Diater Laboratorio de Diagnóstico
y Aplicaciones Terapéuticas, S.A

Summary of product characteristics

Alt a 1 MOL
Powder and solvent for suspension for injection

1. NAME OF THE MEDICINAL PRODUCT

Alt a 1 MOL 0.046 µg powder and solvent for suspension for injection.
Alt a 1 MOL 0.46 µg powder and solvent for suspension for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The active substance is lyophilized allergen extract of Alt a 1, a major allergen of the mould *Alternaria alternata*.

Each vial A contains 0.046 µg of Alt a 1 lyophilized.
Each vial B contains 0.46 µg of Alt a 1 lyophilized.

Alt a 1 MOL is presented with a solvent for reconstitution, to obtain an allergen diluted in aluminium hydroxide.

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 Therapeutics indications

Alt a 1 MOL is a specific immunotherapy product (allergenic vaccine) and individual, for the treatment of allergic patients with rhinitis, conjunctivitis, allergic asthma and other pathologies with immediate hypersensitivity type I to the *Alternaria alternata* mould.

Alt a 1 MOL is indicated in adults, children and adolescents.

4.2 Posology and method of administration

Posology

The general recommended dosage is (although the physician can modify it according to its therapeutic criterion):

1. **Initiation**: the objective is to increase the dose of this medicine gradually until the maximum tolerated dose is reached, it will be the maintenance dose. Due to differences in sensitivity to allergens, the treatment of each patient should be followed by their physician. The dose should be increased only if the previous dose is well tolerated.

2. **Continuation:** consists in administer the maximum tolerated dose for a period of 2 years, as indicated by the physician. It is important that Alt a 1 MOL will be used regularly through all the treatment period to its effectiveness.

Alt a 1 is intended for subcutaneous administration.

Each vial of Alt a 1 MOL must be reconstituted immediately prior to use. For reconstitution instructions prior to use, see section 6.6.

Two administration schedules are recommended: the conventional schedule, in which the allergen concentration is progressively increased, and the cluster schedule, in which the treatment begins with the maximum allergen concentration. It is under physician criterion the modification of the schedule based on the tolerability and the individual grade of sensitization, the appearance of incursive processes throughout the immunotherapy and/or the allergen exposure.
The following schedules should be followed except in case the physician indicates otherwise:

Initiation treatment

Conventional schedule:

Check first that the treatment package consists of two vials A, four vials B and six vials of solvent for reconstitution.

Always start the administration with the vial A which correspond to the lower concentration of lyophilized Alt a 1.

Injections should be administered at weekly intervals, except the last vials B, in which the treatment will be administered monthly.

DAY	VIAL	RECOMMENDED DOSE	ADMINISTRATION INTERVAL BETWEEN DOSES	ADMINISTRATION INTERVAL	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	monthly	
Day 52	**B Red Label**	0.8 ml	monthly		
Day 82	**B Red Label**	0.8 ml	monthly		

Cluster schedule

Check first that the treatment package consists of three or six vials B and the same number vials of solvent for reconstitution.

DAY	VIAL	RECOMMENDED DOSE	ADMINISTRATION INTERVAL BETWEEN DOSES	ADMINISTRATION INTERVAL	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 first that the treatment package consists of three or six vials B and the same number vials of solvent for reconstitution.

VIAL	RECOMMENDED DOSE	ADMINISTRATION INTERVAL	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 Alt a 1 MOL in children has not been established. Nonetheless, the use of subcutaneous immunotherapy in children is extensively supported by scientific publications (see section 5.1), although following the recommendations in force on the management of the immunotherapy, Alt a 1 MOL should not be used in children aged 0 to 24 months old, and should be used with caution in children from 2 to 5 years old.

For the treatment of paediatric patients, the physician should have experience in the treatment of allergic diseases in children. The posology will be determined by the treating physician after a critical assessment considering the expected level of effectiveness in this age group (see section 5.1).

Elderly population

The safety and efficacy of Alt a 1 MOL in elderly population (≥ 65 years old) has not been established.

Method of administration

Alt a 1 MOL is intended for subcutaneous use.

It is very important to follow the instructions before the use of Alt a 1 MOL:

- Always start the treatment with the vial A, which corresponds to the lowest concentration

- Shake the vial gently before each extraction
- Extract the dosage of the treatment
- Ensure that the administration route is subcutaneous. The injection will be administered in the dorsal upper arm, 20 cm above the elbow, alternating arms in each administration. Care is taken to ensure it is not administered intravenously
- The treatment will continue in the same way with the next vials

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

Alt a 1 MOL must be reconstituted immediately prior to use. For reconstitution instructions prior to use, see section 6.6.

4.3 Contraindications

Alt a 1 MOL is contraindicated in case of hypersensitivity to any of the excipients listed in section 6.1.

Alt a 1 MOL is additionally contraindicated in the following cases:
- Severe or poorly controlled asthma
- Severe immunological disorders (without response to treatment)
- Malignant neoplasias
- Children under 2 years old
- Immunotherapy treatment should not be initiated during pregnancy
- AIDS
- Pyrexia

Literature references

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

4.4 Special warnings and precautions for use

Following the recommendations in force, the immunotherapy with allergens, including Alt a 1 MOL should be used with caution after appraisal of the individual benefit-risk in the following cases:
- Patients with partially controlled asthma. In patients with partially controlled asthma, stabilization is recommended prior the onset of the immunotherapy
- Children from 2 to 5 years old given the limited cooperation and the less clinical experience with this age group
- Patients with concomitant treatment with beta-blockers (see section 4.5)
- Patients with any preexistence cardiovascular disease (i.e. ischemic cardiopathy or heart arrhythmia). The cardiac status and the patient tolerability should be assessed in the face of an anaphylactic episode and the use of adrenaline
- Autoimmune disease into remission. It is unknown the effect of the immunotherapy on the base disease
- Acquired immunodeficiencies or immunosuppressors use (i.e. to diverse treatments with IgE). It is unknown the its impact on the immunotherapy
- Chronic infectious diseases (i.e. Hepatitis B or C)
- Psychiatric disorders or any other cause that prevents adequate treatment compliance. The patient should be in any case well controlled on the onset of the immunotherapy
- Anamnesis of severe systemic reactions to immunotherapy due to the increased risk to the development to new systemic reactions

Generally, the immunotherapy clinical experience in patients over 65 years old is limited. In these patients, presence of comorbidities and concomitant treatments should be considered.

In children with concomitant asthma and acute upper respiratory tract infection the treatment with Alt a 1 MOL should be suspended temporally until the infection is gone.

It is not recommended to administrate Alt a 1 MOL on the same day as the administration of other immunizations. It is advisable that there should be a difference of at least 10 days between administrations (see section 4.5).

This treatment may pose risks related to generalize reactions, which are sometimes severe (urticaria, asthma, anaphylactic shock, etc.) and therefore the following rules should be followed throughout the duration of the treatment:

- It is of the utmost importance that healthcare personnel should read the administrations requirements carefully before administrating the allergenic vaccine
- Alt a 1 MOL should always be administered under medical supervision
- Alt a 1 MOL should only be applied if there are immediately accessible resources to treat a patient that may suffer a generalised reaction (urticaria, asthma, anaphylactic shock, etc.) such as intramuscular adrenalin or other resources. This is the reason why these treatments must be carried out in adequately equipped physician´s surgeries, primary care centres, clinics or hospitals. They should not under any circumstances be administered in the patient´s home
- After each dose is applied, the patient should stay at the health centre where the preparation is administered for at least 30 minutes
- If any adverse reaction appears, the risk should be assessed by a physician before continuing the treatment
- It is essential for the patient to be monitored on a regular basis by the physician issuing the prescription, who is responsible for any necessary dilutions of the extract or other alteration in the treatment required by the patient

Alt a 1 is for subcutaneous administration, it is necessary to ensure that it is not administered intramuscularly or intravenously.

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

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

Literature references

- Pitsios C. *et al*. (2015) Clinical contraindications to allergen immunotherapy: an EAACI position paper. Allergy; 70: 897–909.
- Roberts G. *et al.* (2017) EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. Allergy; 1-34
- Mailing, H.J., Weeke, B. (1993). Position paper: immunotherapy. Allergy; 48:9-35.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

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

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

There is not clinical experience with the concomitant use treatment with Alt a 1 MOL and the prophylactic vaccine treatment for infectious diseases (i.e., flu, tetanus…).

Literature references

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

4.6 Fertility, pregnancy and lactation

Pregnancy and breast-feeding

No risk to the new-born/infants can be excluded. There is not information on the safety of the medicine during pregnancy or breast-feeding. Immunotherapy treatment, including Alt a 1 MOL should not be initiated during pregnancy.

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of safety profile

Local reactions
In general, local reactions are in the injection site consisting of the appearance of erythema, oedema, inflammation, warmth, pain, pruritus, and hives at the injection site. They usually appear between 10 and 60 minutes after administration and persist for several hours, disappearing without treatment.

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

Moderate systemic reactions
In general, moderate systemic reactions consist of rhinitis, (rhino-)conjunctivitis, asthma, wheezing, bronchospasm, dyspnoea, cough, pruritus or urticarial (including generalised), angioedema.

Additionally, may occur cases of headache, dizziness or malaise, paraesthesia, respiratory tract infection, sinusitis, dermatitis, maculopapular rash, dysmenorrhea, presyncope, hematoma, contusion and musculoskeletal stiffness.

Severe systemic reactions
In exceptional cases, severe systemic reactions may occur, such as anaphylactic shock. For the treatment of anaphylactic reactions, current valid procedures on the management of anaphylactic reactions should be followed.

Tabulated summary of adverse reactions

The table below list the adverse reactions observed from the controlled clinical trial in which Alt a 1 was investigated on adults and children patients suffering of allergic rhinitis or rhino-conjunctivitis with or without mild or moderate asthma sensitized to the major allergen Alt a 1 of *Alternaria alternata*.

Within the classification by organs and systems, adverse reactions identified in 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); very rare (< 1/10,000).

Classification by organs and systems	**Frequency**	**Adverse reaction to the medicine**
Infections and infestations	Common	Conjunctivitis, respiratory tract infection, sinusitis
Skin and subcutaneous tissue disorders	Common	Dermatitis, generalised pruritus, pruritus, maculopapular rash
Reproductive system and breast disorders	Common	Dysmenorrhea
Nervous system disorders	Common	Headache, dizziness, paraesthesia
General disorders and administration site conditions	Very common	Injection/vaccination site reactions (including pain, oedema, erythema, pruritus)
	Common	Injection/vaccination site reactions (including induration, papule, warmth, pain, swelling, inflammation, discomfort, hematoma); general malaise, inflammation
Respiratory, thoracic and mediastinal disorders	Very common	Rhinitis
	Common	Dyspnoea; cough, asthma
Vascular disorders	Common	Presyncope, hematoma
Musculoskeletal and connective tissue disorders	Common	Contusion, musculoskeletal stiffness

Description of selected adverse reactions

If the patient suffers of significant adverse reactions as a result of the treatment, antiallergenic treatment should be considered.

This medicine may produce severe anaphylactic reactions, including anaphylactic shock, and is considered a class effect of immunotherapy. It is therefore a preventive measure that treatment should be supervised by a physician (see section 4.2 and 4.4).

A physician should be contacted immediately in case of severe systemic reactions. In these cases, the treatment must be discontinued permanently or until the physician recommends it.

Paediatric population

In general, the undesirable effects observed in children and adolescents treated with Alt 1 MOL is similar to that observed in adults.

Reporting of suspected adverse reactions

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

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Group V ATC code: V01AA04. Mould fungus and yeast fungus.

Mechanism of action

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

Alt a 1 MOL contains only the purified protein Alt a 1, so exhibit less epitopes to the immune system, which allows the modulation of the immune response and the production of IgG and IgG4 is induced against only one allergen.

Clinical efficacy and safety

In a clinical trial performed by Diater the effects of immunotherapy with low doses of Alt a 1 were studied on bronchial response to adenosine 5'-monophosphate (AMP) and on methacholine and on markers of inflammation in exhaled air (nitric oxide) and in condensate exhaled air (pH and hydrogen peroxide) in asthmatic and patients with allergic rhinitis sensitized to *Alternaria alternata.*

The results are summarized below:

1. In patients with respiratory allergy and asthma and/or rhinitis manifestations sensitized to major antigen *Alternaria* (Alt a 1), immunotherapy with this major purified determinant can induce a systemic immune response, as demonstrated by the significant elevation of fixing capacity IgG4 significantly higher in the group treated with immunotherapy than in the treated with placebo.
2. Immunotherapy with Alt a 1 does not produces significant modifications in bronchial reactivity to direct and indirect agonist or to assumptions bronchial inflammation markers or to systemic inflammatory markers analysed
3. Treatment is tolerated, is not associated with general side effects and the frequency with which induces a local side effects is similar to that observed with placebo
4. Results prove that ENO concentrations in patients with respiratory allergy, basal situation, are correlated with the response to AMP, but not with methacholine response. These results confirm that the bronchial response determination to AMP is more useful to identifying the inflammation intensity than the methacholine response study

Additionally, in the phase III clinical trial, multicentre, double-blind, randomized, placebo-controlled, parallel-group, which assessed the clinical efficacy and safety of the immunotherapy treatment with the purified major allergen Alt a 1. In patients suffering of allergic rhino-conjunctivitis with or without mild or moderate asthma sensitized to Alt a 1, it were studied the effects of the immunotherapy with Alt a 1 in the combined index of frequency, severity of symptoms and medication consumption on the titration of specific IgE, IgG and IgG4 against Alt a 1, and in the cutaneous response to *Alternaria alternata* and Alt a 1, in patients with allergic rhinitis with or without asthma sensitized to Alt a 1.

The results obtained in the clinical trial are summarized below:

1. In patients with respiratory allergy and allergic rhinitis and/or asthma, sensitized to the major allergen of *Alternaria alternata* (Alt a 1), immunotherapy with this purified isolated allergen obtains a statistically significant improvement with respect to placebo in the combined rate of symptoms and medication consumption, achieving an improvement of 63% in the first year of treatment
2. Wheal areas of 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. 47% of the patients with high dose (0.37 μg), obtained negative results on the skin tests to 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 Alt a 1-specific IgG4/IgE showed a decrease of 28-fold after 12 months of treatment and 50-fold after 24 months of treatment in the group treated with the high dose

Paediatric population

Allergen immunotherapy is not a treatment option for children under 2 years old. In children from 2 to 5 years old, it should be considered on a case-by-case basis, under the monitoring of

an experienced physician in identifying and treating emerging signs of anaphylaxis in this age group (Wiley et al, 2006; Pitsios et al, 2015).

A retrospective study of subcutaneous immunotherapy in 239 children below the age of 5 years (8-59 months old), who received a total of 6,689 injections, reported a single systemic reaction 90 min after an injection in a 3-year-old boy. A second study of subcutaneous immunotherapy to treat 22 toddlers with mite-allergic asthma (four of whom were less than 3 years old); 7/22 experienced mild bronchospasm as a side-effect, but continued the treatment (Pitsios et al, 2015).

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

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

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

Literature references

- Incorvaia C. (2013) Preventive capacity of allergen immunotherapy on the natural history of allergy. J Prev Med Hyg; 54(2): 71-74.
- Akdis M., Akdis C. A. (2007) Mechanisms of allergen-specific immunotherapy. J Allergy Clin Immunol; 19(4): 780-791.
- Wiley J. and Sons (2006) Subcutaneous immunotherapy. Allergy; Volume 61, Issue s82 3–5
- Pitsios C. *et al.* (2015) Clinical contraindications to allergen immunotherapy: an EAACI position paper. Allergy; 70: 897–909.
- Jacobsen L. *et al.* (1996) Immunotherapy as a preventive treatment. J Allergy Clin Immunol; 97(abstract): p. 232.
- Kim, J. M., Lin S. Y. *et al.* (2013) Allergen-specific immunotherapy for paediatric asthma and rhino-conjunctivitis: a systematic review. Paediatrics; 131(6): 1155-1167.
- Larenas-Linnemann *et al.* (2011) Evidence of effect of subcutaneous immunotherapy in children:complete and updated review from 2006 onward. Ann Allergy Asthma Immunol; 107:407-16

5.2 Pharmacokinetic properties

There is no data on pharmacokinetic properties of Alt a 1 MOL. Pharmacokinetic studies are not possible for products immunotherapy with allergens. During specific immunotherapy usually plasma concentrations of the active substance are not measurable, due to the nature of the product (CHMP/EWP/18504/2006).

Literature references

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

5.3 Preclinical safety data

No toxic effects were observed in abnormal toxicity studies in rat and mouse employing larger amounts to that of the treatment. The results of a study of non-specific irritant capacity conducted in rat indicate that the product is not irritating because of the absence of clinical signs attributable to the product.

The data from the preclinical studies show no special risk for humans.

6. PHARMACEUTICALS PARTICULARS

6.1 List of excipients

Mannitol

Solvent for reconstitution
Sodium chloride
Aluminium hydroxide
Water for injections

6.2 Incompatibilities

No incompatibility studies have been performed. In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Do not use this medicine after the expiry date which is stated on the label.

Alt a 1 MOL is presented in single-dose containers. Reconstituted medicinal products have to be used immediately after preparation. Any remaining or unused material has to be discarded to avoid confusions.

6.4 Special precautions for storage

Do not store above 25 ºC. Do not freeze.

Store in the original packaging.

6.5 Nature and contents of container

Glass vial (type I) with rubber stopper (type I) and an aluminium flip-off cap.

Alt a 1 MOL is constituted by two presentations: Initiation treatment and continuation treatment.

Containers for Initiation treatment:

Initiation treatment contains 2 vials A (yellow label) containing Alt a 1 MOL (0.046 µg), 4 vials B (red label) containing Alt a 1 MOL (0.46 µg) and 6 units with reconstitution solvent (1 ml).

Initiation treatment contains 3 vials B (red label) containing Alt a 1 MOL (0.46 µg) and 3 units with reconstitution solvent (1 ml).

Initiation treatment contains 6 vials B (red label) containing Alt a 1 MOL (0.46 µg) and 6 units with reconstitution solvent (1 ml).

Containers for Continuation treatment

Continuation treatment contains 3 vials B (red label) containing Alt a 1 MOL (0.46 µg) and 3 units with reconstitution solvent (1 ml).

Continuation treatment contains 6 vial B (red label) containing Alt a 1 MOL (0.46 µg) and 6 units with reconstitution solvent (1 ml).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

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

Do not use Alt a 1 MOL if the vial has lost some of its contents or if the packaging has been damaged.

Reconstitution instructions

To reconstitute the vial which will be administered, withdraw 1 ml of one of the reconstitution solvents and add it to the corresponding vial following the schedule of administration indicated.

Syringes of 1 ml for single use are included, both for reconstitution and to ensure sterile conditions in administration and to facilitate dosage. In its absence, it should be used 1 ml insulin or tuberculin syringes, perfectly balanced and graduated in tenths of a millilitre. Needles should be subcutaneous 4/10 mm calibre.

Shake the reconstituted vial gently for 2 or 3 minutes to homogenize the suspension.

Shake the vial gently before each extraction. Containers may have a slight opacity after shaking. This opacity will increase with the concentration of the vial.

Once the vials have been reconstituted, they have to be used immediately. Do not reconstitute the following vials until appropriate.

After the administration of each dose, discard the vial to avoid confusion.

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

October 2024.