1. NAME OF THE MEDICINAL PRODUCT

Polymerized 100 solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Polymerized 100 is an immunotherapy treatment (vaccine), composed of a mixture of modified allergenic extracts (also named allergoids), to which allergens the patient is sensitized, administered subcutaneously for the treatment of allergic diseases.

Polymerized 100 is prepared individually for each patient because each person is sensitised differently to certain substance called allergens, so it is up to the doctor to assess the composition of Polymerized 100 in each case.

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

3. PHARMACEUTICAL FORM

Solution for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Polymerized 100 is used for the treatment of allergic conditions such as rhinitis, rhino-conjunctivitis or seasonal or perennial bronchial asthma.

4.2 Posology and method of administration

Posology

Polymerized 100 is intended for subcutaneous use.

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

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

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

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

Two administration schedules are recommended: the outpatient schedule, in which the allergen concentration is progressively increased, and the cluster schedule, in which the treatment begins with the maximum allergen concentration and the maximum dose is reached in the same day treatment is

started. It will be at the discretion of the physician to modify the regimen according to tolerability and degree of individual sensitisation, the appearance of the intercurrent processes during the immunotherapy and/or the level of exposure to the allergen.

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

Initial Phase

Outpatient schedule:

Check first that the package consists of one, two or three vials of Polymerized 100 (depending on physician criteria).

Schedule 1:

Injections will be administered at weekly intervals, until the maximum tolerated dose is reached, then the treatment will be administered monthly.

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

Schedule 2:

Always start the treatment with the lowest number vial. This will correspond with the lowest polymerized concentration.

The injections will be administered at weekly intervals, until the maximum dose is reached with the vial 3 of the treatment, in which the treatment will be administered monthly.

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

Rapid schedule (grouped or cluster):

DAY	Vial	RECOMMENDED DOSE	ADMINISTRATION INTERVAL	DATE
Day 1	**3 Red Label**	0.2 + 0.3 ml	30-45 minutes	
Day 31	**3 Red Label**	0.5 ml	1 month	
Day 61	**3 Red Label**	0.5 ml	1 month	
Day 91	**3 Red Label**	0.5 ml	Monthly until finishing the content of the vial	

Continuation Phase

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

Injections will be administered monthly for 3-5 years.

DAY	VIAL	RECOMMENDED DOSE	ADMINISTRATION INTERVAL	DATE
Day 121				
	3 Red label	0.5 ml	1 month	
Day 151				
	3 Red label	0.5 ml	1 month	
Day 181				
	3 Red label	0.5 ml	1 month	
Day 211				
	3 Red label	0.5 ml	1 month	

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

Discontinuation of treatment with increase of the recommended interval between doses

In the event that the interval between doses recommended by your specialist doctor is exceeded during treatment, it is important that you consult your doctor before continuing with the treatment, so that he/she can consider reducing the dose compared to the previous dose administered.
The steps to be taken when the recommended dosing interval is exceeded are given below as a guideline, although the decision to modify the schedule should be taken by the specialist doctor.

Exceeded interval	Recommended dose reduction
Up to 8 weeks	Continue with the same dose

Paediatric population

The safety and efficacy of Polymerized 100 in children has not been established. However, the use of subcutaneous immunotherapy in children is extensively supported by scientific publications (see section 5.1), while following current recommendations for the management of subcutaneous immunotherapy, Polymerized 100 should not be used in children under 2 years old and should be used with caution in children aged 2-5 years.

Method of administration

Polymerized 100 is intended for subcutaneous administration.

It is very important to follow the instructions before the use of Polymerized 100:

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

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

4.3 Contraindications

Hypersensitivity to any of the excipients listed in section 6.1.

According to current recommendations, the use of subcutaneous immunotherapy with aeroallergens, including Polymerized 100, is additionally contraindicated in the following cases:

- Severe or poorly controlled asthma.
- Active autoimmunological diseases (no response to treatment).
- Malignant neoplasias.
- Children under 2 years old.
- Immunotherapy treatment should not be initiated during pregnancy.
- AIDS.

Literature references

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

4.4 Special warnings and precautions for use

Following current recommendations, the use of subcutaneous immunotherapy with aeroallergens, including Polymerized 100, should be used with caution on an individual risk/benefit basis in the following cases:

- Patients with partially controlled asthma. In a patient with partially controlled asthma, stabilization prior starting the treatment is recommended.
- Children aged 2-5 years due to limited cooperation and less clinical experience in this age group.
- Patients with concomitant treatment with beta-blockers. (See section 4.5).
- Patients with pre-existing cardiovascular disease (e.g., ischaemic heart disease or cardiac arrhythmia). It should be assessed the cardiac status and the tolerability of the patient to an anaphylaxis episode and the use of adrenalin.
- Autoimmune disease in remission. It is unknown the effect of the immunotherapy on the underlying disease.
- Acquired immunodeficiencies or use of immunosuppressors (other than anti-IgE treatments). Its impact on the effectiveness of immunotherapy is unknown.
- Chronic infectious disease (i.e., Hepatitis B or C).

- Psychiatric/mental disorders that prevents adequate treatment compliance. The patient should be in any case well controlled on the onset of the immunotherapy.
- Anamnesis of severe systemic reactions to previous immunotherapy due to the increased risk to the development of new systemic reactions.

In general, clinical experience with immunotherapy in patients older than 65 years old is limited. In these patients, the presence of comorbidities and concomitant medications previously described should be considered.

As with other immunotherapies, there is a higher potential risk of adverse reactions at times of increased allergen exposure. Initiation of treatment with subcutaneous immunotherapy, including Polymerized 100, is recommended at least 2 months before pollinic season in the case of seasonal allergens; or when allergen exposure is lower (and avoidance measures have been implemented) in the case of perennial aeroallergens.

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

In children with concomitant asthma and acute upper respiratory tract infection, treatment with Polymerized 100 should be temporarily suspended until the infection is resolved.

It is not recommended to administer Polymerized 100 on the same day as the administration of other prophylactic immunizations. It is advisable to administer prophylactic immunizations (e.g., influenza) at least 7 days after the last dose of Polymerized 100, with the next maintenance dose administered at least 2 weeks later (see section 4.5).

In exceptional cases, this treatment may involve a risk of generalised reactions that are sometimes serious (urticaria, asthma, anaphylactic shock, etc.) Therefore, the following recommendations should be followed throughout the duration of the treatment:

- It is of the utmost importance that the healthcare personnel read the administration requirements carefully before administrating this medicine.
- The allergenic extract should always be administered under medical supervision.
- The allergenic extracts should only be applied if there are immediately accessible resources to treat a patient who may suffer a generalised reaction (urticaria, asthma, anaphylactic shock, etc). such as intramuscular adrenaline or other resources. This is the reason why these treatments must be carried out in adequately equipped physician's surgeries, primary care centres, clinics, or hospitals. They should not under any circumstances be administered at the patient's home.
- After all and each dose is applied, the patient should stay at the health centre where the allergenic extract is administered for at least 30 minutes.
- If any adverse reaction appears, the risk should be appraised by a physician before continuing the treatment.
- It is essential for the patient to be monitored in 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.

Polymerized 100 is a subcutaneous treatment, make sure not to administer it intramuscularly or intravenously.

A mild-moderate local reaction is considered when the papule (redness/swelling) at the injection site is less than 10 cm in diameter. In this case, no dose adjustment would be necessary and the specialist physician should assess the need for symptomatic treatment.
If the size is >10 cm, it is considered to be an extensive local reaction and the specialist physician should establish the symptomatic treatment considered, and should consider possible treatment modifications (e.g., splitting the dose between both arms). (EAACI Allergen Immunotherapy Alvaro-Lozano, et al. User's Guide 2020).

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

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

Literature references

- Pitsios C. *et al*. (2015) Clinical contraindications to allergen immunotherapy: an EAACI position paper. Allergy; 70: 897–909.
- Roberts G. *et al.* (2017) EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. Allergy; 1-34
- Alvaro-Lozano M, Akdis CA, Akdis M, et al. EAACI Allergen Immunotherapy User's Guide. Pediatr Allergy Immunol. 2020;31 Suppl 25(Suppl 25):1-101. doi:10.1111/pai.13189.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

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

The use of beta-blockers should be 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).

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

There are no clinical experience data regarding treatment with Polymerized 100 and administration of prophylactic vaccines for infectious diseases (e.g., influenza, tetanus...). It is recommended as a precaution that prophylactic vaccines are administered in the maintenance phase and at least 7 days after the last dose of Polymerized 100, with the next maintenance dose administered at least 2 weeks later (Pfaar O. Allergol Select., 2022).

Literature references

- Pitsios C. et al. (2015) Clinical contraindications to allergen immunotherapy: an EAACI position paper. Allergy; 70: 897–909.
- Sturm G.J. et al. (2017) EAACI Guidelines on allergen immunotherapy: Hymenoptera venom allergy. Allergy, 73(4): 744-764.
- Pfaar O. Allergol Select. 2022.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of the allergenic extracts/metabolites in pregnant women. Starting an allergen immunotherapy treatment, including Polymerized 100, should not be indicated during pregnancy.

Breastfeeding
It is unknown whether the allergenic extracts/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded.

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

4.7 Effects on ability to drive and use machines

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
During the marketing period, most frequent reactions reported with Polymerized 100 in adults and paediatric patients are local reactions and generally consist of oedema, swelling, redness, itching, pain or warmth at the injection site. They usually occur within 10 and 60 minutes after administration and they persist for several hours, disappearing without treatment.

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

Possible systemic reactions are severe generalised allergic reaction (anaphylaxis), hypotension due to allergic reaction (anaphylactic shock), asthma, chest, dyspnoea, cough, allergic bronchitis, urticaria, angioedema, ocular hyperemia and swelling, increased lacrimation, itching of the eye and/or eye pain, nasal itching, increased upper respiratory tract secretion, rhinoconjunctivitis, fatigue, shivering, nausea, pyrexia and/or malaise. For the treatment of anaphylaxis, the indications contained in the current protocols for action should be followed.

Tabulated list of adverse reactions

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

Respiratory, thoracic and mediastinal disorders
Asthma, dyspnoea, cough, allergic bronchitis, nasal pruritus, increased upper respiratory tract secretion
Frequency: unknown (cannot be estimated from the available data)

General disorders and administration site conditions
Injection/vaccination site reactions, warmth, pain, oedema, erythema, swelling (incl. peripheral), inflammation, rash, pruritus, urticaria at injection site.
Fatigue, shivering, feeling warmth, pyrexia, chest discomfort, malaise, hypersensitivity, swelling.
Frequency: unknown (cannot be estimated from the available data)

Eye disorders
Hyperemia and swelling, lacrimation increased, eye pruritus, eye pain
Frequency: unknown (cannot be estimated from the available data)

Infections and infestations
Conjunctivitis
Frequency: unknown (cannot be estimated from the available data)

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

Skin and subcutaneous tissue disorders
Angioedema, nasal itching, urticaria (including. generalised).
Frequency: unknown (cannot be estimated from the available data)

Vascular disorders
Hypotension.

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

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

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

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

Paediatric population

In general, adverse events observed in children or adolescents treated with Polymerized 100 are similar to those 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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
Recent evidence has provided a plausible explanation for the multiple mechanisms of specific immunotherapy (SIT), which induces rapid desensitization and long-term allergen-specific immune tolerance, as well as the suppression of allergic inflammation in the affected tissue. The described mechanism includes the modification of the allergen presentation by dendritic cells that in turn modify the phenotype of allergen-specific T cells, switching from the Th2-type response, typical of allergic inflammation, to a Th1-type response. An important role is played by allergen-specific T regulatory (Treg) cells, which produce suppressive cytokines such as IL-10 and TGF-beta (Incorvaia 2013). The induction and increase in the secretion of IL-10 by the SIT apparently regulates against allergen specific IgE and this simultaneously increases IgG_4 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 IgG_4 (Akdis and Akdis 2007). Evidence suggests important biological effects of allergen specific IgG_4. 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.

Allergic extracts of Polymerized 100 are modified extracts (polymerization with glutaraldehyde) with the objective of decreasing the capability to produce adverse reactions, maintaining the capacity of inducing an adequate immunological response. Glutaraldehyde reacts covalently with amine groups of polypeptide chains of the different proteins that constitute the allergic extracts, generating a stable and

high molecular weight polymer where the allergenic epitopes recognised by IgEs are hidden, leaving most of the allergenic determinants accessible for processing by phagocytic antigen-presenting cells which transmit the immunological information to IgG antibody-producing cells, thus reducing allergenicity. The reduction in IgE binding, and thus the potential reduction in the ability to induce an allergic reaction, is due to the structure of the molecules formed after polymerization.

The immunogenic activity and allergenicity of polymerized allergic extract (specially *Dermatophagoides pteronyssinus*) were compared with the unmodified native product by Western-blot and inhibition ELISA (Froilan *et al.* 2014). The results show that serum IgE of allergenic patients were not able to recognize the polymerized allergen and a 50-fold higher concentration was required to achieve the same degree of inhibition as that found in the unmodified allergen, indicating a loss of allergenic potency of the polymerized allergen extract of over 95%.

Clinical efficacy and safety

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

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

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

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

Recent meta-analysis has demonstrated that immunotherapy with polymerized extracts is effective to reduce the symptoms and the medication respect to placebo in the allergic rhinitis (Dhami *et al.* 2017).

Paediatric population

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

A retrospective study of subcutaneous immunotherapy in 239 children below the age of 5 years (8–59 months old), who received a total of 6689 injections, reported a single systemic reaction 90 minutes 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 *et al.* 2013).

Another review analyses 31 studies on SCIT in children from 3 to 18 years old 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.
- Froilán S., Pineda F., Rodríguez D. (2014) Caracterización del polimerizado de "Dermatophagoides pteronyssinus" modificado con glutaraldehído. Dianas; 3(1): e20140907.
- Bousquet, Jean *et al.* (1998) Allergen immunotherapy: Therapeutic vaccines for allergic diseases A WHO position paper. Journal of Allergy and Clinical Immunology; Volume 102, Issue 4, 558 - 562
- Burks A. Wesley *et al.* (2013) Update on allergy immunotherapy: American Academy of Allergy, Asthma & Immunology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report. Journal of Allergy and Clinical Immunology, Volume 131, Issue 5, 1288 - 1296.e3
- Roberts G. *et al.* (2017) EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. Allery; 1-34
- Cox L. S., Hankin C., *et al*. (2014) Allergy immunotherapy adherence and delivery route: location does not matter. J Allergy Clin Immunol Pract; 2(2): 156-160.
- Ravi, A., Rank M. A. (2013) Reducing and managing systemic reactions to immunotherapy. Curr Opin Allergy Clin Immunol; 13(6): 651-655.
- Calderon, M. A., R. J. Boyle, *et al*. (2011) Immunotherapy: The meta-analyses. What have we Learned? Immunol Allergy Clin North Am; 31(2): 159-173, vii.
- Dhami S. *et al.* (2017) Allergen immunotherapy for allergic rhinoconjunctivitis; A systematic review and meta-analysis. Allergy; 2017; 72: 1597-1631
- Wiley J. and Sons (2006) Subcutaneous immunotherapy. Allergy; Volume 61, Issue s82 3–5
- Pitsios C. *et al*. (2015) Clinical contraindications to allergen immunotherapy: an EAACI position paper. Allergy; 70: 897–909.
- Jacobsen L. *et al*. (1996) Immunotherapy as a preventive treatment. J Allergy Clin Immunol; 97(abstract): p. 232.
- 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
- 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.

5.2 Pharmacokinetic properties

There is no data on pharmacokinetic properties of Polymerized 100. Pharmacokinetic studies are not possible for products of specific immunotherapy. During specific immunotherapy usually plasma concentrations of the active substance are not measurable, due to the nature of the product (CHMP/EWP/18504/2006).

Literature references

- 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

Studies of abnormal toxicity and irritant capacity were performed on the solvent used in Polymerized 100, constituted by the excipients (see section 6.1). The abnormal toxicity studies were performed in

mice and guinea pigs, where a dose corresponding to 700-fold the maximum human dose showed no signs of toxicity. The study of non-specific irritant capacity, performed in rats, where a dose corresponding to 700-fold the maximum human dose, showed that the solvent used in Polymerized 100 is mildly irritant.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Phenol.
Sodium Chloride.
Monopotassium phosphate.
Disodium phosphate.
Water for injection

The allergenic extracts of Polymerized 100 have been polymerized with glutaraldehyde and do not contain aluminium hydroxide.

6.2 Incompatibilities

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

6.3 Shelf life

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

6.4 Special precautions for storage

Store in a refrigerator (2ºC – 8°C). Do not freeze.

Store in original package.

Do not use Polymerized 100 if the vial has lost some of its contents or if the packaging has been damaged.

6.5 Nature and contents of container

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

Polymerized 100 consist of two presentations packages: initiation treatment and continuation treatment.

Initiation treatment

Package may contain one, two or three vials of allergenic extract. The possible packages are:

- Package with one vial of polymerized product (3).
- Package with two vials of polymerized product (3-3).
- Package with three vials of polymerized product (1-2-3).

	Vial	No. vials	Concentration	Volume
Active Substance - allergen	No. 1 Green Label	0 or 1 vial	1/100 of No. 3 vial	3 ml
	No. 2 Yellow Label	0 or 1 vial	1/10 of No. 3 vial	3 ml
	No. 3 Red Label	1 or 2 vials	Maximum Concentration (different to each allergen)	3 ml

Continuation treatment

The package may contain one (3) or two (3-3) vials of No. 3.

	Vial	No. vials	Concentration	Volume
Active Substance - allergen	No. 3 Red Label	1 or 2 vials	Maximum Concentration (different to each allergen)	3 ml

1 mL single use syringes are included to ensure sterile conditions in administration and to facilitate dosing.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

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

Do not use this medicine if you observe any signs of deterioration.

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

December 2023