treatments). Its impact on the effectiveness of immunotherapy is unknown.
- Chronic infectious disease (i.e., Hepatitis B or C).
- Psychiatric/mental disorders that prevents adequate treatment compliance. The patient should be in any case well controlled on the onset of the immunotherapy.
- Anamnesis of severe systemic reactions to immunotherapy due to the increased risk to the development of new systemic reactions.

In general, clinical experience with immunotherapy in elderly patients is limited. In these patients, the presence of comorbidities and concomitant medications previously described should be considered.

As with other immunotherapies, there is a higher risk of adverse reactions at times of increased allergen exposure. Initiation of treatment with subcutaneous immunotherapy, including Diater Polymerized, is recommended at least two months before the pollen season in case of seasonal allergens; or when allergen exposure is lowest (and avoidance measures have been implemented) in case of perennial aero-alergens.

Once immunotherapy is initiated, possible dose reduction during co-seasonality should be considered.

In children with concomitant asthma and acute upper respiratory tract infection, treatment with Diater Polymerized should be temporarily suspended until the infection is resolved.

It is not recommended to administer Diater Polymerized on the same day as the administration of other prophylactic immunizations. It is advisable to administer prophylactic immunizations (e.g., influenza) at least 7 days after the last dose of Diater Polymerized, with the next maintenance dose administered at least 2 weeks later (see section 4.5).

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 administration 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 adrenaline 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 at 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 required by the patient.

Diater Polymerized 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 23 mg sodium (1 mmol) per dose, this i.e., essentially "sodium-free".

This medicinal product contains less than 39 mg potassium (1 mmol) per dose, this i.e., essentially "potassium-free".

Literature 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 and reduce the risk of mild reactions.

The use of beta-blockers should be considered, as in case of anaphylaxis it would interact with the adrenalin and would increase the risk of more severe systemic reactions, so that the specialist should assess the risk/benefit balance. When feasible, beta-blockers should be substituted with an alternative (Pitsios et al. 2015).

High environmental exposure to the allergen causing the symptoms concomitant with the administration of immunotherapy increases the risk of systemic reactions. The presence of an acute infection concomitant with the administration of immunotherapy increases the risk of systemic reactions (EAACI Allergen Immunotherapy Alvaro Lozano, et al. User's Guide 2020).

There are no clinical experience data regarding treatment with Diater Polymerized 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 Polymerized, 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.
- Sturm G.J. et al. (2017) EAACI Guidelines on allergen immunotherapy: Hymenoptera venom allergy. Allergy, 73(4): 744-764.
- Pfaar O. Allergol Select. 2022.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Lactation

It is unknown whether the 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 Polymerized has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Safety profile summary:

During the marketing period, the most frequent reactions reported with Diater Polymerised in adult and paediatric patients are local reactions and generally consist of erythema, oedema, swelling, rash, pruritus, urticaria, heat, pain or hypoaesthesia at the injection site. They usually occur within 10 to 60 minutes after administration and persist for several hours, disappearing without treatment.

The swelling/erythema of the injection site is normal, as long as it does not exceed 10 cm in diameter. In case of a larger local reaction, the use of oral antihistamines and/or topical corticosteroids is advised.

Possible systemic reactions are: severe generalised allergic reaction (anaphylaxis), hypotension due to allergic reaction (anaphylactic shock), wheezing, asthma, dyspnoea, swelling, urticaria, erythema, increased lacrimation, itching of the eye and/or eye pain, fatigue, chills, nausea, pyrexia and/or malaise. For the treatment of anaphylaxis, the indications contained in the current protocols should be followed.

Tabulated list of adverse reactions

Immune system disorders
Anaphylactic shock
Frequency: unknown (cannot be estimated from the available data)

Respiratory, thoracic and mediastinal disorders
Dyspnoea, asthma, wheezing
Frequency: unknown (cannot be estimated from the available data)

General disorders and administration site conditions
Injection/vaccination site reactions, heat, pain, oedema, erythema, swelling, inflammation, pruritus, urticaria, hypoaesthesia at the injection site or injection site.
Fatigue, shivering, pyrexia, malaise.
Frequency: unknown (cannot be estimated from the available data)

Eye disorders
Increased lacrimation, itching of the eye, eye pain
Frequency: unknown (cannot be estimated from the available data)

Gastrointestinal disorders
Nausea
Frequency: unknown (cannot be estimated from the available data)

Skin and subcutaneous tissue disorders
Urticaria (including. generalised).
Frequency: unknown (cannot be estimated from the available data)

Vascular disorders
Hypotension
Frequency: unknown (cannot be estimated from the available data)

Description of selected adverse reactions

If the patient experiences significant adverse reactions to treatment, the use of anti-allergic medication should be considered.

In the post-marketing phase, severe anaphylactic reactions, including anaphylactic shock, have been reported. Therefore, as an important precautionary measure, initiation of treatment should be supervised by a physician (see sections 4.2 and 4.4).

A doctor should be contacted immediately in case of severe systemic reactions. In such cases, treatment should be discontinued permanently, or until recommended by a doctor.

Paediatric population

Overall, the adverse reactions found in children and adolescents after treatment with Diater Polymerized are similar to those found 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.

5.1 Overdose

Taking higher doses than the recommended daily dose may increase the risk of adverse reactions, including risk of systemic reactions or severe local reactions. In these cases, the treatment must be discontinued permanently or until the physician recommends it.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Group V (Various), ATC Code: V01AA. Allergenic extracts.

Mechanism of action

Recent evidence has provided a plausible explanation for the multiple mechanisms of specific immunotherapy (SIT), which induces rapid desensitization and long-term allergen-specific immune tolerance, as well as the suppression of allergic inflammation in the affected tissue. The described mechanism includes the modification

of the allergen presentation by dendritic cells that in turn modify the phenotype of allergen-specific T cells, switching from the Th2-type response, typical of allergic inflammation, to a Th1-type response. An important role is played by allergen-specific T regulatory (Treg) cells, which produce suppressive cytokines such as IL-10 and TGF-beta (Incorvaia 2013). The induction and increase in the secretion of IL-10 by the SIT apparently regulates against allergen specific IgE and this simultaneously increases IgG4 production. Accordingly, IL-10 not only generates tolerance in T cells but regulates the formation of specific isotypes and biases the IgE-specific response to a dominant phenotype IgG4 (Akdis and Akdis 2007). Evidence suggests important biological effects of allergen specific IgG4. These effects include the IgG-dependent ability of post-immunotherapy serum to inhibit the binding of allergen-IgE complexes to B-cells, the blocking of subsequent IgE-facilitated allergen presentation and activation of allergen-specific T-lymphocytes, and the prevention of allergen-IgE dependent activation of peripheral basophils.

Diater Polymerised allergen extracts are extracts that have been modified (polymerisation with glutaraldehyde) with the aim of reducing the capacity to produce adverse reactions while maintaining the capacity to induce an adequate immunological response. Glutaraldehyde reacts covalently with the amino groups of the polypeptide chains of the different proteins that constitute the allergenic extracts, generating a stable, high molecular weight polymer where the allergenic epitopes recognised by IgEs are hidden, leaving most of the allergenic determinants accessible for processing by phagocytic antigen-presenting cells which transmit the immunological information to IgG antibody-producing cells, thus reducing allergenicity. The reduction in IgE binding, and thus the potential reduction in the ability to induce an allergic reaction, is due to the structure of the molecules formed after polymerisation.

Western-blot and ELISA inhibition techniques have been used to compare the immunogenic activity and allergenicity of polymerised Diater (specifically *Dermatophagoides pteronissynus*) with the unmodified native product (Froilan *et al.* 2014). The results show that serum IgE from allergic patients were not able to recognise the polymerised allergens and that a 50-fold higher concentration was required to achieve the same degree of inhibition as that found in the unmodified allergen, indicating a loss of allergenic potency of Diater Polymerized by more than 95%.

Clinical efficacy and safety

The current guides on immunotherapy from the World Health Organization (Bousquet *et al,* 1998) and the European Academy of Allergy and Clinical Immunology allergic (Burks *et al,* 2013) consider that immunotherapy is clinically effective against rhino-conjunctivitis and asthma.

Clinical benefits include a reduction in the number and severity of allergic symptoms and a decreased reliance on the use of symptomatic drug treatments. Benefits can persist for up to 12 years after 3 to 5 years of specific immunotherapy, and greater treatment duration is associated with longer-lasting clinical benefit. In addition, immunotherapy may decrease the risk of developing new sensitivities to other inhalant allergens in both patients who are mono-sensitized and those who are poly-sensitized (Cox, Hankin *et al.* 2014).

Adverse reactions are classified into two main categories, local and systemic. The severity of the systemic reactions induced by subcutaneous immunotherapy may range from mild symptoms to anaphylaxis. In a survey between 2007 and 2009, which included approximately 8 million injection visit per year, the reported rate of systemic reactions was 0.1% of the injections, with no fatalities reported. The majority of the systemic reactions (86%) occurred within 30 minutes after injection. Most delayed-onset systemic reactions were mild, but severe delayed-onset reactions did occur (Burks *et al,* 2013).

The risk of systemic reactions to specific immunotherapy based on conventional build-up protocols is approximately 0.2% per injection (1 in 500) (Ravi and Rank 2013). Systematic reviews have shown that subcutaneous immunotherapy (SCIT) is safe when prescribed to selected patients in a specialist clinic with adequate facilities and trained health personnel. SCIT can produce both local and systemic adverse reactions; however, in the majority of cases these symptoms are readily reversible if recognized early and with prompt treatment. Adverse effects may occur with all allergen preparations whether using standardized extracts, allergoids, or recombinant allergens (Calderon, Boyle *et al.* 2011).

Recent meta-analyses have shown that immunotherapy with allergoid/polymerised extracts are effective in reducing symptoms and medication compared to placebo in the treatment of allergic rhinitis (Dhami *et al.* 2017).

Paediatric population

Allergen immunotherapy is not a treatment option for children under 2 years old. In children from 2 to 5 years old, it should be considered on a case-by-case basis, under the monitoring of an experienced physician in identifying and treating emerging signs of anaphylaxis in this age group (Wiley *et al,* 2006) (Pitsios *et al,* 2015).

A retrospective study of subcutaneous immunotherapy in 239 children below the age of 5 years (8–59 months old), who received a total of 6689 injections, reported a single systemic reaction 90 min after an injection in a 3-year-old boy. A second study of subcutaneous immunotherapy to treat 22 toddlers with mite-allergic asthma (four of whom were less than 3 years old); 7/22 experienced mild bronchospasm as a side-effect, but continued the treatment (Pitsios *et al,* 2015).

Early initiation of appropriate immunotherapy treatment in children with allergic rhinoconjunctivitis, with or without asthma reduces the risk of allergic disease progression. This effect is sustained during the subsequent years after completion of immunotherapy treatment (Jacobsen *et al.* 1996; Larenas-Linnemann *et al.* 2011).

Evaluating the differential effects of immunotherapy based on the developmental stage of children and adolescents can help to optimize treatment and identify the optimal dose, frequency, treatment duration, and age for initiating treatment in children (Kim, Lin et al. 2013).

Another review analyses 31 studies on SCIT in children, and concludes that there is acceptable evidence that grass pollen, *Alternaria alternata*, and house dust mites SCIT is beneficial in allergic children (Larenas-Linnemann *et al,* 2011).

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.
- Froilán S., Pineda F., Rodríguez D. (2014) Caracterización del polimerizado de "Dermatophagoides pteronyssinus" modificado con glutaraldehído. Dianas; 3(1): e20140907.
- Bousquet, Jean et al. (1998) Allergen immunotherapy: Therapeutic vaccines for allergic diseases A WHO position paper. Journal of Allergy and Clinical Immunology, Volume 102, Issue 4, 558 - 562
- Burks, A. Wesley et al. (2013) Update on allergy immunotherapy: American Academy of Allergy, Asthma & Immunology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report. Journal of Allergy and Clinical Immunology, Volume 131, Issue 5, 1288 - 1296.e3
- Roberts G. *et al.* (2017) EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. Allery; 1-34
- Cox, L. S., C. Hankin, et al. (2014). "Allergy immunotherapy adherence and delivery route: location does not matter." J Allergy Clin Immunol Pract 2(2): 156-160.
- Ravi, A. and M. A. Rank (2013). "Reducing and managing systemic reactions to immunotherapy." Curr Opin Allergy Clin Immunol 13(6): 651-655.
- Calderon, M. A., R. J. Boyle, et al. (2011). "Immunotherapy: The meta-analyses. What have we Learned?" Immunol Allergy Clin North Am 31(2): 159-173, vii.
- Dhami S. *et al.* (2017) Allergen immunotherapy for allergic rhinoconjunctivitis; A systematic review and meta-analysis. Allergy; 2017; 72: 1597-1631
- Wiley J. and Sons (2006) Subcutaneous immunotherapy. Allergy; Volume 61, Issue s82 3–5
- Pitsios C*, et al.* (2015) Clinical contraindications to allergen immunotherapy: an EAACI position paper. Allergy; 70: 897–909.
- Jacobsen L. *et al*. (1996) Immunotherapy as a preventive treatment. J Allergy Clin Immunol; 97(abstract): p. 232.

Kim, J. M., Lin S. Y. *et al*. (2013) Allergen-specific immunotherapy for paediatric asthma and rhino-conjunctivitis: a systematic review. Paediatrics; 131(6): 1155-1167.

- Larenas-Linnemann *et al.* (2011) Evidence of effect of subcutaneous immunotherapy in children: complete and updated review from 2006 onward. Ann Allergy Asthma Immunol; 107:407-16

5.2 Pharmacokinetic properties

There is no data on pharmacokinetic properties of Diater Polymerized. Pharmacokinetic studies are not possible for products of specific immunotherapy. During specific immunotherapy usually plasma concentrations of the active substance are not measurable, due to the nature of the product (CHMP/EWP/18504/2006).

Literature references

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

5.3 Preclinical safety data

Studies of abnormal toxicity and irritant capacity were performed on the solvent used in Diater Polymerized, constituted by the excipients (see section 6.1). The abnormal toxicity studies were performed in mice and guinea pigs, where a dose corresponding to 700-fold the maximum human dose showed no signs of toxicity. The study of non-specific irritant capacity, performed in rats, where a dose corresponding to 700-fold the maximum human dose, showed that the solvent used in Diater Polymerized is mildly irritant

A fourth study was conducted to evaluate the irritant effect of *Dermatophagoides pteronyssinus* polymerized extract, dosing 2.5 mg/kg at a concentration of 0.17 mg/mL in rabbits. No irritation was observed in study subjects.

No evidence of toxicity with subcutaneous polymerized immunotherapy has been found in the literature.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Phenol
Sodium Chloride
Monopotassium phosphate
Disodium phosphate
Water for injection

The allergenic extracts of Diater Polymerized have been polymerized with glutaraldehyde and do not contain aluminium hydroxide.

6.2 Incompatibilities

No incompatibilities studies have 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 this medicine after the expiry date which is stated on the label.

6.4 Special precautions for storage

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

Store in original packaging.

Do not use Diater Polymerized if the vial has lost some of its contents or if the packaging has been damaged.

6.5 Nature and contents of container

The container is a glass vial (type I) with rubber stopper and a flip-off seal (aluminium).

Diater Polymerized consist of two presentations packages: initiation treatment and continuation treatment.

Initiation treatment

The treatment may contain one, two or three extract vials. Possible presentations are:

- Presentation with one vial of polymerized (3)
- Presentation with two vials of polymerized (3-3)
- Presentation with three vials of polymerized (1-2-3)

	Vial	**Nº of vials**	**Concentration**	**Volume**
Active substance - allergen	Nº 1 Green label	0 or 1 vials	1/100 of vial Nº 3	3 mL
	Nº 2 Yellow label	0 or 1 vials	1/10 of vial Nº 3	3 mL
	Nº 3 Red label	1 or 2 vials	Maximum concentration (different for every allergen)	3 mL

Continuation treatment

The treatment may contain one (3) or two (3-3) glass vials number 3.

	Vial	**Nº of vials**	**Concentration**	**Volume**
Active substance – allergen	Nº 3 Red label	1 or 2 vials	Maximum concentration (different for every allergen)	3 mL

1 mL single use syringes are included to ensure sterile conditions in 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 medicinal product if there are visible signs of damage.

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

December 2023