Diater Laboratorio de Diagnóstico
y Aplicaciones Terapéuticas, S.A

Summary of product characteristics

DIATER Depot
Injectable suspension

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1. NAME OF THE MEDICINAL PRODUCT

Diater Depot

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Diater Depot is an immunotherapy treatment (vaccine), consisting of allergenic extracts to which the patient is sensitized, adsorbed in aluminium hydroxide in order to allow a slow release of the antigen in the organism, intended for subcutaneous administration for the treatment of allergic conditions.

Diater Depot 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 Depot in each case.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Injectable suspension

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Diater Depot is used for the treatment for allergic diseases that trigger rhinitis, rhino-conjunctivitis or seasonal or perennial bronchial asthma.

Diater Depot is indicated for adults, children and adolescents.

4.2 Posology and method of administration

Diater Depot should be always prescribed by a specialist.

Posology

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

1. **An initial phase:** the aim is to increase the dose stepwise until the maximum tolerable dose, 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. **A maintenance phase** in which the maximum tolerated dose is injected monthly, usually for a period of 3 to 5 years.

Diater Depot is intended for subcutaneous administration.

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.

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

Initial Treatment

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

Injections will be administered at weekly intervals, except the last dose with the vial number 3 is reached, in which the treatment will be administered after 4 weeks.

Vial	Volume to be injected	Intervals between administration	Date
No. 1 Green Label	0.1 mL	1 week	
	0.2 mL	1 week	
	0.4 mL	1 week	
	0.8 mL	1 week	

Vial	Volume to be injected	Intervals between administration	Date
No. 2 Yellow Label	0.1 mL	1 week	
	0.2 mL	1 week	
	0.4 mL	1 week	
	0.8 mL	1 week	

Vial	Volume to be injected	Intervals between administration	Date
No. 3 Red Label	0.1 mL	1 week	
	0.2 mL	1 week	
	0.4 mL	1 week	
	0.6 mL	1 week	
	0.8 mL	1 week	
	Maximum tolerated dose	4 weeks	

Maintenance treatment

Check that the package contains one or two vials No.3, according with the medical prescription.

Vial	Volume to be injected	Intervals between administration	Date
No. 3 Red Label	Maximum tolerated dose	1 month	
	Maximum tolerated dose	1 month	
	Maximum tolerated dose	1 month	
	Maximum tolerated dose	1 month	

Vials may seem opaque (after they are shaken). This opacity will increase with the vial concentration

Do not administer a double dose if a dose is missed

It is important that Diater Depot is used on regular basis during the treatment period in order to be effective.

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

Paediatric population

The safety and efficacy of Diater Depot in children has not been established. However the use of subcutaneous immunotherapy in children is extensively supported by scientific publications (see section 5.1).

Method of administration

Diater Depot is intended for subcutaneous administration.

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

- Always start the treatment with the lowest numbered vial which corresponds to the lowest concentration
- Before each extraction, shake the vial gently
- 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. Care is taken to ensure it is not administered intravenously
- The treatment will continue in the same way with the next vials, in ascending numerical order

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

4.3 Contraindications

The use of Diater Depot is contraindicated in the following cases:

- Hypersensitivity to any of the excipients listed in section 6.1.
- Severe or poorly controlled asthma
- Severe immunological disorders e.g. autoimmune disorders or immunodeficiencies
- Malignant neoplasias
- Concomitant treatment with beta-blockers (see section 4.5)
- Cardiovascular diseases or any pathology that contraindicates the use of adrenaline in case of anaphylaxis

- Children under 2 years old. In children between 2-5 years each case should be considered individually (see section 5.1)
- Immunotherapy treatment should not be initiated during pregnancy. In case of pregnancy during an on-going treatment, it is recommended to continue if the immunotherapy is well-tolerated.
- Psychiatric disorders or any other cause that prevents adequate treatment compliance

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

Diater Depot is a subcutaneous treatment, be sure not administrate Diater Depot intramuscularly or intravenously.

Redness at the injection site is normal, as long as it does not exceed 5 cm diameter (Mailing et al, 1993). If the size of the reaction is greater than this, necessary measures should be taken, according to physician criterion, for such reaction.

In children with concomitant asthma and acute upper respiratory tract infection the treatment with Diater Depot should be suspended temporally until the infection is gone.

This treatment may pose risks related to generalize reactions, which are sometimes severe (urticaria, asthma, anaphylactic shock, etc.) and therefore the following rules 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 applying the allergenic vaccine.
- Allergen vaccines should always be administered under medical supervision.
- 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 each dose is applied, the patient should stay at the health centre where the preparation is administered for at least 30 minutes.
- If any adverse reaction appears, the risk should be assessed 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.

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

Literature references

- Mailing, H.J., Weeke, B. (1993). Position paper: immunotherapy. Allergy; 48:9–35.

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 β-blocker should be taken into account, 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).

Literature references

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

4.6 Fertility, pregnancy and lactation

Pregnancy and Breastfeeding

A risk to the new-borns/infants cannot be excluded. There are no data available on the safety of the medicinal product during pregnancy or breastfeeding.

Fertility

There are no data of fertility related to the medicinal product.

4.7 Effects on ability to drive and use machines

There are no reports regarding the effect on the ability to drive and the use of tools or machinery, so no special precautions are required.

4.8 Undesirable effects

Local reactions consist on pruritus, urticaria, rash, oedema or inflammation at the injection site. They usually appear between 10 and 60 minutes after administration and persist for several hours, disappearing without treatment.

The induration and/or erythema of the injection site is normal, as long as it does not exceed 5 cm in diameter. In the case of a larger local reaction, the use of oral antihistamines and/or topical corticosteroids is advised. Measures and/or medications indicated by the physician should be followed.

In general, systemic reactions consist on conjunctivitis or eye pruritus, rhinitis, rhinoconjunctivitis, obstruction or nasal congestion, rhinorrhoea, urticaria, pruritus, (angi)oedema, sneezing, lip or eyelid oedema, erythema, paraesthesia, wheezing, dyspnoea, cough, hypoventilation or respiratory distress, tachypnoea, tachycardia, dysphagia, chest discomfort, hypotension, vision blurred, pyrexia, hyperhidrosis, malaise, that may occur between 15 minutes and 4-6 hours after the injection.

In case of bronchospasm it is recommended using bronchodilators. Occasionally this medicine may cause shock or anaphylactic reaction. Exceptionally asthma or generalised urticaria may occur.

List of adverse reactions

Immune system disorders
Anaphylactic shock, anaphylactic reaction.
Frequency: not know (cannot be estimated from the available data)

Eye disorders
Eyelid oedema, rhinoconjunctivitis, eye pruritus, vision blurred.
Frequency: not know (cannot be estimated from the available data)

Respiratory, thoracic and mediastinal disorders
Dyspnoea, cough, bronchospasm, asthma, rhinitis, rhinorrhoea, obstruction or nasal congestion, wheezing, hypoventilation or respiratory distress, sneezing, tachypnoea.
Frequency: not know (cannot be estimated from the available data)

General disorders and administration site conditions
Injection/vaccination site reaction, urticaria, erythema, pruritus, rash, induration, oedema or inflammation at the injection site, oedema or peripheral swelling, chest discomfort, malaise, pyrexia.
Frequency: not know (cannot be estimated from the available data)

Skin and subcutaneous tissue disorders
Urticaria (including. generalised), pruritus (including. generalised), (angi)oedema, erythema (including. generalised).
Frequency: not know (cannot be estimated from the available data)

Gastrointestinal disorders
Lip oedema, dysphagia.
Frequency: not know (cannot be estimated from the available data)

Nervous system disorders
Paraesthesia
Frequency: not know (cannot be estimated from the available data)

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

Cardiac disorders
Tachycardia
Frequency: not know (cannot be estimated from the available data)

Paediatric population

Overall, the adverse reactions found in children and adolescents after treatment with Diater Depot 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.

4.9 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 include 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.

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).

Also, the following studies have been performed with Diater Depot:

- In a study with 10 patients between 17 and 60 years with rhinoconjunctivitis (2 with associated bronchial asthma) monosensitized to *Parietaria judaica* pollen treated with Diater Depot, it was compared the allergen recognition by immunoglobulins IgE, IgG4, IgG1 and IgA at the beginning of the immunotherapy and one year later, upon reaching the maximum dose, and symptoms were

evaluated following the visual analogue scale from 0 to 100 points. After a year of treatment it was found that there was a higher recognition of the studied immunoglobulins, and a decrease of seasonal symptomatology between 10 and 80 points (Montoro et al. 2006).

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, is the best guarantee of a correct evolution of this disease, preventing the continuation during adulthood (Jacobsen, Moeller 1996; Arêde et al 2013).

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, 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.
- 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
- 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.
- Montoro J, Pineda F, Moragues T, Pesudo S. (2006) “Inmunoterapia con Parietaria judaica. Seguimiento con Western blot” Journal Investig Allergol Clin Immunology. S2:181.
- John Wiley 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, D.S., Moeller C y cols. (1996) Immunotherapy as a preventive treatment. J Allergy Clin Immunol. 97(abstract): p. 232.
- Arêde, C., *et al*. (2013) Ultrarush specific’s immunotherapy safety using modified extracts in pediatric age. Rev. Port. Imunoalergologia. 21(2): p. 91-102.
- Kim, J. M., S. Y. Lin, *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 Depot. 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

A study was conducted to evaluate the unspecific irritant capacity of the excipients used in Diater Depot. The study was performed in rats, where a dose corresponding to 700-fold the maximum human dose showed no signs of local toxicity, finding that the excipients are not-irritant.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Phenol
Sodium Chloride
Aluminium hydroxide
Water for injections

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 Depot if the vial has lost some of its contents or if the packaging has been damaged.

6.5 Nature and contents of container

Glass vial (Type I) with rubber closure and aluminium capsule.

Diater Depot consist of two presentations packages: initiation treatment and maintenance treatment.

Initial treatment

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

- Presentation with three vials (1-2-3)
- Presentation with two vials (2-3)
- Presentation with three vials (2-3-3)

	Vial	No. of vials	Concentration	Volume
Active substance - allergen	No. 1 Green label	0 or 1 vials	1/100 of vial No. 3	3.6 mL
	No. 2 Yellow label	1 vial	1/10 of vial No. 3	3.6 mL
	No. 3 Red label	1 or 2 vials	Maximum concentration (different for every allergen)	4.5 mL

Maintenance 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)	4.5 mL

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

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8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

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