Diater Laboratorio de Diagnóstico
y Aplicaciones Terapéuticas, S.A

Summary of product characteristics

DIATER Sublingual Spray Maxi
Sublingual Spray solution

SUMMARY OF PRODUCT CHARACTERISTICS

SUMMARY OF PRODUCT CHARACTERISTICS

DIATER Sublingual Spray Maxi. Sublingual Spray solution

1. NAME OF THE MEDICINAL PRODUCT

Diater Sublingual Spray Maxi, sublingual spray solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Diater Sublingual Spray Maxi is an immunotherapy treatment (vaccine), consisting of allergenic extracts to which the patient is sensitised, for sublingual administration for the treatment of allergic conditions.

Diater Sublingual Spray Maxi 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 Sublingual Spray Maxi in each case.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sublingual spray solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Diater Sublingual Spray Maxi should be always prescribed by an allergy specialist.

Posology

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

1. **Initial treatment**: 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. **Maintenance treatment**: in which the maximum tolerated dose is administered daily for a period of 3 to 5 years, as determined by the physician.

Diater Sublingual Spray Maxi is intended for sublingual use.

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 rush schedule, in which the treatment begins with the maximum allergen concentration.

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

Initial Treatment

Conventional schedule:

Check first that the package consists of one vial C and two vials D. Always start the administration in alphabetical order, corresponding with an increase on the drug substance concentration.

The sprays are administered daily.

Vial	Dose	Interval of administration	Date
C Yellow label	1 spray	day 1	
	2 sprays	day 2	
	3 sprays	day 3	
	4 sprays	day 4	

Vial	Dose	Interval of administration	Date
D Red label	1 spray	1 spray daily until the vial is finished	

Rush schedule:

Check first that the package consists of one or two vials D.

Vial	Dose	Interval of administration	Date
D Red label	1 spray	1 spray daily until the vial is finished	

Maintenance treatment

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

The sprays are administered daily for 3-5 years.

Vial	Dose	Interval of administration	Date
D Red label	1 spray	1 spray daily until the vial is finished	

Do not administer a double dose if a dose is missed.

It is important that Diater Sublingual Spray Maxi 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 Sublingual Spray Maxi in children has not yet been established.
However the use of sublingual immunotherapy in children is extensively supported by scientific publications (see section 5.1).

Method of administration

Diater Sublingual Spray Maxi is intended for spray administration via sublingual route (under the tongue).

It is very important following the next instructions before using Diater Sublingual Spray Maxi:

- In the Initial treatment, use the vials following an alphabetical order, corresponding with an increase on concentration.
- Diater Sublingual Spray Maxi is intended exclusively for sublingual use.
- Shake the vial gently before administering each corresponding dose.
- The vial should be kept upright without turning upside down.
- Before administering the first dose, press the pump 3 or 4 times directed into the air, to ensure that the circuit and valve are completely full.
- Press the pump the number of times prescribed, maintaining the liquid under the tongue until it is completely absorbed. Swallowing must be avoided for approximately 1 minute. Do not eat or drink for five minutes after the administration.
- The doses are administered daily
- It is normal for liquid to be left over in the vials to cover the possibility of the doctor prescribing a possible repetition or modification of the dose.

4.3 Contraindications

The use of Diater Sublingual Spray Maxi 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 Sublingual Spray Maxi should be administered sublingually (under the tongue)

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

In case of oral surgery, e.g. dental extractions or loss of first teeth in children, treatment should be stopped for 7 days to allow for the cure of the oral cavity.

The initiation of the treatment should be carefully evaluated and the equipment to treat any possible adverse reactions should be available.

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

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 on 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

The most frequent local reactions are throat irritation, oral and tongue burn or itch.

In some cases, an increase of allergy symptomatology/allergic disease like rhinitis may occur. In most of the patients, these reactions appear at the beginning of the treatment for a few minutes and tend to disappear spontaneously after 1 or 2 hours.

It is possible that other symptoms may appear e.g. urticaria and asthma, tongue oedema, bronchospasm, headache, dizziness, vomiting, fever.

Adverse reactions in sublingual immunotherapy

Eye disorders
Pruritus, erythema, conjunctivitis, lacrimation.
Frequency: not known (cannot be estimated from the available data)

Respiratory, thoracic and mediastinal disorders
Asthma, bronchospasm, cough, dysphonia, dyspnoea, laryngeal or tongue oedema, rhinitis allergic, wheezing, throat irritation.
Frequency: not known (cannot be estimated from the available data)

General disorders and administration site conditions
Chest discomfort, fatigue, sensation of foreign body.
Frequency: not known (cannot be estimated from the available data)

Investigations
Blood pressure decreased.
Frequency: not known (cannot be estimated from the available data)

Skin and subcutaneous tissue disorders
Angioedema, erythema (localised o generalised), pruritus (localised o generalised), urticaria.
Frequency: not known (cannot be estimated from the available data)

Gastrointestinal disorders
Dysgeusia, lip swelling, oedema mucosal, swollen tongue, glossodynia, mouth and tongue ulceration, nausea, vomiting, abdominal pain upper, abdominal pain, diarrhoea.
Frequency: not known (cannot be estimated from the available data)

Nervous system disorders
Dizziness, headache, loss of consciousness, syncope.
Frequency: not known (cannot be estimated from the available data)

Ear and labyrinth disorders
Ear pruritus.
Frequency: not known (cannot be estimated from the available data)

Vascular disorders
Flushing, hypotension.
Frequency: not known (cannot be estimated from the available data)

Paediatric population

Overall, the adverse reactions found in children and adolescents after treatment with Diater Sublingual Spray Maxi 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

Sublingual immunotherapy increases allergen tolerance via immune mechanisms, with reorientation of allergen-specific CD4+ T-cell responses from a T helper 2 (Th2) to Th1 and regulatory T-cell profiles. Allergen exposure modifies serum levels of allergen-specific IgE and IgG, although there is considerable debate as to whether these parameters are related to clinical efficacy. Sublingual immunotherapy appears to elicit mucosal IgA responses, which may contribute significantly to tolerance induction (Calderón MA, 2012)

Clinical efficacy and safety

The current guidelines on sublingual immunotherapy from the World Allergy Organization (Canonica et al. 2014) and the European Academy of Allergy and Clinical Immunology (Burks et al. 2013) consider that, in general, the sublingual immunotherapy is clinically effective against rhino-conjunctivitis and asthma. It also presents a higher security profile than subcutaneous immunotherapy, with local reactions as the most common adverse event, usually during the first days of treatment, and disappearing by itself without further intervention.

Taking into account 18 double blind placebo-controlled trials, the effectiveness of sublingual immunotherapy with grass pollen, house dust mite, birch pollen and Parietaria sp. pollen extracts in terms of symptomatology´s improvement and/or reduction of the intake of medications is demonstrated. In addition, systemic immunological effects (i.e. increase in IgG1-IgG4, reduction in skin reactivity) were observed. (Passalacqua G., 2001)

Sublingual immunotherapy has a safe profile because oral antigen-presenting cells (mostly Langerhans and myeloid dendritic cells) exhibit a tolerogenic phenotype, despite constant exposure to danger signals from food and microbes. This reduces the induction of pro-inflammatory immune responses leading to systemic allergic reactions.

Based on 66 published studies, representing 4,378 patients and approximately 1,181,000 doses, it is reported that local, oral mucosal reactions occurred in 40–75% of patients (especially during the initiation and dose build-up) but usually did not lead to dose reduction or interruption of treatment. Serious adverse reaction mainly consisted of asthmatic reactions, abdominal pain/vomiting, uvula oedema, and urticarial. Eleven cases of induced anaphylaxis are reported, equate to around one case per 100 million of administrations or per 526,000 treatment years (Calderón MA, 2012).

Also, the following studies have been performed with Diater Sublingual Spray Maxi:

- Diater Sublingual Spray Maxi showed to be safe in 77 patients (14 to 40 years old). Only 4% of the patients presented mild mouth itching (Cruz AN).
- In a study with 40 patients (30 adults and 10 children) sensitized to different allergens, 8 (20%) presented any adverse event: urticaria (1), bad taste (1), tongue swelling (2), nausea (1), sneezing (1), fever (1), wheezing (2), rhinorrhea (1). All adverse events disappeared after following with the immunotherapy. Patients evaluated, in a scale from 0 to 5: convenience (4.3), practicability (4.2), comprehension of instructions (4.0) and general scores (3.5) (Palma-Carlos, 720, 2007).
- In a study with 40 patients sensitized to mites they were treated with Diater Sublingual Spray Maxi (50% mix of *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*) through a conventional schedule, reaching the maximum dose after 13 days of build-up, and then holding said dose for 2 more months. One patient withdrew from the study due to tongue swelling and nausea. Patients evaluated the treatment with 3.5 on a 0-5 scale. Medical evaluation was good in 12 cases or very good in 24 cases (Palma-Carlos, 727, 2007).

Paediatric population

Sublingual immunotherapy with grass pollen it has been proved effective against seasonal allergic rhinitis in children above 5 years old and probably also in children between 4 and 5 years old. Treatment with grass pollen or dust mites may be used in children with allergic rhinitis and asthma. Also, pre-coseasonal sublingual immunotherapy with grass pollen in children might be as effective as continuous treatment. Sublingual immunotherapy must not be suggested as monotherapy for treating asthma in children (Canonica et al. 2014).

Also, the following studies have been performed with Diater Sublingual Spray Maxi:

- Diater Sublingual Spray Maxi is well tolerated in children (n=67, 4 to 17 years), being the adverse events mild mouth and throat itching (1.5%) and persistent urticaria (1.5%) (Lopes do Santos J, 2007).

Literature References

- Calderón MA, S. F. (2012). Sublingual allergen immunotherapy: mode of action and its relationship with the safety profile. *Allergy.*, 67(3):302-11.
- Canonica GW, Cox L, Pawankar R, et al. (2014) Sublingual immunotherapy: World Allergy Organization position paper 2013 update. The World Allergy Organization Journal;7(1):6. doi:10.1186/1939-4551-7-6.
- 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
- Passalacqua G., C. G. (2001). Allergen-Specific Sublingual Immunotherapy for Respiratory allergy. *BioDrugs 9*, 15 (8): 509-519.
- Cruz AN, A. A. (n.d.). Tolerability of allergen Immunotherapy administered by sublingual spray-rush cluster. Poster.
- Palma Carlos A.G. (2007) Safety and compliance of sublingual immunotherapy in spray 720, World Allergy Congress 2007, Bangkok
- Palma Carlos A.G. (2007) Short-term efficacy of sublingual spray immunotherapy 727, World Allergy Congress 2007, Bangkok
- Lopes do Santos J, P. J. (2007). Acceptance and tolerability of allergen inmunotherapy administered by sublingual spray. Study in paedriatic population. Revista Portuguesa de Inmunoalergología, Panel.

5.2 Pharmacokinetic properties

There is no data on pharmacokinetic properties of Diater Sublingual Spray Maxi. 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

Two studies of abnormal toxicity and one of irritant capacity have been performed on the solvent used in Diater Sublingual Spray Maxi, constituted by the excipients (see section 6.1). The studies of abnormal toxicity in mice and in guinea pigs, where a dose corresponding to 700-fold the maximum human dose, show no signs of toxicity, classifying the solvent as non-toxic. The study of irritant capacity in rats, where a dose corresponding to 700-fold the maximum human dose, shows that the solvent in Diater Sublingual Spray Maxi is mildly irritant.

Allergens come from natural sources and are present in the environment of the sensitized patient, so non-clinical studies have not been performed to evaluate their safety.

No indications have been found in literature about toxicity in sublingual allergen immunotherapy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Phenol
Glycerine (E-422)
Sodium Chloride
Sodium dihydrogen phosphate monohydrate
Disodium Hydrogen Phosphate di-hydrate
Water for injection

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 the original packaging.

Do not use Diater Sublingual Spray Maxi 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 a nebulizer.

Diater Sublingual Spray Maxi consists of two presentation packages: initial treatment and maintenance treatment.

Initial Treatment

Conventional schedule:

The package consists of three vials of allergen extract: one vial C and two vials D (C-D-D). Concentrations are increasing in alphabetical order.

	Vial	**No. of vials**	**Concentration**	**Volume**
Active substance - allergen	C Yellow label	1 vial	1/5 vial D	3 mL
	D Red label	2 vials	Maximum concentration (different for every allergen)	9 mL

Rush schedule:

The package consists of one (D) or two (D-D) vials D of allergen extract at maximum concentration.

	Vial	**No. of vials**	**Concentration**	**Volume**
Active substance - allergen	D Red label	1 or 2 vials	Maximum concentration (different for every allergen)	9 mL

Maintenance treatment

The package consists of one (D), two (D-D) or three (D-D-D) vials D of allergen extract at maximum concentration.

	Vial	**No. of vials**	**Concentration**	**Volume**
Active substance - allergen	D Red label	1, 2 or 3 vials	Maximum concentration (different for every allergen)	9 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

Not applicable.

8. MARKETING AUTHORISATION NUMBER(S)

Not applicable.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not applicable.

10. DATE OF REVISION OF THE TEXT

June 2023