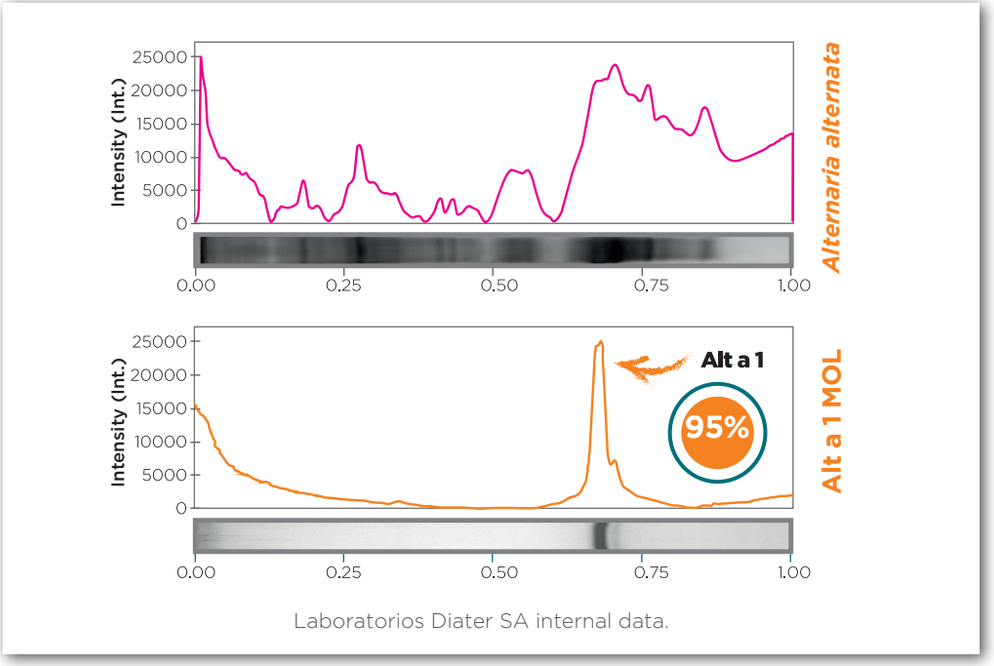

Welcome to
IMMUNOPRECISION
DIATER
PIONEERING
IMMUNOTHERAPY

MOLECULAR IMMUNOTHERAPY WITH Alt a 1 MOL:

HIGH-PURITY IMMUNOTHERAPY[1]

The electrophoresis profile of Alt a 1 MOL shows a single peak for Alt a 1 demonstrating a **purity of more than 95%**.[1]



Laboratorios Diater SA internal data.

CLINICALLY BACKED[2]

A phase III, multicentre, double-blind, randomised, placebo-controlled clinical trial[2]:

Objective	To evaluate the **clinical efficacy and safety** of immunotherapy with the purified major allergen Alt a 1 in patients with allergic rhinoconjunctivitis with or without mild or moderate asthma, sensitised to the fungus *A. alternata*.
Material and methods	111 patients 12-55 years of age. Multicentre: 17 centres. 3 groups: placebo (N = 29), active group 1 (0.2 µg Alt a 1/ml, N = 37), active group 2 (0.37 µg Alt 1 MOL/ml, N = 45).
Results	• **Reduction in the combined index of symptoms and medication** from the first year. • Good safety profile.

PUBLISHED IN JACI

Clinically proven efficacy and safety

from the first year[2]

the right dose

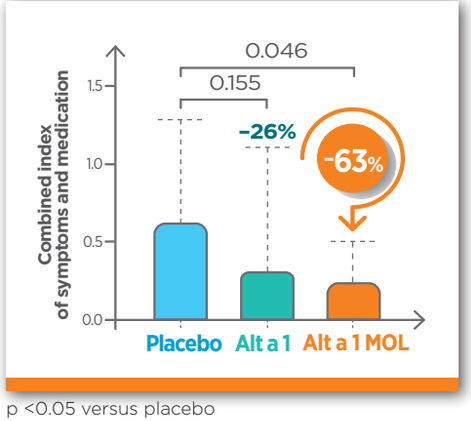
REDUCTION OF SYMPTOMS AND MEDICATION[2]

-63%

Statistically significant reduction (63%) in the combined index of symptoms and medication during the first year of treatment[2].

Good safety profile regardless of dose[2].

Reduction with Alt a 1 MOL of the combined index of symptoms and medication[2]



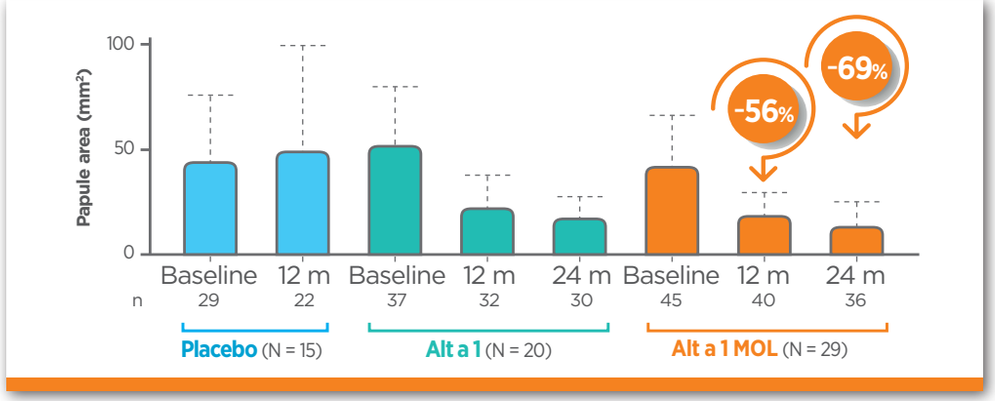
p <0.05 versus placebo

REDUCTION OF SKIN RESPONSE[2]

-69%

With Alt a 1 MOL, **47%** of patients had **negative** skin tests in the second year of treatment, with a **69% reduction in skin response**[2].

Reduction with Alt a 1 MOL of the middle area of the papules[2]



p <0.05 versus baseline; after one and two years of immunotherapy; n = patients evaluated at each visit

MOLECULAR IMMUNOTHERAPY: THE SOLUTION FOR POLYSENSITISED PATIENT

EFFICACY AND SAFETY[4,5]

Alt a 1 MOL Mix is a mixture of the molecular allergen Alt a 1 (at 0.37 µg) and a high-dose polymerised extract[4]:

Alt a 1 MOL + *Olea europaea* / *Wild grasses* / *Dermatophagoides pteronyssinus*

Alt a 1 MOL

OPTIMAL DOSE 0.37 µg

- **Efficacy** of Alt a 1 MOL **from the first year[2]** added to the **safety** of Polymerised 100[5].

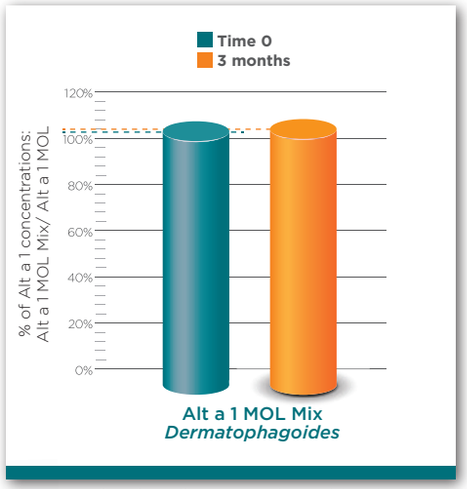
1+1

OPTIMAL POTENCY AND QUANTIFICATION[10]

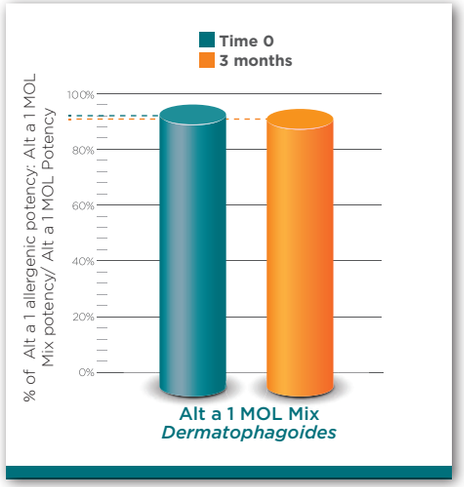
The concentration of Alt a 1 in Alt a 1 MOL Mix is **kept within the specified limits**[10].

The **allergenic potency** of Alt a 1 MOL Mix **remains stable** in the mix[10].

ALLERGEN QUANTIFICATION[10]



ALLERGEN POTENCY[10]



Alt a 1 molecular allergen evaluated in vitro at 5°C both individually and in combination with polymerised *Dermatophagoides pteronyssinus allergen extracts.*

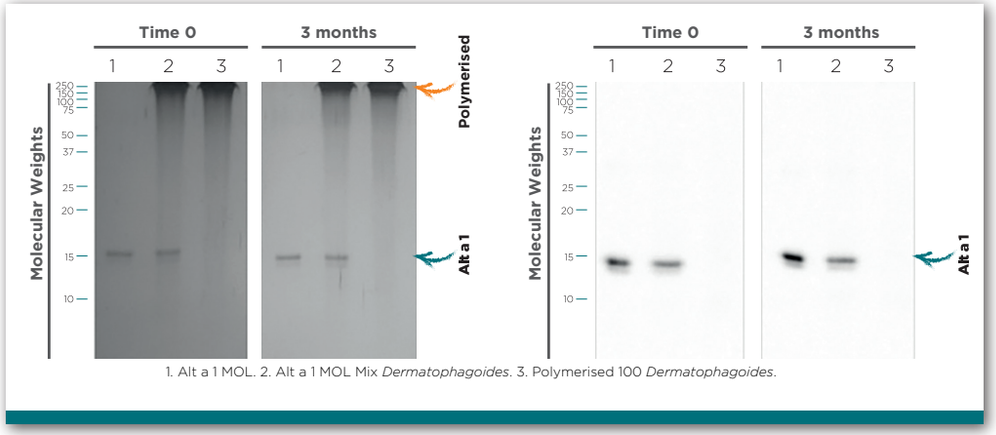
polysensitised patients [2,4,5]

INTEGRITY OF Alt a 1
NO PROTEOLYTIC ACTIVITY

Combining the allergen Alt a 1 with polymerised extracts **does not affect the integrity of Alt a 1 proteins.**[10].

Alt a 1 MOL Mix: mix with **no proteolytic activity**[10].

Alt a 1 MOL + *Dermatophagoides pteronyssinus*[10]



1. Alt a 1 MOL. 2. Alt a 1 MOL Mix *Dermatophagoides*. 3. Polymerised 100 *Dermatophagoides*.

Alt a 1 molecular allergen evaluated ***in vitro*** at 5°C both individually and in combination with polymerised allergenic extracts from ***Dermatophagoides pteronyssinus***.

Cup a 1 MOL

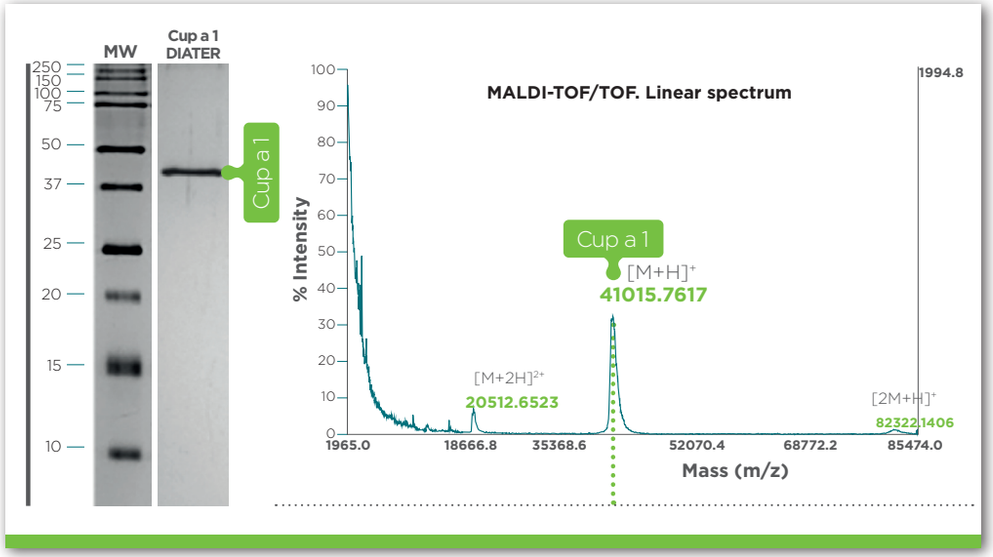
A leading role IN ALLERGY TO POLYSENSITISED PATIENT

CLOSE TO 100% PURITY[6]

100% **Up to 100%** of patients allergic to *Cupressaceae* are **sensitised** to group 1 allergens[7,8].

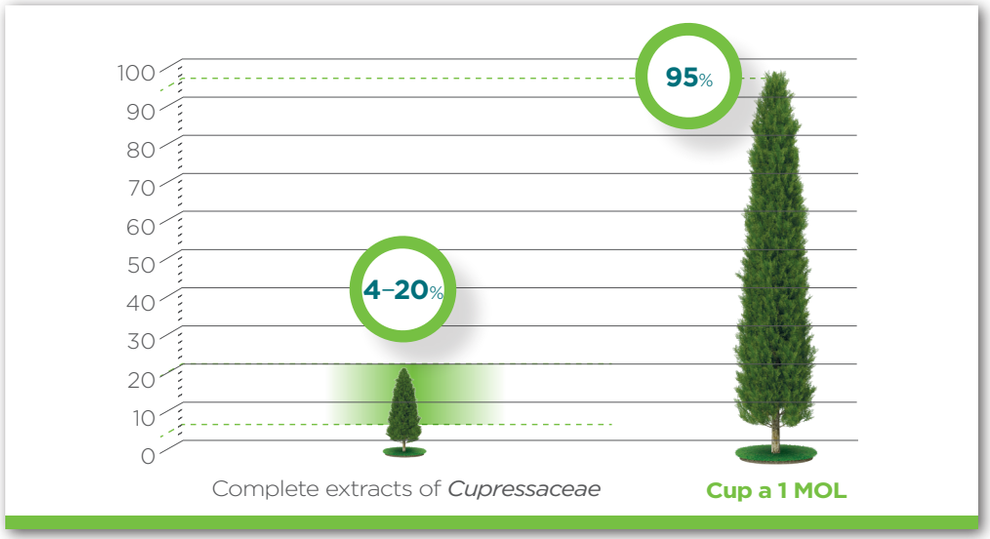
Cup a 1 MOL is isolated and purified from an **extract of *Cupressus arizonica* to obtain Cup a 1 protein** with **a purity of more than** **95%**[6]

SDS-PAGE and Mass Spectrum for Cup a 1 MOL[6]



HIGH PROTEIN PERCENTAGE[11-13]

Protein percentage

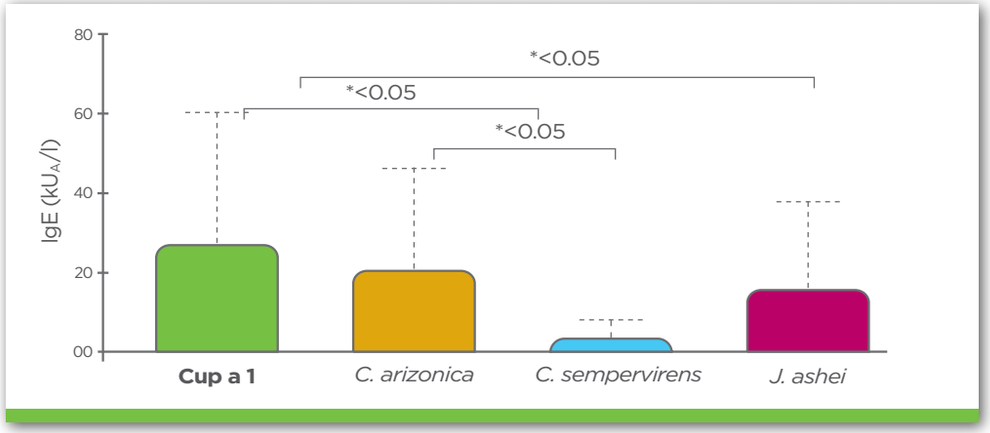


CUPRESSACEAE[7-9]: Cup a 1

DIAGNOSTIC AND THERAPEUTIC ACCURACY[6-9]

- Cup a 1 MOL has been **biologically standardised** to arrive at a diagnostic and therapeutic concentration for patients allergic to Cupressaceae[6].
- **Diagnostic concentration:** with **32 µg/ml**, 95% of the sensitised population is diagnosed[6].
- **Therapeutic dose** of Cup a 1 MOL: **2.4µg**[6] of Cup a 1.

Higher degree of IgE recognition for Cup a 1 MOL*



94% of patients recognise Cup a 1 and have higher levels of IgE for Cup a 1.

*Unpublished internal data.

A unique model in molecular immunotherapy [1,4,6]

The **right immunisation** at the **right dose** for the patient sensitised to ***Alternaria* or *Cupressaceae***

SPECIFIC TREATMENT WITH THE MAJOR ALLERGEN TO WHICH THE PATIENT IS SENSITISED [3, 7-9]

Accurate **and specific immunisation**	Immunotherapy with a **single purified and** isolated **protein**	**Scientifically backed** results

MOLECULAR IMMUNOTHERAPY

Alt a 1 MOL

Alt a 1 MOL mix

Cup a 1 MOL

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Alt a 1 MOL: THE PIONEER IN MOLECULAR IMMUNOTHERAPY[1,2]

Alt a 1, major allergen from the fungus Alternaria alternata

SENSITISATION TO Alt a 1

It occurs in more than **98%**

OF PATIENTS WITH ALLERGY TO *Alternaria alternata*[3]

Alt a 1 MOL MIX: THE SOLUTION FOR POLYSENSITISED PATIENTS:[2-5]

Alt a 1 + Olea
Alt a 1 + Grasses
Alt a 1 + Dermatophagoides

1+1

Efficacy and safety

CLINICALLY PROVEN FOR Alt a 1 MOL[2] ADDED TO THE *safety on a rapid regimen* OF POLIMERIZADO100[5]

Cup a 1 MOL[6-8]: THE LEAD ROLE

Cup a 1, leading major allergen in allergy to Cupressaceae[7-9]

UP TO **100%** *of patients* ALLERGIC TO CUPRESSACEAE *are sensitised* TO GROUP 1 ALLERGENS[7,8]

THE *right immunisation* OR THE PATIENT

Alt a 1 MOL / Alt a 1 MOL mix	Cup a 1 MOL
• *Efficacy demonstrated* in a phase III clinical trial[2]. • *Clinical benefit* in the first year of treatment[2]. • *Good safety profile*[2]. • Single dose vials[2]: **0.37 µg Alt a1.** PUBLISHED IN JACI • *Single dose*[1,4].	• *Standardised* diagnosis and treatment[6]. • *Higher degree of recognition* of specific IgE[6]. • Diagnostic concentration[6]: **32 µg/ml**. • Single dose vials[6]: **2.4 µg**. • Suspension *for injection*[6]. • *Single dose*[6].

REFERENCES: 1. *Summary of product characteristics for Alt a 1 MOL.* ***2.*** *Tabar AI, Prieto L, Alba P, Nieto A, Rodríguez M, Torrecillas M, et al. Double-blind, randomized, placebo-controlled trial of allergen-specific immunotherapy with the major allergen Alt a 1. J Allergy Clin Immunol. 2019;144(1):216-223.e3.* ***3.*** *Simon-Nobbe B, et al. The Spectrum of Fungal Allergy. Int Arch Allergy Immunol. 2008;145(1):58-86.* ***4.*** *Summary of product characteristics for Alt a 1 MOL Mix, Diater.* ***5.*** *DiaterPharmacovigilanceDepartment.2018internaldata.* ***6.*** *SummaryofproductcharacteristicsforCupa1MOL,Diater.* ***7.*** *PichlerU,etal.Pectatelyasepollenallergens:sensitizationprofilesandcross-reactivitypattern.PLoSOne2015;10(5):e0120038.* ***8.*** *Charpin D, Pichot C, Belmonte J, Sutra JP, Zidkova J, Chanez P, et al. Cypress Pollinosis: from Tree to Clinic. Clin Rev Allergy Immunol. 2019;56(2):174-195.* ***9.*** *Domínguez-Ortega J, et al. Prevalence of allergic sensitization to conifer pollen in a high cypress exposure area. Allergy Rhinol (Providence) 2016;7(4):200-6.* ***10.*** *Estudio de estabilidad INF20181120 - Mezcla de Alt a 1 con extractos polimerizados [Stability study INF20181120 - Mix of Alt a 1 with polymerised extracts]. Diater.* ***11.*** *C. Afferni et al. Role of carbohydrate moieties in IgE binding to allergenic components of Cupressus arizonica pollen extract. Clinical and Experimental Allergy, 1999, Volume 29, pages 1087–1094.* ***12.*** *R. Ariano et al. In Vitro and In Vivo Biological Activities of Old and Fresh Cupressus arizonica Pollen. J Investig Allergol Clin Immunol 2006; Vol. 16(3): 177-182.* ***13.*** *Y. Shahali et al. Instability of the structure and allergenic protein content in Arizona cypress pollen. Allergy 2009: 64: 1773–1779.*

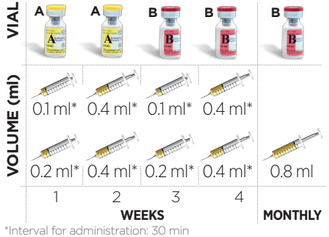
MOLECULAR IMMUNOTHERAPY

DIATER PIONEERING IMMUNOTHERAPY

Alt a 1 MOL

GUIDE FOR **RECONSTITUTION**[1]

ADMINISTRATION **REGIMEN**[1]



*Interval for administration: 30 min

VOLUME OF **ADMINISTRATION**[1]

0.8 ml

(maintenance dose)

DURATION OF TREATMENT[1]

Continuation:

Alt a 1 MOL

Alt a 1 MOL: THE PIONEER IN MOLECULAR IMMUNOTHERAPY[1,2]

Alt a 1, major allergen from the fungus Alternaria alternata

REFERENCES: 1. Summary of product characteristics for Alt a 1 MOL. Diater. **2.** Tabar AI, Prieto L, Alba P, Nieto A, Rodriguez M, Torrecillas M, et al. Double-blind, randomized, placebo-controlled trial of allergenspecific immunotherapy with the major allergen Alt a 1. J Allergy Clin Immunol. 2019;144(1):216-223.e3.

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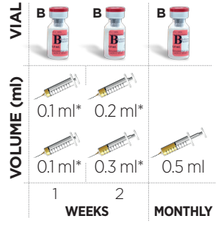
Alt a 1 MOL mix

GUIDE FOR **RECONSTITUTION**[1]

ADMINISTRATION **REGIMEN**[1]



*Interval for administration: 30 min

VOLUME OF **ADMINISTRATION**[1]

0.5ml

(maintenance dose)

DURATION OF TREATMENT[1]

Continuation:

Alt a 1 MOL mix

Alt a 1 MOL MIX: THE SOLUTION FOR THE POLYSENSITISED PATIENT:[1-3]

Alt a 1 + Olea
Alt a 1 + Grasses
Alt a 1 + Dermatophagoides

REFERENCES: 1. Summary of product characteristics for Alt a 1 MOL Mix. Diater. **2.** Tabar AI, Prieto L, Alba P, Nieto A, Rodriguez M, Torrecillas M, et al. Double-blind, randomized, placebo-controlled trial of allergen-specific immunotherapy with the major allergen Alt a 1. J Allergy Clin Immunol. 2019;144(1):216-223.e3. **3.** Diater Pharmacovigilance Department. 2018 internal data.

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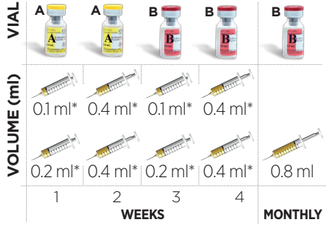
Cup a 1 MOL

SUSPENSION FOR INJECTION

ADMINISTRATION **REGIMEN**[1]



*Interval for administration: 30 min

VOLUME OF **ADMINISTRATION**[1]

0.8 ml

(maintenance dose)

DURATION OF TREATMENT[1]

Continuation:

Cup a 1 MOL

Cup a 1 MOL:[1-3] A LEADING ROLE

Cup a 1, leading major allergen in allergies to Cupressaceae[2-4]

REFERENCES: 1. Summary of product characteristics for Cup a 1 MOL. Diater. **2.** Charpin D, Pichot C, Belmonte J, Sutra JP, Zidkova J, Chanez P, et al. Cypress Pollinosis: from Tree to Clinic. Clin Rev Allergy Immunol. 2019;56(2):174-195. **3.** Pichler U, et al. Pectate lyase pollen allergens: sensitization profiles and cross-reactivity pattern: PLoS One 2015;10(5):e0120038. **4.** Domínguez-Ortega J, et al. Prevalence of allergic sensitization to conifer pollen in a high cypress exposure area. Allergy Rhinol (Providence). 2016;7(4):200-6.

DIATER

SUMMARY OF PRODUCT CHARACTERISTICS Alt a 1 MOL

1. NAME OF THE MEDICINAL PRODUCT. Alt a 1 MOL. **2. QUALITATIVE AND QUANTITATIVE COMPOSITION.** The active substance is the purified protein Alt a 1, the major allergen of the fungus *Alternaria alternata*. Vial A: 0.046 micrograms of lyophilised Alt a 1. Vial B: 0.46 micrograms of lyophilised Alt a 1. It is provided with a reconstitution solvent to obtain an allergen suspension adsorbed in aluminium hydroxide, for subcutaneous administration. For the full list of excipients, see section 6.1. **3. PHARMACEUTICAL FORM.** Powder and solvent for suspension for injection. **4. CLINICAL PARTICULARS. 4.1 Therapeutic indications.** Alt a 1 MOL is an individualised specific immunotherapy product (allergen vaccine) for the treatment of allergic patients with rhinitis, conjunctivitis, allergic asthma and other diseases caused by a type I hypersensitivity to the fungus *Alternaria alternata*. Alt a 1 MOL is indicated in adults, children and adolescents. **4.2 Posology and method of administration.** Posology. The recommended general regimen is as follows (although this can be modified by the physician): **1. Initiation**: the goal is to gradually increase the dose of allergen until the maximum tolerated dose is reached, which will be the maintenance or continuation dose. Due to differences in sensitivity to the allergen, the treatment for each patient should be controlled by his/her doctor. The dose should only be increased in the event that the previous dose is well tolerated. **2. Continuation**: this consists of the administration of the maximum tolerated dose over a period of 2 years. For it to be effective, it is important that Alt a 1 MOL be used on a regular basis throughout the treatment period. Alt a 1 MOL is a subcutaneous treatment. Each vial of Alt a 1 MOL must be reconstituted immediately before administration. For instructions on reconstitution prior to administration, see section 6.6. Alt a 1 MOL is presented in single-dose containers. After the administration of each dose, discard the vial to avoid any confusion. Do not reconstitute the following vials until administration is required. Two different initiation regimens are recommended: the conventional regimen, in which the allergen concentration is increased progressively; and a rapid initiation regimen, which is started by directly injecting the highest allergen concentration. It will be at the discretion of the physician to modify the regimen based on the tolerability and degree of individual sensitisation, the onset of intercurrent processes during the course of immunotherapy and/or the level of exposure to the allergen. These regimens should always be followed, except when indicated otherwise by the physician: (see table on the right). *Paediatric population.* The safety and efficacy of Alt a 1 MOL in the paediatric population has not been determined. In any case, treatment with subcutaneous immunotherapy in children is widely supported by scientific publications (see section 5.1), although, adhering to the current recommendations for the management of subcutaneous immunotherapy, Alt a 1 MOL should not be used in children under 2 years of age and should be used with caution in children aged from 2 to 5. For treatment in paediatric patients, the physician must have experience in the treatment of allergic diseases in children. The posology will be determined by the physician after careful consideration, taking into account the level of efficacy expected in that age group (see section 5.1). *Elderly patients.* The safety and efficacy of Alt a 1 MOL in the elderly has not yet been established. Method of administration. Alt a 1 MOL is intended for subcutaneous administration. It is very important to follow the instructions before using Alt a 1 MOL: • Always begin the administration of the treatment with vial A, which is 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 must be given in the upper dorsal side of the arm, 20 cm above the

Initiation treatment. ***Conventional regimen:*** Check that the presentation consists of two vials A, four vials B and six vials of reconstitution solvent. Always begin administering the treatment using vial A, corresponding to the lowest concentration of lyophilised Alt a 1. Injections should be administered once a week, except for the final two B-vials, which must be spaced one month apart.

DAY	VIAL	RECOMMENDED DOSES	INTERVAL BETWEEN DOSES	FREQUENCY OF ADMINISTRATION	DATE
Day 1	**A Yellow label**	1st Dose: 0.1 ml 2nd Dose: 0.2 ml	30 minutes	weekly	
Day 8	**A Yellow label**	1st Dose: 0.4 ml 2nd Dose: 0.4 ml	30 minutes	weekly	
Day 15	**B Red label**	1st Dose: 0.1 ml 2nd Dose: 0.2 ml	30 minutes	weekly	
Day 22	**B Red label**	1st Dose: 0.4 ml 2nd Dose: 0.4 ml	30 minutes	weekly	
Day 52	**B Red label**	0.8 ml	monthly		
Day 82	**B Red label**	0.8 ml	monthly		

Rapid regimen ***(grouped or cluster):*** Check that the presentation consists of three or six B vials and the same number of vials of reconstitution solvent, according to the physician's prescription.

DAY	VIAL	RECOMMENDED DOSES	INTERVAL BETWEEN DOSES	FREQUENCY OF ADMINISTRATION	DATE
Day 1	**B Red label**	1st Dose: 0.1 ml 2nd Dose: 0.2 ml	30 minutes	weekly	
Day 8	**B Red label**	1st Dose: 0.4 ml 2nd Dose: 0.4 ml	30 minutes	weekly	
Day 38	**B Red label**	0.8 ml	monthly		

Continuation Treatment. Check that the presentation consists of three or six B vials and the same number of vials of reconstitution solvent, according to the physician's prescription. The injections will be administered monthly over a period of 2 years.

VIAL	RECOMMENDED DOSES	FREQUENCY OF ADMINISTRATION	DATE
B Red label	0.8 ml	monthly	
B Red label	0.8 ml	monthly	
B Red label	0.8 ml	monthly	

elbow, alternating arms with each administration, ensuring that it is not administered intravenously. • Proceed in the same way as applicable with the following vials. After the application of each dose, the patient should remain at the centre where the medicine has been administered for at least 30 minutes. For the treatment to be effective, it is important that Alt a 1 MOL be administered regularly throughout the entire treatment period. Do not administer a double dose to make up for a forgotten dose. Alt a 1 MOL should be reconstituted immediately before administration. For instructions on reconstituting the medication before administration, see section 6.6. **4.3 Contraindications.** The use of Alt a 1 MOL is contraindicated in the case of hypersensitivity to any of the excipients included in section 6.1. The use of Alt a 1 MOL is also contraindicated in the following cases: • Severe or poorly controlled asthma. • Active autoimmune diseases (no response to treatment). • Malignant neoplasms. • Children under 2 years of age. • Immunotherapy treatment should not be started during pregnancy. • AIDS. • Fever. **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.** Alt a 1 MOL should be used with caution, assessing the benefit/risk ratio on an individual basis, in the following cases: - Patients with partially controlled asthma. In the case of a patient with partially controlled asthma, stabilisation prior to initiating immunotherapy is recommended. - Children aged 2-5 years given the limited cooperation and the lesser clinical experience in this age group. - Patients undergoing treatment with beta-blockers (see section 4.5). - Patients with pre-existing cardiovascular disease (e.g. ischaemic heart disease or cardiac arrhythmia). The cardiological status and tolerability of the patient in the event of an episode of anaphylaxis and the use of adrenaline should be evaluated. - Autoimmune disease in remission. The effect of immunotherapy on the underlying disease is unknown. - Acquired immunodeficiencies or use of immunosuppressants (other than anti-IgE treatments). Its impact on the efficacy of immunotherapy is unknown. - Chronic infections (e.g. hepatitis B or C). - Psychiatric/mental disorders that interfere with the patient's good compliance and collaboration. - The patient must in any case be well controlled before the start of immunotherapy. - History of severe systemic reactions to previous immunotherapy, given the increased risk of developing new systemic reactions. In general, clinical experience with immunotherapy in patients aged over 65 is limited. In these patients, the presence of previously described comorbidities and concomitant medications should be taken into account. In children with concomitant asthma and acute upper respiratory tract infection, treatment with Alt a 1 MOL should be temporarily discontinued until the infection has disappeared. The administration of Alt a 1 MOL on the same day of administration of other immunisations is not recommended. A gap of at least 10 days between administrations is advisable (see section 4.5). In exceptional cases, this treatment may involve a risk of generalised reactions which may be serious (urticaria, asthma, anaphylactic shock, etc.); therefore, the following guidelines should be followed throughout the entire duration of the treatment: • It is of the utmost importance that the health personnel carefully read the administration requirements before applying this medication. • Alt a 1 MOL should always be administered under medical supervision. • Alt a 1 MOL should only be applied if immediately accessible means are available to allow for treatment of a patient who may possibly suffer from a generalised reaction (urticaria, asthma, anaphylactic shock, etc.), such as intramuscular adrenaline, or others. Therefore, this treatment should be administered at medical surgeries, primary care centres, outpatient centres or appropriately equipped hospitals. It should not, under any circumstances, be administered in the patient's home. • After the application of each and every dose, the patient must remain at the centre where the medication was administered for at least 30 minutes. • If any adverse reaction occurs, before proceeding with the treatment, the risk should be evaluated by the physician. • It is essential that the patient be regularly monitored by the prescribing physician, who is responsible for any dilution of the medication or other alteration necessary in the treatment. In case of moderate systemic reactions, the administration of intravenous corticosteroids or antihistamines is recommended. In the case of bronchospasms, the use of bronchodilators is recommended. Alt a 1 MOL is a subcutaneous treatment; make sure not to administer it intramuscularly or intravenously. Redness at the injection site is normal, provided the diameter does not exceed 5 cm (Malling & Weeke 1993). In the event of a major reaction, the necessary measures for said reaction should be taken, at the discretion of the physician. Each dose of this medicine contains less than 1 mmol of sodium (23 mg); thus it is considered as "sodium free". **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. Malling 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 of medications for the symptomatic treatment of allergy (e.g. antihistamines, corticosteroids) may increase the patient's tolerance to immunotherapy. The use of beta-blockers should be taken into account, since, in the event of anaphylaxis, the capacity to respond to emergency medication may be compromised and the risk of more serious systemic reactions increased. It is recommended that beta blockers be replaced with another alternative treatment if possible (Pitsios *et al.* 2015). There is no clinical experience regarding treatment with Alt a 1 MOL and simultaneous prophylactic vaccination for infectious diseases (e.g. influenza, tetanus, etc.). **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. Risks for babies/new-born children cannot be ruled out. No information is available on the safety of the medicine during pregnancy or breast-feeding. The initiation of allergen immunotherapy, including Alt a 1 MOL, is contraindicated during pregnancy. Fertility. No information is available on the safety of the medicine for fertility. **4.7 Effects on ability to drive and use machines.** No effects have been reported that affect the ability to drive and operate tools or machines; therefore, no special precautions are required. **4.8 Undesirable effects.** Summary of the safety profile. *Local reactions.* In general, the local reactions described consist of the appearance of erythema, oedema, inflammation, heat, pain, pruritus, hives (urticaria) at the injection site. They usually occur between 10 and 60 minutes after administration and persist for several hours, disappearing without requiring treatment. Induration and/or erythema of the injection site is normal, provided the diameter does not exceed 5 cm. In case of a major local reaction, the use of oral antihistamines and/or topical corticosteroids is recommended. *Moderate systemic reactions.* In general, the moderate systemic reactions described consist of rhinitis, (rhino)conjunctivitis, asthma, wheezing, bronchospasm, dyspnoea, cough, pruritus or urticaria (generalised) and angioedema. In these cases, the administration of intravenous corticosteroids (100 mg prednisolone or an equivalent glucocorticoid) is recommended. This therapy can be repeated if necessary. Intravenous antihistamines and high doses of corticosteroids (250-1,000 mg prednisolone) can also be administered. In the case of bronchospasm, the use of bronchodilators is recommended. Additionally, there may be cases of headache, dizziness or discomfort, paresthesia, respiratory tract infection, sinusitis, dermatitis, maculopapular rash, dysmenorrhoea, pre-syncope, bruising, contusion and musculoskeletal stiffness. *Severe systemic reactions.* In exceptional cases, severe systemic reactions may occur, such as anaphylactic reaction or anaphylactic shock. For the treatment of anaphylaxis, the indications included in the current protocols of action must

be followed. In the case of severe hypotension, a plasma volume expander may be required. *Tabulated list of adverse reactions.* The following table of adverse reactions is based on data from a controlled clinical trial where Alt a 1 was investigated in adult and child patients with rhinitis or allergic rhinoconjunctivitis with or without mild or moderate asthma, sensitised to the major allergen Alt a 1 of the fungus *Alternaria alternata*. Adverse reactions are divided into groups, according to the MedDra frequency convention: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000): (see table below). Description of selected adverse reactions. If the patient experiences significant adverse reactions as a result of the treatment, the use of anti-allergic medication should be considered. This medication can produce severe anaphylactic reactions, including anaphylactic shock, considered a class effect of immunotherapy. Therefore, as an important precaution, the treatment must be supervised by a physician (see section 4.2 and 4.4). In the case of severe systemic reactions, a physician should be contacted immediately. In these cases, treatment should be suspended permanently, or until recommended by the physician. Paediatric population. In general, the nature of the adverse effects observed in children and adolescents treated with Alt a 1 MOL is similar to those observed in adults. Reporting of suspected adverse reactions. Reporting suspected adverse reactions after authorisation of the medicinal product is important. This allows for continued monitoring of the benefit/risk ratio of the medicinal product. Health professionals are asked to report suspected adverse reactions through the national notification system. Spanish Pharmacovigilance System for Medicinal Products for Human Use *[Sistema Español de Farmacovigilancia de Medicamentos de Uso Humano]* www.notificaRAM.es. **4.9 Overdose.** If the dose given is higher than the 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 must be suspended permanently or until recommended by the physician. **5. PHARMACOLOGICAL PROPERTIES. 5.1 Pharmacodynamic properties.** Pharmacotherapeutic group: Group V (Various), ATC code: V01AA04. Mould fungus and yeast fungus. It has been found that 90% of patients with allergic rhinitis and/or asthma sensitised to the fungus *Alternaria alternata* are sensitive to the major allergen Alt a 1. Thus, immunotherapy treatment based solely on that allergen would cover the majority of patients allergic to *Alternaria alternata*. As the treatment contains only purified Alt a 1, this allows the preparation of the final product at a more precise dose. The use of a controlled product carries a lower risk of adverse effects. Mechanism of action. Immunotherapy improves tolerance to the allergen through immunological mechanisms, redirecting the CD4 + response of specific T cells (Th2) for the allergen to regulatory Th1 and T profiles. Exposure to the allergen modifies the serum levels of allergen-specific IgE and IgG, although there is no consensus on whether these parameters are related to clinical efficacy. Immunotherapy would seem to induce responses that can contribute significantly to the induction of tolerance. Alt a 1 MOL contains only the purified protein Alt a 1. Therefore, it presents fewer epitopes to the immune system, which allows the modulation of the immune response and the production of specific type-4 IgG (IgG4) against only one allergen. Clinical efficacy and safety. In a clinical trial conducted by Diater, the effects of immunotherapy with Alt a 1 were studied in the titration of specific IgE and IgG4 antibodies against Alt a 1, in the bronchial response to adenosine 5'- monophosphate (AMP) and in methacholine and in the inflammation markers in exhaled air (nitric oxide) and exhaled air condensate (pH and hydrogen peroxide) in asthmatic patients with allergic rhinitis sensitised to *Alternaria alternata*. This is the first study conducted to date to determine the tolerance and immunogenicity of immunotherapy with the major allergen of *Alternaria alternata* (Alt a 1) in patients with allergic rhinitis (associated or not with bronchial asthma) sensitised to the same. The results are summarised below: 1. In patients with respiratory allergy and asthma and/or rhinitis sensitised to the major allergen of *Alternaria alternata* (Alt a 1), immunotherapy with this purified major allergen can induce a systemic immune response, as demonstrated by the significant increase in the production of allergen-specific IgG4 antibodies from the group treated with immunotherapy versus those treated with placebo. 2. Immunotherapy with Alt a 1 MOL produces no significant modifications in the bronchial reactivity against direct and indirect agonists or in the markers of bronchial inflammation suppositions or in the markers of inflammatory systemic response analysed. 3. The treatment is well tolerated, is not associated with general adverse effects, and the frequency with which it induces a local adverse effect is similar to that observed with placebo. 4. The results prove that the concentrations of exhaled nitric oxide (FeNO) in patients with respiratory allergy, at baseline, correlate with the response to AMP, but not with the response to methacholine. These results confirm that the determination of the bronchial response to AMP is more useful for identifying the intensity of inflammation than the study of the response to methacholine. Paediatric population. Allergen immunotherapy is not a treatment indicated for children under 2 years of age. In children aged between 2 and 5, it should be considered on a case by case basis under the full supervision of a physician experienced in the identification and treatment of signs of anaphylaxis in this age group (Wiley *et al.* 2006; Pitsios *et al.* 2015). A retrospective study of subcutaneous immunotherapy in 239 children aged under 5 (8-59 months of age), who received 6,689 injections reported one systemic reaction 90 minutes after administration in a 3-year-old child. In a second study of subcutaneous

System organ class	Frequency	Adverse Reaction to the Drug
Infections and infestations	Common	Conjunctivitis, respiratory tract infection, sinusitis
Skin and subcutaneous tissue disorders	Common	Dermatitis, generalised pruritus, maculopapular rash, pruritus
Reproductive system and breast disorders	Common	Dysmenorrhoea
Nervous system disorders	Common	Headache, dizziness, paresthesia
General disorders and administration site conditions	Very common	Pain in the injection area, oedema in the injection area, erythema in the injection area, pruritus in the injection area, reaction in the injection area
	Common	Induration of the injection area, discomfort, papule at the injection site, heat at the injection site, pain, swelling at the injection area, inflammation, inflammation of the injection area, discomfort in the injection area, bruising in the injection area
Respiratory, thoracic and mediastinal disorders	Very common	Rhinitis
	Common	Dyspnoea; cough, asthma
Vascular disorders	Common	Pre-syncope, bruising
Musculoskeletal and connective tissue disorders	Common	Contusion, musculoskeletal stiffness

immunotherapy to treat allergic asthma due to mites in 22 babies, of which four were under 3 years of age, mild bronchospasm was observed in 7 of the 22 babies as an adverse reaction, although they continued with 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 continuation during adulthood (Jacobsen *et al.* 1996; Arêde *et al.* 2013). The evaluation of the differential effects of immunotherapy based on the stage of development of children and adolescents can help to optimise the treatment and to identify the optimal dose, frequency, duration and treatment initiation age in children (Kim *et al.* 2013). Another review analyses 31 studies on SCIT in children aged 3 to 18, and concludes that there is acceptable evidence that subcutaneous immunotherapy with grass pollen, *Alternaria alternata* and dust mites is beneficial in allergic children (Larenas- Linnemann *et al.* 2011). **References.** 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. 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., 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.** No information is available on the pharmacokinetic properties of Alt a 1 MOL. It is not possible to conduct pharmacokinetic studies of specific immunotherapy products as 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). **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 toxic effects have been observed in abnormal rat and mouse toxicity studies using amounts higher than the treatment. The results of a non-specific irritant capacity study in rats show that the product is not an irritant, as there are no clinical signs attributable to the product. Non-clinical study data show no special risks for human beings. **6. PHARMACEUTICAL PARTICULARS. 6.1 List of excipients.** Mannitol. Reconstitution solvent. Sodium chloride. Aluminium hydroxide. Water for injection. **6.2 Incompatibilities.** No compatibility studies have been performed. In the absence of compatibility studies, this medicinal product should not be mixed with others. **6.3 Shelf life.** Do not use this medicine after the expiry date which is stated on the package. Alt a 1 MOL is presented in single-dose containers. Once the vials have been reconstituted, they should be used immediately. After the administration of each dose, discard the vial to avoid any confusion. **6.4 Special precautions for storage.** Do not store above 25°C. Do not freeze. Store in the original packaging. Do not use Alt a 1 MOL if you notice any of the vials' contents are missing or if the pack is damaged. **6.5 Nature and contents of container.** Glass vial (Type I), with rubber stopper (Type I) and aluminium capsule. Alt a 1 MOL consists of two presentations: initiation and continuation treatment: (see table below). It may be the case that only some of the presentations are marketed. 1-ml single-use syringes are included, both for reconstitution and to ensure sterility conditions during administration and to facilitate filling. **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 regulations. Do not use this medicinal product if you notice visible signs of deterioration. **Reconstitution instructions.** To reconstitute the vial to be administered, extract 1 ml from one of the reconstitution solvent vials and slowly introduce it into the corresponding vial of Alt a 1 according to the indicated administration regimen. 1-ml single-use syringes are included, both for reconstitution and to ensure sterility conditions during administration and to facilitate filling. In the absence of these syringes, you should use 1 ml insulin or tuberculin syringes, perfectly balanced and graduated in tenths of a millilitre. The needles should be subcutaneous with a calibre of 4/10 mm. Then shake the reconstituted vial gently for 2 or 3 minutes, to homogenise the suspension. Shake the vial gently before each extraction. The containers may appear slightly opaque after shaking. This opacity will increase with the concentration of the vial. Once the vials have been reconstituted, they should be used immediately. Do not reconstitute the following vials until necessary. After the administration of each dose, discard the vial to avoid any confusion. **7. MARKETING AUTHORISATION HOLDER.** DIATER Laboratorio de Diagnósticos y Aplicaciones Terapéuticas, S.A. Avenida Gregorio Peces Barba, Parque Tecnológico de Leganés. 28918 Leganés (Madrid) Spain. Tel: +34 91 496 60 13. Fax: +34 91 460 60 12. e-mail: info@diater.com. **8. MARKETING AUTHORISATION NUMBER(S). 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION 10. DATE OF REVISION OF THE TEXT.** July 2018.

Initiation treatment. The presentation may contain three or six vials of active substance and six vials of reconstitution solvent. The possible presentations are: - Presentation with six vials of active substance (A-A-B-B-B-B) and six vials of reconstitution solvent. - Presentation with three vials of active substance (B-B-B) and three vials of reconstitution solvent. - Presentation with six vials of active substance (B-B-B-B-B-B) and six vials of reconstitution solvent.

	Vial	No. of vials	Amount of Alt a 1	Volume
Active substance Alt a 1	A Yellow label	0 or 2 vials	0.046 µg	-
	B Red label	3, 4 or 6 vials	0.46 µg	-
Reconstitution solvent	Grey label	6 vials	-	1.3 ml

Continuation Treatment. The presentation may contain three (B-B-B) or six (B-B-B-B-B-B) B vials and the same number of vials of reconstitution solvent.

	Vial	No. of vials	Amount of Alt a 1	Volume
Active substance Alt a 1	B Red label	3 or 6	0.46 µg	-
Reconstitution solvent	Grey label	3 or 6	-	1.3 ml

SUMMARY OF PRODUCT CHARACTERISTICS: Alt a 1 MOL Mix. Powder and solvent for suspension for injection. 1. NAME OF THE MEDICINAL PRODUCT. Alt a 1 MOL Mix powder and solvent for suspension for injection. Maximum dose of Alt a 1: 0.37 µg. **2. QUALITATIVE AND QUANTITATIVE COMPOSITION.** The active substance consists of the purified protein Alt a 1, a major allergen of the fungus *Alternaria alternata* in combination with a polymerised allergenic extract of *Dermatophagoides pteronyssinus*, wild grasses (*Dactylis glomerata, Lolium perenne, Phleum pratense* and *Poa pratensis)* or *Olea europaea*. Each vial of Alt a 1 MOL Mix contains 0.518 µg of the purified Alt a 1 protein and the corresponding polymerised extract at the usual treatment concentration. It comes with a reconstitution solvent to yield a suspension of the mix adsorbed in aluminium hydroxide, for subcutaneous administration. For the full list of excipients, see section 6.1. **3. PHARMACEUTICAL FORM.** Powder and solvent for suspension for injection. **4. CLINICAL PARTICULARS. 4.1 Therapeutic indications.** Alt a 1 MOL Mix is an individualised allergen immunotherapy product (allergen vaccine) for the treatment of polysensitised allergic patients with symptoms of rhinitis, rhinoconjunctivitis or seasonal or perennial bronchial asthma, caused by type I hypersensitivity to the allergens present in the formulation. **4.2 Posology and method of administration.** Posology. The recommended general regimen (although the physician can modify it according to treatment criteria) is: 1. **Initiation:** the objective is to gradually increase the dose of the drug until reaching the maximum tolerated dose, which will be the maintenance or continuation dose. Due to differences in sensitivity to allergens, each patient's treatment should be monitored by his or her physician. The dose should be increased only if the previous dose is well-tolerated. 2. **Continuation:** this consists of administering the maximum tolerated dose once a month for a period of 3-5 years. It is important to use Alt a 1 MOL Mix regularly throughout the treatment period for the treatment to be effective. Alt a 1 MOL Mix is a subcutaneous treatment. Each vial of Alt a 1 MOL Mix must be reconstituted immediately before it is administered. For instructions on reconstitution prior to administration, see section 6.6. Alt a 1 MOL Mix is presented in single-dose containers. After administering each dose, discard the vial to avoid confusion. Do not reconstitute the subsequent vials until it is time to administer them. The regimen for administration may be modified at the physician's discretion based on tolerability and the degree of individual sensitisation, the appearance of intercurrent processes in the course of immunotherapy and/or the level of exposure to the allergen. The regimen should always be followed except as otherwise indicated by the physician: *Paediatric population.* The safety and efficacy of Alt a 1 MOL Mix in the paediatric population has not been determined. In any case, treatment with subcutaneous immunotherapy in children is widely supported by scientific publications (see section 5.1), although according to the current recommendations for the management of subcutaneous immunotherapy, Alt a 1 MOL Mix should not be used in children under 2 years of age and should be used with caution in children 2 - 5 years of age. For treatment in paediatric patients, the physician must have experience in treating allergic diseases in children. The posology will be determined by the physician following careful consideration, taking into account the expected level of efficacy in that age group (see section 5.1). *Elderly patients.* The safety and efficacy of Alt a 1 MOL Mix in the elderly (over 65 years of age) have not been established. Form of administration. Alt a 1 MOL Mix is intended for subcutaneous administration. It is very important to follow the instructions before using Alt a 1 MOL Mix: • Gently shake the vial before each extraction. • Extract the treatment doses. • Ensure that the route of administration is subcutaneous. The injections must be given in the upper dorsal side of the arm, 20 cm above the elbow, alternating arms with each of the administrations and ensuring that they are not administered intravenously. • Reconstitute in the same way as necessary with the following vials. Following administration of each dose, the patient must remain at the centre where the medicine has been administered for at least 30 minutes. Alt a 1 MOL Mix must be reconstituted immediately before it is administered. For instructions on reconstitution of the medicinal product before administration, see section 6.6.

DAY	DOSE RECOM-MENDED	INTERVAL BETWEEN DOSES	FREQUENCY OF ADMINIS-TRATION	DATE
Day 1	1st Dose: 0.1 ml 2nd Dose: 0.1 ml	30 minutes		weekly
Day 8	1st Dose: 0.2 ml 2nd Dose: 0.3 ml	30 minutes		weekly
Day 38	0.5 ml		Monthly	
-	0.5 ml		Monthly	

4.3 Contraindications. Hypersensitivity to any of the excipients included in section 6.1. The use of Alt a 1 MOL Mix is also contraindicated in the following cases: • Severe or poorly controlled asthma. • Active autoimmune diseases (which do not respond to treatment). • Malignant neoplasms. • Children under 2 years of age. • Immunotherapy treatment should not be started during pregnancy. • Acquired immunodeficiency syndrome (AIDS). • Pyrexia. **Bibliographic 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.** According to current recommendations, the use of aeroallergen immunotherapy, including Alt a 1 MOL Mix, should be pursued with caution, assessing the risks and benefits individually in the following cases: - Patients with partially controlled asthma. In a patient with partially controlled asthma, stabilisation prior to the start of immunotherapy is recommended. - Children 2-5 years of age, given the limited cooperation and lesser clinical experience in this age group. - Patients receiving beta-blockers (see section 4.5). - Patients with pre-existing cardiovascular disease (e.g. ischaemic heart disease or cardiac arrhythmia). Cardiac status and tolerability in the patient should be assessed in the event of an episode of anaphylaxis and the use of adrenaline. - Autoimmune disease in remission. The effect of immunotherapy on the underlying disease is unknown. - Acquired immunodeficiencies or use of immunosuppressants (other than anti-IgE treatments) Their impact on the efficacy of immunotherapy is unknown. - Chronic infections (e.g. hepatitis B or C). - Psychiatric disorders/mental illnesses that interfere with patient compliance and cooperation. In all cases, the patient must be well-managed before the start of immunotherapy. - History of serious systemic reactions to prior immunotherapy given the higher risk of developing new systemic reactions. In general, clinical experience with immunotherapy in patients over 65 years of age is limited. The presence of the above-mentioned comorbidities and concomitant medications must be taken into account in these patients. As with other immunotherapies, there is a higher potential risk of adverse reactions in stages of increased allergen exposure. It is recommended that treatment with subcutaneous immunotherapy, including Alt a 1 MOL Mix, be started at least two months before the pollen season in case of seasonal allergens, or when exposure to the allergen is the lowest. In children with concomitant asthma and acute upper respiratory tract infection, treatment with Alt a 1 MOL Mix should be temporarily discontinued until the infection has resolved. Administration of Alt a 1 MOL Mix on the same day as other immunisations is not recommended. It is advisable to let at least 10 days pass between administrations (see section 4.5). In rare cases, this treatment may carry a risk of systemic reactions which are sometimes serious (urticaria, asthma, anaphylactic shock, etc.). The following rules should therefore be followed throughout the duration of the treatment: • It is extremely important that healthcare personnel read the administration requirements carefully before administering this medicine. • Alt a 1 MOL Mix should always be administered under medical supervision. • Alt a 1 MOL Mix should only be used if immediately accessible means are available to treat patients who might experience a generalised reaction (urticaria, asthma, anaphylactic shock, etc.), such as adrenaline administered subcutaneously or by other routes. Therefore, this treatment should be administered at medical surgeries, primary care centres, outpatient centres and duly equipped hospitals. Under no circumstances should it be administered at the patient's home. • Following administration of each and every dose, the patient must remain at the centre where the medicine has been administered for at least 30 minutes. • In the event of the onset of an adverse reaction, before the treatment is continued, the risk should be evaluated by the physician. • It is essential for the patient to be regularly monitored by the prescribing physician, who is responsible for any drug dilution or other necessary treatment alteration. Alt a 1 MOL Mix is a subcutaneous treatment. It must be ensured that it is not administered intramuscularly or intravenously. Redness at the injection site is

normal, provided the diameter does not exceed 5 cm (Malling & Weeke 1993). In the event of a major reaction, the necessary measures must be taken at the discretion of the physician for the reaction. This medicine contains less than 1 mmol of sodium (23 mg) per dose and is therefore considered essentially 'sodium-free'. **Bibliographic 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. • Malling 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. Concomitant use of medications for symptomatic allergy treatment (e.g. antihistamines or corticosteroids) may increase the patient's tolerance to immunotherapy. The use of beta-blockers should be taken into account, since in the event of anaphylaxis the ability to respond to emergency medication may be compromised and the risk of more serious systemic reactions would be increased. It is recommended that beta-blockers be replaced with an alternative treatment if possible (Pitsios *et al.* 2015). There is no clinical experience regarding treatment with Alt a 1 MOL Mix and simultaneous prophylactic vaccination for infectious diseases (e.g. influenza, tetanus). **Bibliographic 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 breast-feeding. Risks for the baby/neonate cannot be ruled out. No information is available on the safety of the medicinal product when used during pregnancy or breast-feeding. The start of immunotherapy with allergens, including Alt a 1 MOL Mix, is contraindicated during pregnancy. Fertility. No information is available on the safety of the medicinal product for fertility. **4.7 Effects on ability to drive and use machines.** Effects that affect the ability to drive or use tools and machines have not been reported; therefore, no special precautions are required. **4.8 Adverse reactions.** Summary of the safety profile. *Local reactions*. In general, the local reactions reported consist of the onset of erythema, oedema, inflammation, warmth, induration, pain and pruritus at the injection site. They usually occur 10-60 minutes after administration, persist for several hours and disappear without requiring treatment. Additionally, in immunotherapy treatments with subcutaneous allergens, cases of urticaria (wheal), papule, rash, and/or eczema at the administration site have been reported. Induration and/or erythema at the injection site is normal, provided the diameter does not exceed 5 cm. In the event of a major local reaction, the use of oral antihistamines and/or corticosteroids for topical use is advised. *Moderate systemic reactions*. In general, the moderate systemic reactions reported consist of rhinitis, (rhino-)conjunctivitis, eye or chest discomfort, asthma, wheezing, bronchospasm, dyspnoea, cough, pruritus or urticaria (generalised), or angio-oedema. In addition, there may be cases of headache, dizziness or malaise, paraesthesia, bronchitis, respiratory tract infection, sinusitis, dermatitis, maculopapular rash, dysmenorrhoea, presyncope, bruising, musculoskeletal contusion and stiffness, chills, fatigue, fever, nausea, or general malaise. *Serious systemic reactions*. In rare cases, severe systemic reactions such as anaphylactic reaction or anaphylactic shock can occur. For the treatment of anaphylaxis, the instructions that appear in the current protocols for action must be followed. *Tabulated list of adverse reactions.* Alt a 1 allergen: The following table of adverse reactions is based on data from a controlled clinical trial where Alt a 1 was investigated in adult and child patients with allergic rhinitis or rhinoconjunctivitis with or without mild or moderate asthma, sensitised to the major allergen Alt a 1 from the fungus *Alternaria alternata*. Within System Organ Classes, the adverse reactions identified during the clinical trial are listed by frequency (number of patients expected to experience the reaction), using the following categories: Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000) and Very rare (<1/10,000). Polymerised allergen: The following table of adverse reactions is based on data from post-marketing experience with polymerised allergens. Within System Organ Classes, the adverse reactions identified during the marketing period for the polymerised allergens are listed by frequency (number of patients expected to experience the reaction), using the following category: frequency not known (cannot be estimated from available data).

System Organ Class	Frequency	Adverse Drug Reaction
Infections and infestations	Common	Conjunctivitis, respiratory tract infection, sinusitis
Skin and subcutaneous tissue disorders	Common	Dermatitis, generalised pruritus, maculopapular rash, pruritus
Reproductive system and breast disorders	Common	Dysmenorrhoea
Nervous system disorders	Common	Headache, dizziness, paraesthesia
General disorders and administration site conditions	Very common	Injection site reactions (including pain, oedema, erythema, pruritus)
	Common	Injection site reactions (including induration, papule, warmth, swelling, inflammation, discomfort, bruising); general malaise, pain, inflammation
Respiratory, thoracic and mediastinal disorders	Very common	Rhinitis
	Common	Dyspnoea; cough, asthma
Vascular disorders	Common	Presyncope, bruising
Musculoskeletal and connective tissue disorders	Common	Contusion, musculoskeletal stiffness
Immune system disorders	Frequency not known (cannot be estimated from the available data)	Anaphylactic reaction; anaphylactic shock
Respiratory, thoracic and mediastinal disorders	Frequency not known	Bronchospasm, dyspnoea, asthma
General disorders and administration site conditions	Frequency not known	Injection/vaccination site reactions (including warmth, pain, oedema, erythema, swelling, inflammation, pruritus); fatigue, chills, fever, malaise
Eye disorders	Frequency not known	Eye discomfort
Gastrointestinal disorders	Frequency not known	Nausea
Skin and subcutaneous tissue disorders	Frequency not known	Urticaria (including generalised)

Description of selected adverse reactions. If the patient experiences significant adverse reactions as a result of treatment, the use of allergy medication should be considered. This medicine can cause severe anaphylactic reactions, including anaphylactic shock, which is considered a class effect of immunotherapy. Therefore, as an important precautionary measure, the treatment should be supervised by a physician (see sections 4.2 and 4.4). In the event of severe systemic reactions, a physician must be contacted immediately. In these cases, the treatment should be suspended permanently, or until the physician recommends that it be resumed. Paediatric population. In general, the nature of the adverse effects observed in children and adolescents treated with subcutaneous allergen immunotherapy 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 Sistema Español de Farmacovigilancia de Medicamentos de Uso Humano [Spanish Pharmacovigilance System of Medicines for Human Use]: www.notificaRAM.es. **4.9 Overdose.** If the delivered dose is higher than the recommended daily dose, it may increase the risk of adverse reactions, including the risk of systemic reactions or severe local reactions. In these cases, the treatment should be suspended permanently, or until the physician recommends that it be resumed. **5. PHARMACOLOGICAL PROPERTIES. 5.1 Pharmacodynamic properties.** Pharmacotherapeutic group: Group V (Various), ATC code: V01AA (allergen extracts). Mechanism of action. Recent evidence offers a plausible explanation for the multiple mechanisms of allergen immunotherapy (AIT): it induces rapid desensitisation and long-term allergen-specific immune tolerance, and suppresses allergic inflammation in affected tissue. The mechanism described includes modification of the presentation of the allergen by dendritic cells, which for their

part modify the phenotype of allergen-specific T lymphocytes, thus shifting from a Th2 response, which is typical of allergic inflammation, to a Th1 response. Allergen-specific regulatory T cells (Tregs) play a significant role, producing suppressing cytokines such as IL-10 and transforming growth factor beta (TGF-beta) (Incorvaia 2013). The induction of and increase in secretion of IL-10 due to AIT apparently regulates against allergen-specific IgEs and that simultaneously increases IgG4 production. As a result, IL-10 not only generates tolerance in T lymphocytes, but also regulates formation of specific isotopes and influences the IgE-specific response to an IgG4-dominant phenotype (Akdis & Akdis 2007). The testing suggests that allergen-specific IgG4 has significant biological effects. These effects include the IgG-dependent capacity of post-immunotherapy serum to inhibit the binding of IgE-allergen complexes to B lymphocytes, thus blocking the subsequent presentation of the allergen facilitated by IgE and the activation of allergen-specific T lymphocytes, and the prevention of allergen/IgE-dependent activation of peripheral basophils. Alt a 1 MOL Mix contains the purified protein Alt a 1 in combination with a glutaraldehyde-polymerised extract. Glutaraldehyde reacts covalently with the amino groups of the polypeptide chains of the different proteins that make up the allergen extracts to yield a stable, high–molecular-weight polymer where allergen epitopes recognised by IgEs remain inaccessible, leaving most allergen determinants accessible for processing by antigen-presenting phagocytic cells. These transmit immunological information to IgG antibody-producing cells, thus reducing allergenicity. The reduction in IgE binding, and therefore the potential reduction in the capacity to induce an allergic reaction, is due to the structure of the molecules formed following polymerisation. Using the western blot technique and inhibition ELISA, the immunogenic activity and allergenicity of the polymerised allergenic extract (specifically *Dermatophagoides pteronyssinus)* have been compared to the unmodified native product (Froilan *et al.* 2014). The results showed that the IgE antibodies from the serum of allergic patients were not capable of recognising the allergens in the polymerisation and that a 50-fold concentration was needed to achieve the same degree of inhibition as that found in the unmodified allergen, indicating a loss of allergenic potency of the polymerised allergen extract of more than 95%. Clinical efficacy and safety. The World Health Organization (Bousquet *et al.* 1998) and the European Academy of Allergy and Clinical Immunology (Burks *et al.* 2013; Roberts *et al.* 2017) consider allergen immunotherapy to be an effective treatment against rhinoconjunctivitis and allergic asthma. Clinical benefits include reduction in the number and severity of allergy symptoms and less dependence on the use of medications to treat symptoms. Benefits can be sustained for up to 12 years following 3-5 years of allergen immunotherapy, and a longer treatment duration is associated with longer-lasting clinical benefits. Furthermore, immunotherapy may decrease the risk of developing new sensitivities to other inhaled allergens in both monosensitised and polysensitised patients (Cox *et al.* 2014). Adverse reactions are classified as local or systemic. The severity of systemic reactions induced by subcutaneous immunotherapy can range from mild symptoms to anaphylaxis. A survey conducted in 2007 and 2009 following administration of 8 million injections per year found that the systemic reactions recorded accounted for 0.1% of the injections, none of which had a fatal outcome. The majority of these systemic reactions (86%) occurred within 30 minutes following the administration of the injection. Regarding delayed systemic reactions, most were mild, though severe ones were also observed (Burks *et al.* 2013). The risk of systemic reactions to allergen immunotherapy based on conventional dose-titration protocols is approximately 0.2% per injection (1 in 500) (Ravi & Rank 2013). Systematic reviews have found that subcutaneous immunotherapy (SCIT) is safe when prescribed to selected patients in a specialist's practice with suitable facilities and trained medical personnel. SCIT may cause both local and systemic adverse reactions; however, in most cases, these symptoms are easily reversible if they are recognised in time and treated properly. Adverse reactions may occur with allergen preparations whether they are standardised extracts, allergoids or recombinant allergens (Calderon *et al.* 2011). Recent meta-analyses have found that immunotherapy with allergoids/polymerised extracts are effective in reducing symptoms and medication compared to placebo in treating allergic rhinitis (Dhami *et al.* 2017). During clinical development by Diater, the effects of immunotherapy only with Alt a 1 at low doses were studied in the titration of specific IgE and IgG4 antibodies against Alt a 1, in the bronchial response to adenosine 5'-monophosphate (AMP) and in methacholine as well as in the inflammation markers in exhaled air (nitric oxide) and in exhaled breath condensate (pH and hydrogen peroxide) in patients with asthma and allergic rhinitis sensitised to *Alternaria alternata*. The results are summarised below: 1. In patients with respiratory allergy and asthma and/or rhinitis sensitised to the major allergen of *Alternaria alternata* (Alt a 1), immunotherapy with this purified major allergen can induce a systemic immune response, as demonstrated by the significant increase in the production of allergen-specific IgG4 antibodies in the group treated with immunotherapy versus those treated with placebo. 2. Immunotherapy with Alt a 1 does not cause significant changes in bronchial reactivity to direct or indirect agonists, nor does it cause significant changes in the markers of presumed bronchial inflammation or in the markers of systemic inflammatory response analysed. 3. The treatment is well tolerated, it is not associated with general adverse effects and the frequency with which it induces a local adverse effect is similar to that observed with placebo. 4. The results demonstrate that exhaled nitric oxide (FeNO) levels in patients with respiratory allergy, at baseline, correlate with response to AMP, but not with response to methacholine. These results confirm that the determination of the bronchial response to AMP is more useful for identifying inflammation severity than the study of the response to methacholine. In addition, a phase III, multicentre, double-blind, randomised, parallel-group, placebo-controlled clinical trial evaluated the clinical efficacy and safety of immunotherapy with the major purified allergen Alt a 1, in patients with allergic rhinoconjunctivitis with or without mild or moderate asthma, sensitised to Alt a 1. The trial studied the effects of immunotherapy with Alt a 1 on the combined index of frequency, severity of symptoms and use of medication on the titration of specific IgE, IgG and IgG4 antibodies against Alt a 1 and on the skin response to *Alternaria alternata* and Alt a 1, in patients with allergic rhinitis with or without asthma sensitised to Alt a 1. The results of the clinical trial are summarised below: 1. In patients with respiratory allergy and allergic rhinitis and/or asthma, sensitised to the major allergen of *Alternaria alternata* (Alt a 1), immunotherapy with this purified isolated allergen yielded a statistically significant improvement compared to placebo in the combined index of symptoms and medication use — 63% in the first year of treatment. 2. The areas of the papules from the skin tests with *Alternaria alternata* and Alt a 1 were significantly reduced in the two active groups studied at 12 months of treatment. 3. Among patients with a high dose (0.37 µg), 47% had negative skin tests for the major allergen of *Alternaria alternata* (Alt a 1). 4. Serological kinetics showed a 29% reduction in IgE at 24 months in the high-dose group. 5. The ratio of IgG_4 to IgE specific to Alt a 1 showed a 28-fold decrease following 12 months of treatment, and a 50-fold decrease following 24 months of treatment in the group treated with the high dose. Paediatric population. Allergen immunotherapy is not a treatment indicated for children under 2 years of age. In children 2-5 years of age, its use must be considered on a case-by-case basis under the full supervision of a physician with experience in identifying and treating signs of anaphylaxis in this age group (Wiley *et al.* 2006; Pitsios *et al.* 2015). A retrospective study on subcutaneous immunotherapy in 239 children under 5 years of age (8-59 months of age), who received 6,689 injections, recorded one systemic reaction 90 minutes after administration in a 3-year-old child. A second study on subcutaneous immunotherapy for the treatment of allergic asthma due to mites, in 22 infants and young children, four of whom were under 3 years of age, found mild bronchospasm in 7/22 of them as an adverse reaction, though they continued the treatment (Pitsios *et al.* 2015). An early start to suitable immunotherapy in children with allergic rhinoconjunctivitis with or without asthma is the best way to ensure that this disease follows a favourable course and thus prevent it from worsening in adulthood (Jacobsen *et al.* 1996; Arêde *et al.* 2013). Evaluation of the different effects of immunotherapy by developmental stage in children and adolescents may aid in optimising treatment and in identifying the optimal dose frequency, duration and age for starting treatment in children (Kim *et al.* 2013). Another review analysed 31 studies in SCIT in children 3-18 years of age and concluded that there is acceptable evidence that SCIT with pollen from grasses, *Alternaria alternata* and dust mites is beneficial in allergic children (Larenas-Linnemann *et al.* 2011). **Bibliographic references.**

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• 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 toxic effects have been observed in abnormal toxicity studies in rats and mice using amounts greater than those used for treatment. The results of a non-specific irritant capacity study conducted in rats show that the product is not irritant since there are no clinical signs that could be attributed to the product. Non-clinical data reveal no special hazard for humans. **6. PHARMACEUTICAL PARTICULARS. 6.1 List of excipients.** Mannitol. Reconstitution solvent. Sodium chloride. Aluminium hydroxide. Water for injection. **6.2 Incompatibilities.** No compatibility studies have been conducted. 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 carton. Alt a 1 MOL Mix is presented in single-dose containers. Once the vials are reconstituted, they should be used immediately. **6.4 Special precautions for storage.** Store in a refrigerator (2°C – 8°C). Do not freeze. When the interval between doses is 30 minutes, do not discard the vials and store in a refrigerator (2°C – 8°C). Do not freeze. For all other doses, discard the vials after administering them to avoid confusion. Store in the original packaging. Do not use Alt a 1 MOL Mix if you notice loss of content in the vials or deterioration of the container. **6.5 Nature and contents of container.** Glass vial (Type I), with a rubber stopper (Type I) and an aluminium cap. Pack sizes of 3 (B-B-B) and 6 (B-B-B-B-B-B) vials of active substance and the same number of vials of reconstitution solvents. Not all presentations may be marketed. Single-use 1-ml syringes are included to reconstitute the vials, to ensure sterile conditions during administration and to facilitate dosing. **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 regulations. Do not use this medicine if you notice visible signs of deterioration. **Instructions for reconstitution.** To reconstitute the vial to be administered, extract 0.7 ml from one of the vials of reconstitution solvent and slowly add it to the vial of Alt a 1 MOL Mix. Single-use 1-ml syringes are included to reconstitute the vials, to ensure sterile conditions during administration and to facilitate dosing. In the absence of this syringe, you must use 1-ml insulin or tuberculin syringes, perfectly balanced and graduated in tenths of a millilitre. The needles used should be subcutaneous with a calibre of 4/10 mm. Next, gently shake the reconstituted vial for 2-3 minutes to thoroughly mix and homogenise the suspension. Gently shake the vial before each extraction. The containers may appear slightly opaque after shaking. Once vials are reconstituted, they should be used immediately. Do not reconstitute subsequent vials until they are needed. After administering each dose, discard the vial to avoid confusion. **7. MARKETING AUTHORISATION HOLDER.** DIATER Laboratorio de Diagnósticos y Aplicaciones Terapéuticas, S.A. Avenida Gregorio Peces Barba, n° 2. Parque Tecnológico de Leganés. 28918 Leganés (Madrid) Spain. Tel.: (+34) 91 496 60 13. Fax: (+34) 91 460 60 12. E-mail: info@diater.com. **8. MARKETING AUTHORISATION NUMBER(S). 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION. 10. DATE OF REVISION OF THE TEXT**. July 2019.

SUMMARY OF PRODUCT CHARACTERISTICS. Cup a 1 MOL. Suspension for injection. **1. NAME OF THE MEDICINAL PRODUCT.** Cup a 1 MOL 0.3 µg/ml suspension for injection. Cup a 1 MOL 3 µg/ml injection for suspension. **2. QUALITATIVE AND QUANTITATIVE COMPOSITION.** The active substance consists of the purified and isolated protein of Cup a 1, a major allergen of *Cupressus arizonica*, a gymnosperm belonging to the family Cupressaceae. Each vial A contains 0.3 micrograms per millilitre of Cup a 1. Each vial B contains 3 micrograms per millilitre of Cup a 1. For the full list of excipients, see section 6.1. **3. PHARMACEUTICAL FORM.** Suspension for injection. **4. CLINICAL PARTICULARS. 4.1 Therapeutic indications.** Cup a 1 MOL is an individualised specific immunotherapy product (allergen vaccine) for the treatment of allergic patients with rhinitis, conjunctivitis, allergic asthma and other diseases caused by type I hypersensitivity to the pollen of the Cupressaceae family. **4.2 Posology and method of administration.** Posology. The recommended general regimen (although the physician can modify it according to treatment criteria) is: 1. **Initiation:** the objective is to gradually increase the dose of the drug until reaching the maximum tolerated dose, which will be the maintenance or continuation dose. Due to differences in sensitivity to the allergen, each patient's treatment should be monitored by his or her physician. The dose should be increased only if the previous dose is well-tolerated. 2. **Continuation:** this consists of administering the maximum tolerated dose for a period of 3-5 years. It is important to use Cup a 1 MOL regularly throughout the treatment period for the treatment to be effective. Cup a 1 MOL is a subcutaneous treatment. Cup a 1 MOL is presented in single-dose containers. Following administration of each dose, discard the vial to avoid confusion. The recommended regimen is a cluster regimen, in which the allergen concentration is gradually increased. The regimen for administration may be modified at the physician's discretion based on tolerability and the degree of individual sensitisation, the appearance of intercurrent processes in the course of immunotherapy and/or the level of exposure to the allergen. The regimen should always be followed except as otherwise indicated by the physician: **Initiation Treatment.** Check that the presentation consists of two vials A and four vials B. Always start administering treatment with the vial A containing the lowest concentration of the Cup a 1 allergen. Injections must be administered once weekly, except for the last vial B, which is to be administered after the lapse of a month.

VIAL	RECOM-MENDED DOSES	INTERVAL BETWEEN DOSES	FREQUENCY OF ADMINISTRATION	DATE
Day 1	**A Yellow label**	1st Dose: 0.1 ml 2nd Dose: 0.2 ml	30 minutes	weekly
Day 8	**A Yellow label**	1st Dose: 0.4 ml 2nd Dose: 0.4 ml	30 minutes	weekly
Day 15	**B Red label**	1st Dose: 0.1 ml 2nd Dose: 0.2 ml	30 minutes	weekly
Day 22	**B Red label**	1st Dose: 0.4 ml 2nd Dose: 0.4 ml	30 minutes	weekly
Day 37	**B Red label**	0.8 ml	monthly	
Day 67	**B Red label**	0.8 ml	monthly	

Continuation Treatment. Check that the presentation consists of three or six B vials, depending on the physician's prescription. Injections are to be administered monthly for 3-5 years.

VIAL	RECOM-MENDED DOSES	FREQUENCY OF ADMINIS-TRATION	DATE
B Red label	0.8 ml	monthly	
B Red label	0.8 ml	monthly	
B Red label	0.8 ml	monthly	

Paediatric population. The safety and efficacy of Cup a 1 MOL in the paediatric population has not been determined. In any case, treatment with subcutaneous immunotherapy in children is widely supported by scientific publications (see section 5.1), although according to the current recommendations for the management of subcutaneous immunotherapy, Cup 1 MOL should not be used in children under 2 years of age and should be used with caution in children 2-5 years of age. For treatment in paediatric patients, the physician must have experience in treating allergic diseases in children. The posology will be determined by the physician following careful consideration, taking into account the expected level of efficacy in that age group (see section 5.1). *Elderly patients*. The safety and efficacy of Cup a 1 MOL in the elderly (over 65 years of age) have not yet

been established. Form of administration. Cup a 1 MOL is intended for subcutaneous administration. It is very important to follow the instructions before using Cup a 1 MOL: • Always start administering treatment with Vial A, which contains with the lowest concentration. • Gently shake the vial before each extraction. • Extract the treatment doses. • Ensure that the route of administration is subcutaneous. The injections must be given in the upper dorsal side of the arm, 20 cm above the elbow, alternating arms with each of the administrations and ensuring that they are not administered intravenously. • Reconstitute in the same way as necessary with the following vials. Following administration of each and every dose, the patient must remain at the centre where the medicine has been administered for at least 30 minutes. **4.3 Contraindications.** Hypersensitivity to any of the excipients listed in section 6.1. The use of Cup a 1 MOL is also contraindicated in the following cases: • Severe or poorly controlled asthma. • Active autoimmune diseases (which do not respond to treatment). • Malignant neoplasms. • Children under 2 years of age. • Immunotherapy treatment should not be started during pregnancy. • Acquired immunodeficiency syndrome (AIDS). • Pyrexia. **Bibliographic 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.** According to current recommendations, the use of aeroallergen immunotherapy, including Cup a 1 MOL, should be pursued with caution, assessing the risks and benefits individually in the following cases: - Patients with partially controlled asthma. In a patient with partially controlled asthma, stabilisation prior to the start of immunotherapy is recommended. - Children 2-5 years of age, given the limited cooperation and lesser clinical experience in this age group. - Patients receiving beta-blockers (see section 4.5). - Patients with pre-existing cardiovascular disease (e.g. ischaemic heart disease or cardiac arrhythmia). Cardiac status and tolerability in the patient should be assessed in the event of an episode of anaphylaxis and the use of adrenaline. - Autoimmune disease in remission. The effect of immunotherapy on the underlying disease is unknown. - Acquired immunodeficiencies or use of immunosuppressants (other than anti-IgE treatments) Their impact on the efficacy of immunotherapy is unknown. - Chronic infections (e.g. hepatitis B or C). - Psychiatric disorders/mental illnesses that interfere with patient compliance and cooperation. In all cases, the patient must be well-managed before the start of immunotherapy. - History of serious systemic reactions to prior immunotherapy given the higher risk of developing new systemic reactions. In general, clinical experience with immunotherapy in patients over 65 years of age is limited. The presence of the above-mentioned comorbidities and concomitant medications must be taken into account in these patients. As with other immunotherapies, there is a higher potential risk of adverse reactions in stages of increased allergen exposure. It is recommended that treatment with subcutaneous immunotherapy, including Cup a 1 MOL, be started at least two months before the pollen season or when exposure to the allergen is the lowest. In children with concomitant asthma and acute upper respiratory tract infection, treatment with Cup a 1 MOL should be temporarily discontinued until the infection has resolved. Administration of Cup a 1 MOL on the same day as other immunisations is not recommended. It is advisable to let at least 10 days pass between administrations (see section 4.5). In rare cases, this treatment may carry a risk of systemic reactions which are sometimes serious (urticaria, asthma, anaphylactic shock, etc.). The following rules should therefore be followed throughout the duration of the treatment: • It is extremely important that healthcare personnel read the administration requirements carefully before administering this medicine. • Cup a 1 MOL should always be administered under medical supervision. • Cup a 1 MOL should only be used if immediately accessible resources are available to treat patients who might experience a generalised reaction (urticaria, asthma, anaphylactic shock, etc.), such as adrenaline administered subcutaneously or by other routes. Therefore, this treatment should be administered at medical surgeries, primary care centres, outpatient centres and duly equipped hospitals. Under no circumstances should it be administered at the patient's home. • Following administration of each and every dose, the patient must remain at the centre where the medicine has been administered for at least 30 minutes. • In the event of the onset of an adverse reaction, before the treatment is continued, the risk should be evaluated by the physician. • It is essential for the patient to be regularly monitored by the prescribing physician, who is responsible for any drug dilution or other necessary treatment alteration. Cup a 1 MOL is a subcutaneous treatment. It must be ensured that it is not administered intramuscularly or intravenously. Redness at the injection site is normal, provided the diameter does not exceed 5 cm (Malling & Weeke 1993). In the event of a major reaction, the necessary measures must be taken at the discretion of the physician for the reaction. This medicine contains less than 1 mmol of sodium (23 mg) per dose and is therefore considered essentially 'sodium-free'. **Bibliographic 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. • Malling 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. Concomitant use of medications for symptomatic allergy treatment (e.g. antihistamines or corticosteroids) may increase the patient's tolerance to immunotherapy. The use of beta-blockers should be taken into account, since in the event of anaphylaxis the ability to respond to emergency medication may be compromised and the risk of more serious systemic reactions would be increased. It is recommended that beta-blockers be replaced with an alternative treatment if possible (Pitsios *et al.* 2015). There is no clinical experience regarding treatment with Cup a 1 MOL and simultaneous prophylactic vaccination for infectious diseases (e.g. influenza, tetanus). **Bibliographic 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 breast-feeding. Risks for the baby/neonate cannot be ruled out. No information is available on the safety of the medicinal product when used during pregnancy or breast-feeding. The start of immunotherapy with allergens, including Cup a 1 MOL, is contraindicated during pregnancy. Fertility. No information is available on the safety of the medicinal product for fertility. **4.7 Effects on ability to drive and use machines.** Effects that affect the ability to drive or use tools and machines have not been reported; therefore, no special precautions are required. **4.8 Adverse reactions.** Summary of the safety profile. Local reactions consist of the onset of pruritus, urticaria, warmth, pain, oedema and inflammation at the injection site. They usually occur 10-60 minutes after administration, persist for several hours and disappear without requiring treatment. Induration and/or erythema at the injection site is normal, provided the diameter does not exceed 5 cm. In the event of a major local reaction, the use of oral antihistamines and/or corticosteroids for topical use is advised. Measures must be taken and/or medicinal products must be used as indicated by the physician. In general, systemic reactions consist of allergic rhinitis or rhinoconjunctivitis, nasal obstruction or congestion, rhinorrhoea, sneezing, erythema, pruritus, paraesthesia, angioedema, lip or eyelid oedema, wheezing, dyspnoea, cough, hypoventilation or respiratory distress, dysphagia, chest discomfort, hypotension, dizziness, pyrexia, headache, or general malaise. These may occur 15 minutes to 4-6 hours following subcutaneous injection. In the event of bronchospasm, it is recommended that bronchodilators be used. Rarely, this medicine can cause asthma, generalised urticaria, anaphylaxis, shock or anaphylactic reaction. Tabulated list of adverse reactions: The following table of adverse reactions is based on data from post-marketing experience with allergen extracts in a suspension, adsorbed in aluminium hydroxide. Within System Organ Classes, the adverse reactions identified during the marketing period are listed by frequency (number of patients expected to experience the reaction), using the following category: frequency not known (cannot be estimated from the available data). Description of selected adverse reactions. If the patient experiences significant adverse

System Organ Class	Frequency	Adverse drug reaction
Immune system disorders	Frequency not known (cannot be estimated from the available data)	Anaphylaxis, anaphylactic reaction; anaphylactic shock
Respiratory, thoracic and mediastinal disorders	Frequency not known	Dyspnoea, cough, bronchospasm, asthma, wheezing, allergic rhinitis, rhinorrhoea, nasal obstruction or congestion, sneezing, hypoventilation, or respiratory distress
General disorders and administration site conditions	Frequency not known	Injection/vaccination site reactions (including erythema, hives, pruritus, warmth, pain, induration, oedema or inflammation); peripheral oedema or swelling, chest discomfort, general malaise, pyrexia
Eye disorders	Frequency not known	Eyelid oedema, allergic rhino-conjunctivitis, allergic conjunctivitis
Gastrointestinal disorders	Frequency not known	Lip oedema, dysphagia
Skin and subcutaneous tissue disorders	Frequency not known	Urticaria, pruritus, angioedema, erythema (including generalised)
Nervous system disorders	Frequency not known	Paraesthesia, dizziness, headache
Vascular disorders	Frequency not known	Hypotension

reactions as a result of treatment, the use of allergy medication should be considered. This medicine can cause severe anaphylactic reactions, including anaphylactic shock, which is considered a class effect of immunotherapy. Therefore, as an important precautionary measure, the treatment should be supervised by a physician (see sections 4.2 and 4.4). In the event of severe systemic reactions, a physician must be contacted immediately. In these cases, the treatment should be suspended permanently, or until the physician recommends that it be resumed. Paediatric population. In general, the nature of the adverse effects observed in children and adolescents treated with subcutaneous immunotherapy 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 Sistema Español de Farmacovigilancia de Medicamentos de Uso Humano [Spanish Pharmacovigilance System of Medicines for Human Use]: www.notificaRAM.es. **4.9 Overdose.** If the delivered dose is higher than the recommended daily dose, it may increase the risk of adverse reactions, including the risk of systemic reactions or severe local reactions. In these cases, the treatment should be suspended permanently, or until the physician recommends that it be resumed. **5. PHARMACOLOGICAL PROPERTIES. 5.1 Pharmacodynamic properties.** Pharmacotherapeutic group: Group V (Various), ATC code: V01AA05. Tree pollen. Mechanism of action. Recent evidence offers a plausible explanation for the multiple mechanisms of allergen immunotherapy (AIT): it induces rapid desensitisation and long-term allergen-specific immune tolerance, and suppresses allergic inflammation in affected tissue. The mechanism described includes modification of the presentation of the allergen by dendritic cells, which for their part modify the phenotype of allergen-specific T lymphocytes, thus shifting from a Th2 response, which is typical of allergic inflammation, to a Th1 response. Allergen-specific regulatory T cells (Tregs) play a significant role, producing suppressing cytokines such as IL-10 and transforming growth factor beta (TGF-beta) (Incorvaia 2013). The induction of and increase in secretion of IL-10 due to AIT apparently regulates against allergen-specific IgEs and that simultaneously increases IgG4 production. As a result, IL-10 not only generates tolerance in T lymphocytes, but also regulates formation of specific isotopes and influences the IgE-specific response to an IgG4-dominant phenotype (Akdis & Akdis 2007). The testing suggests that allergen-specific IgG4 has significant biological effects. These effects include the IgG-dependent capacity of post-immunotherapy serum to inhibit the binding of IgE-allergen complexes to B lymphocytes, thus blocking the subsequent presentation of the allergen facilitated by IgE and the activation of allergen-specific T lymphocytes, and the prevention of allergen/IgE-dependent activation of peripheral basophils. Cup a 1 MOL contains only the purified and isolated protein Cup a 1, and therefore presents fewer epitopes to the immune system, which enables modulation of the immune response and the production of specific IgG subclass 4 (IgG4) antibodies against only one allergen. Clinical efficacy and safety. The World Health Organization (Bousquet *et al.* 1998) and the European Academy of Allergy and Clinical Immunology (Burks *et al.* 2013; Roberts et al. 2017) consider allergen immunotherapy to be an effective treatment against rhinoconjunctivitis and allergic asthma. Adverse reactions are classified as local or systemic. The severity of systemic reactions induced by subcutaneous immunotherapy can range from mild symptoms to anaphylaxis. A survey conducted in 2007 and 2009 following administration of 8 million injections per year found that the systemic reactions recorded accounted for 0.1% of the injections, none of which had a fatal outcome. The majority of these systemic reactions (86%) occurred within 30 minutes following the administration of the injection. Regarding delayed systemic reactions, most were mild, though severe ones were also observed (Burks *et al.* 2013). The risk of systemic reactions to allergen immunotherapy based on conventional dose-titration protocols is approximately 0.2% per injection (1 in 500) (Ravi & Rank 2013). Systematic reviews have found that subcutaneous immunotherapy (SCIT) is safe when prescribed to selected patients in a specialist's practice with suitable facilities and trained medical personnel. SCIT may cause both local and systemic adverse reactions; however, in most cases, these symptoms are easily reversible if they are recognised in time and treated properly. Adverse reactions may occur with allergen preparations whether they are standardised extracts, allergoids or recombinant allergens (Calderon *et al.* 2011). Paediatric population. Allergen immunotherapy is not a treatment indicated for children under 2 years of age. In children 2-5 years of age, its use must be considered on a case-by-case basis under the full supervision of a physician with experience in identifying and treating signs of anaphylaxis in this age group (Wiley *et al.* 2006; Pitsios *et al.* 2015). A retrospective study on subcutaneous immunotherapy in 239 children under 5 years of age (8-59 months of age), who received 6,689 injections, recorded one systemic reaction 90 minutes after administration in a 3-year-old child. A second study on subcutaneous immunotherapy for the treatment of allergic asthma due to mites, in 22 infants and young children, four of whom were under 3 years of age, found mild bronchospasm in 7/22 of them as an adverse reaction, though they continued the treatment (Pitsios *et al.* 2015). An early start to suitable immunotherapy in children with allergic rhinoconjunctivitis with or without asthma is the best way to ensure that this disease follows a favourable

course and thus prevent it from worsening in adulthood (Jacobsen et al. 1996; Arêde *et al.* 2013). Evaluation of the different effects of immunotherapy by developmental stage in children and adolescents may aid in optimising treatment and in identifying the optimal dose frequency, duration and age for starting treatment in children (Kim *et al.* 2013). Another review analysed 31 studies in SCIT in children 3-18 years of age and concluded that there is acceptable evidence that SCIT with pollen from grasses, Alternaria alternata and dust mites is beneficial in allergic children (Larenas-Linnemann *et al.* 2011). **Bibliographic 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., Akdis C. A. (2007) Mechanisms of allergen-specific immunotherapy. J Allergy Clin Immunol; 19(4): 780-791. • Froilán S., Pineda F., Rodríguez D. 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Ann Allergy Asthma Immunol; 107:407-16. **5.2 Pharmacokinetic properties.** No information is available on the pharmacokinetic properties of Cup a 1 MOL. It is not possible to conduct pharmacokinetic studies of allergen immunotherapy products, as plasma levels of active substance are too low to be measured, given the nature of the product. (CHMP/EWP/18504/2006). **Bibliographic 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.** Data from preclinical studies reveal no special hazards for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. **6. PHARMACEUTICAL PARTICULARS. 6.1 List of excipients.** Sodium chloride. Aluminium hydroxide. Water for injection. **6.2 Incompatibilities.** No data from compatibility studies are available. 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 carton. **6.4 Special precautions for storage.** Store in a refrigerator (2°C – 8°C). Do not freeze. When the interval between doses is 30 minutes, do not discard the vials and store in a refrigerator (2°C – 8°C). Do not freeze. For all other doses, discard the vials after administering them to avoid confusion. Store in the original packaging. Do not use Cup a 1 MOL if you notice loss of content in the vials or deterioration of the container. **6.5 Nature and contents of container.** Glass vial (Type I), with a rubber stopper (Type I) and an aluminium cap. Cup a 1 MOL consists of two presentations: initiation treatment and continuation treatment. **Container for initial treatment.** Initiation treatment consists of 2 units of vial A (yellow label) which hold 1 ml of solution containing 0.3 µg of Cup a 1, and 4 units of vial B (red label) which hold 1 ml of solution containing 3 µg of Cup a 1. **Containers for continuation treatment.** Continuation treatment consists of 3 units of vial B (red label) which hold 1 ml of solution containing 3 µg of Cup a 1. Continuation treatment consists of 6 units of vial B (red label) which hold 1 ml of solution containing 3 µg of Cup a 1. Not all presentations 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 regulations. **7. MARKETING AUTHORISATION HOLDER.** DIATER Laboratorio de Diagnósticos y Aplicaciones Terapéuticas, S.A. Avenida Gregorio Peces Barba, n° 2. Parque Tecnológico de Leganés. 28918 Leganés (Madrid) Spain. Tel.: (+34) 91 496 60 13. Fax: (+34) 91 460 60 12. E-mail: info@diater.com. **8. MARKETING AUTHORISATION NUMBER(S). 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION. 10. DATE OF REVISION OF THE TEXT.** September 2019.