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SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Staloral 300 sublingual solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 10 or 300 IR/ ml (standardised allergen extract), of one allergen extract or a mixture of several allergen extracts (the list of allergen extracts is presented hereafter).
The active substance corresponds to a mannitoled freeze-dried allergen extract, or to a glycerinated mannitoled allergen extract solution.

- *IR (Index of Reactivity): An allergen extract has a titre of 100 IR/ml if in a prick-test performed using a Stallerpoint® in 30 subjects sensitised to the allergen in question, it produces a wheal of 7 mm in diameter (geometric mean). Skin reactivity in these subjects is simultaneously demonstrated by a positive response to a prick-test with codeine phosphate 9% or 10 mg/ml histamine dihydrochloride.*

Individual allergens and allergen mixtures are listed in the following table:

POLLENS extracts		
Weeds (*ALLERGENA MUCORUM POLLEN*)	**Grasses (*ALLERGENA GRAMINIS POLLEN*)**	**Trees (*ALLERGENA ARBORIS POLLEN*)**
- *Ambrosia elatior* (Ragweed) - *Parietaria officinalis* (Erect Wall pellitory) - *Artemisia vulgaris* (Mugwort)	- *Secale cereale L.* (Rye) ⁜ 5 grasses : - *Dactylis glomerata L.* (Cocksfoot) - *Anthoxanthum odoratum L.* (sweet vernal-grass) - *Lolium perenne L.* (Rye-grass) - *Poa pratensis L.* (Meadow grass) - *Phleum pratense L.* (Timothy) ⁜ 5 grasses + 4 cereals	- *Betula alba* (Birch) - *Carpinus betulus* (Hornbeam) - *Coryllus avelana* (Hazel) - *Alnus glutinosa* (Alder) - *Fraxinus excelsior* (Ash) ⁜ Betulaceae : - *Alnus glutinosa* (Alder) - *Betula pendula Roth* (Birch) - *Corylus avellana L.* (Hazel)

MITES *(Allergena acarorum)*
- *Dermatophagoides pteronyssinus* - *Dermatophagoides farinae* - *Dermatophagoides pteronyssinus, Dermatophagoides farinae*

For excipients, refer to section 6.1 “List of excipients”.

3. PHARMACEUTICAL FORM

Sublingual solution.
Description: colourless till brownish solution according to concentration of allergen.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Type I allergies (Gell and Coombs classification) mainly involving rhinitis, conjunctivitis, rhino-conjunctivitis or asthma (mild to moderate) of a seasonal or perennial nature.
Allergenic immunotherapy (AIT) prevents the development of the clinical manifestations induced by the contact of the sensitised organism with the allergen.

4.2. Posology and method of administration

The advantages of instituting allergen immunotherapy early in the evolution of the disease should be considered.

Allergen immunotherapy is not recommended before the age of 5.

Posology must be adjusted to the patient's tolerance and other illnesses (i.e. respiratory infections).

For seasonal allergies, it is recommended to start the treatment before the pollen season and pursue until the end of the season.
For perennial allergies, it is recommended to maintain the treatment all year round.

The therapy consists of two phases:
- an initiation phase with dose escalation;
- a maintenance phase with constant dose.

1. The initial treatment*: *dose escalation

The dose is escalated every day until the optimal dose is reached (maintenance dose)
Treatment regimen example is proposed hereafter:

1st Week			2nd Week		
Vial concentration: 10 IR/ml blue cap			Vial concentration: 300 IR/ml purple cap		
Day	Number of actuations	Dose (IR)	Day	Number of actuations	Dose (IR)
1	1	2	6	1	60
2	2	4	7	2	120
3	3	6	8	3	180
4	4	8	9	4	240
5	5	10			

Note: This therapeutic scheme is only indicative and may be modified according to the reactivity and the clinical condition of the patient

2. The maintenance treatment: constant dose

Once the initiation phase is completed, the maintenance dose is administered:
- either daily: 120 to 240 IR corresponding to 2 to 4 pressures with the 300 IR/ml vial concentration
  or
- 3 times/week: 240 IR corresponding to 4 pressures with the 300 IR/ml vial concentration

In general, daily administration is associated with better compliance than 3 times/week administration. Therefore daily administration is recommended.

Staloral 300 clinical studies confirmed that a daily dose of 300 IR is well tolerated.

- **<u>Duration of treatment</u>**

Allergen immunotherapy should continue for 3 to 5 years.

Treatment should be reassessed in absence of significant improvement of symptoms after 1 year (perennial allergy) or after the first pollen season (seasonal allergy).

- **Temporary Interruption of the treatment**

For interruption of less than 1 week, it is recommended to resume the treatment at the last dose. For interruption of more than 1 week, it is recommended to resume the treatment with one actuation of the last vial used and to increase the dose according to the initiation scheme until the maintenance dose is reached.

- **Method of administration**

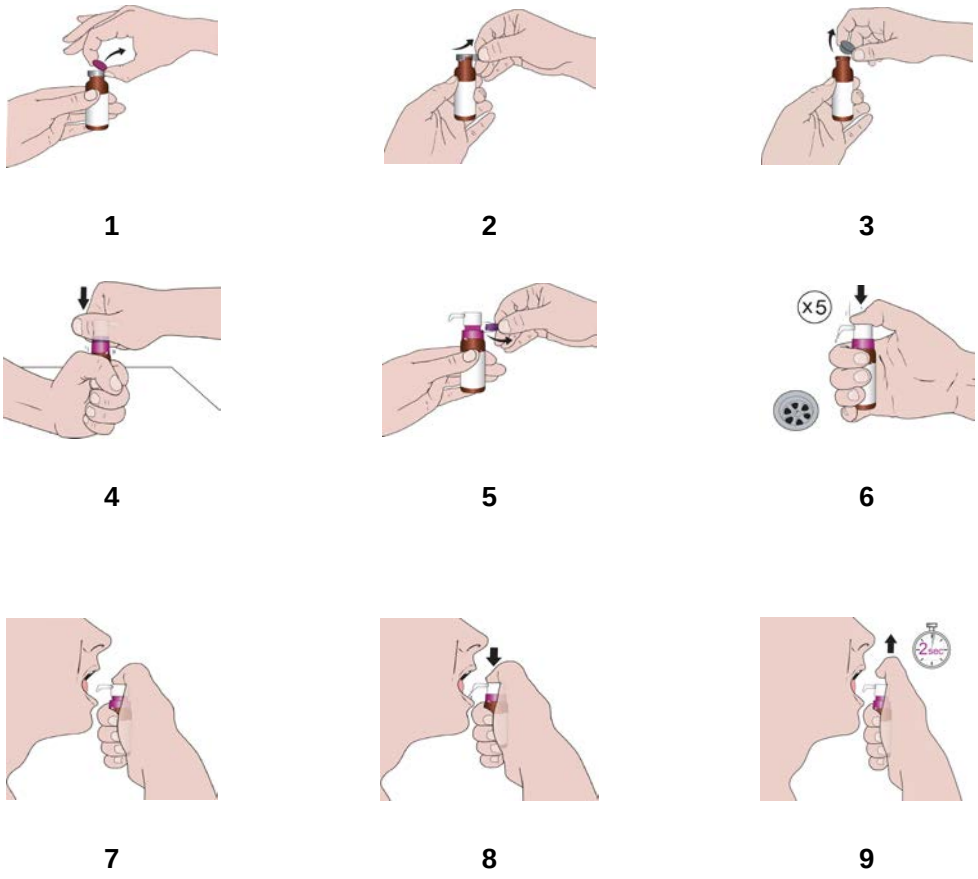
It is recommended to take the treatment during the day, in a mouth without food or beverage.
The solution is to be placed directly under the tongue and kept there for two minutes before being swallowed.
Use by children should be supervised by an adult.

In the case of administration of product prepared for a particular patient is necessary before the application always check the name of the patient, composition, concentration and time of application.

Before each treatment, check:

- the expiry date;
- that the vial to be used matches the prescription (composition, name of the patient, concentration, schedule)

Information on taking for the first time:
For safety reasons and to ensure the vials remain intact, they are hermetically sealed.



When taking for the first time, proceed as follows:

1. Remove the coloured plastic part.
2. Pull on the metal tab and remove the aluminium capsule entirely.
3. Remove the grey stopper.
4. Take the pump out of its protective casing. Place the vial on a flat surface and, hold it firmly with one hand and secure the pump onto the vial by pressing it down hard.
5. Remove the safety ring.
6. **Before first use, fill the pump by pushing it down hard until maximum possible depression at least 5 times**.
   Discard any solution obtained this way.
   After filling the pump by 5 depressions, the pump will always dispense a full dose.
7. Place the tip of the pump in your mouth and push it under your tongue.
8. Push hard until maximum possible depression. In order to apply the maximum pressure, use the finger with which this movement is the easiest.
9. Release the pump and let it return to the original position. **Wait at least 2 seconds until every subsequent depression of the pump.**
10. Repeat the procedure in order to administer the number of doses prescribed by the doctor. **Keep the solution under the tongue for 2 minutes and then swallow.**
11. Wipe the tip of the pump after use and put the safety ring back on.

For subsequent doses, remove the safety ring and then proceed as described in step 7 and onwards.

4.3. Contraindications

- Hypersensitivity to any of the excipients listed in section 6.1;
- Immune complex diseases or immune deficiency diseases;
- Malignant disease;
- Patients with uncontrolled or severe asthma (FEV1 < 70% of predicted value);
- Oral inflammations such as oral lichen planus oral ulcerations or oral mycosis.

4.4. Special warnings and precautions for use

Before starting the treatment, symptoms of allergy should be stabilised with an appropriate symptomatic therapy if necessary. Treatment should be postponed in case of significant clinical symptoms of the allergic disease at the time of the treatment initiation.

Eosinophilic esophagitis has been reported in association with sublingual immunotherapy. During treatment with Staloral 300, if severe or persistent gastro esophageal symptoms including dysphagia or chest pain occur, Staloral 300 should be interrupted and the patient evaluated by their physician. Treatment should only be resumed upon instruction of the physician.

In case of occurrence of allergen-mediated symptoms, use of medications such as corticoids, H1-antihistamines and β2-agonists can be necessary.

Allergen immunotherapy in patients treated with tricyclic antidepressants and mono amine oxidase inhibitors (MAOIs) should be considered carefully.

In case of mycosis, aphta, mucosa lesions, dental loss or oral surgery, including dental extraction; treatment with Staloral 300 should be stopped until complete healing.

Patients taking beta-adrenergic blockers may be unresponsive to the usual doses of epinephrine used to treat serious systemic reactions, including anaphylaxis. Specifically, beta-adrenergic blockers antagonize the cardiostimulating and bronchodilating effects of epinephrine.

This medicine contains 590 mg of sodium chloride per vial (in a 10 ml solution). It should be taken into account for patients following a strict low sodium diet, particularly for children.

Patient should inform physician of any recent intercurrent disease or any worsening of allergic disease.

4.5. Interaction with other medicinal products and other forms of interactions

No interaction studies have been performed.

No interactions were reported in clinical trials with Staloral 300.

In case of severe allergic reactions, use of epinephrine may be necessary. In patients treated with tricyclic antidepressants and mono amine oxidase inhibitors (MAOIs), risk of undesirable effects of epinephrine can be increased with possible fatal consequences. This risk would have to be considered prior to treatment initiation.

Clinical experience concerning simultaneous vaccination during Staloral 300 treatment is missing. Vaccination may be given without Staloral 300 discontinuation after medical evaluation of the general condition of the patient.

4.6 Fertility, pregnancy and lactation

Pregnancy
No clinical data are available for the use of Staloral 300 in pregnant women.
Animal studies do not indicate reproductive toxicity.

As a precautionary measure, it is preferable to avoid initiating Staloral 300 during pregnancy. If pregnancy occurs during treatment, the treatment may be continued with close supervision.

Breast-feeding
It is not known whether Staloral 300 is excreted in human breast milk.
No animal studies were conducted to investigate excretion of Staloral 300 into milk.
A risk to the newborns/infants cannot be excluded.
A decision must be made whether to discontinue breast-feeding or to discontinue Staloral 300 therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
In non clinical studies no fertility study was conducted with Staloral 300. However histopathological examination of the male and female reproductive organs in some repeat-dose toxicity studies with pollen and mite extract contained in Staloral 300 revealed no adverse findings.

4.7. Effects on ability to drive and use machines

Staloral 300 has no known influence on the ability to drive and use machines.

4.8 Undesirable effects

During treatment, patients are exposed to allergens that may induce reactions which can occur immediately after administration or be delayed.

As with any allergen immunotherapy, severe allergic reactions including severe laryngopharyngeal disorder (such as dysphonia, oropharyngeal discomfort and pharyngeal oedema) or systemic allergic reactions (i.e., acute onset of an illness with involvement of the skin, mucosal tissue, or both, respiratory compromise, persistent digestive complaints such as crampy abdominal pain or vomiting, or reduced blood pressure and/or associated symptoms such as hypotonia or syncope) can occur. Inform patients of the associated signs and symptoms and have them seek immediate medical care and discontinue therapy should these occur. Treatment should only be resumed at the instruction of a physician.

Tolerance of a given dose in a patient may vary over time depending on the patient's condition and the environment.

Pre-treatment with anti-allergic agents (for example antihistamines) may reduce frequency and severity of adverse reaction.

In case of occurrence of an adverse reaction, the treatment regimen should be reconsidered.

The adverse reactions are presented by MedDRA preferred terms, and classified by MedDRA System Organ Class and by frequency according to the convention below:
Common (≥ 1/100 to <1/10)
Uncommon (≥ 1/1,000 to <1/100)
Rare (≥ 1/10,000 to <1/1,000)

The following adverse reactions were either reported in clinical trials or spontaneously reported in pharmacovigilance settings.

System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders	rare	lymphadenopathy
Immune system disorders	uncommon	hypersenzitivity

	rare not known	serum-sickness like reaction Angioedema*, anaphylactic shock*
Nervous system disorders	uncommon rare not known	paraesthesia headache dysgeusia*, vertigo*
Eye disorders	common uncommon	eye pruritus conjunctivitis
Ear and labyrinth disorders	common	ear pruritus
Respiratory, thoracic and mediastinal disorders	common uncommon	throat irritation, pharyngeal edema, oropharyngeal blistering, rhinitis, cough asthma, dyspnea, dysphonia, nasopharyngitis
Gastrointestinal disorders	common not known	lip edema, oral puritus, mouth edema, tongue edema, paraesthesia oral, oropharyngeal discomfort, stomatitis, salivary gland disorders, nausea, abdominal pain, vomiting, diarrhea oral pain, gastritis, oesophageal spasm, dry mouth*, oropharyngeal oedema*, pharynx oedema*, eosinophilic esophagitis*
Skin and subcutaneous tissue disorders	common uncommon rare	pruritus, erythema urticaria eczema
Musculoskeletal and connective tissue disorders	rare	arthralgia, myalgia
General disorders and administration site conditions	rare	asthenia, pyrexia

***** Preferred terms reported from post-marketing experience

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 at the following address:
Státní ústav pro kontrolu léčiv
Šrobárova 48
100 41 Praha 10
Webové stránky: www.sukl.cz/nahlasit-nezadouci-ucinek

4.9 Overdose

If doses higher than recommended are taken, the risk of occurrence of adverse reaction and its severity may be increased.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Allergen extracts
ATC code: V01AA

The precise mechanism of action of allergens administered during the course of allergen immunotherapy (AIT) is not clearly understood.

Treatment with Allergen immunotherapy has shown to induce changes in T-lymphocyte responses, followed by elevations in allergen-specific IgG4,and/or IgG1 and sometimes IgA and decrease of specific IgE, A second and probably later immunologic response is immune deviation with a shift in the allergen specific T cell response.

5.2 Pharmacokinetic properties

The greater part of allergens in Staloral 300 is a mixture of proteins and glycoproteins. Due to the nature of the extracts, there is no expected blood bioavailability of intact allergens
after sublingual administration.
Therefore, no pharmacokinetic studies in animals or in human have been carried out to investigate the pharmacokinetic profile and metabolism of allergen extracts.

5.3 Preclinical safety data

Non clinical data reveal no special hazard for humans based on conventional studies conducted with allergen extracts contained in Staloral 300 to evaluate safety pharmacology, repeat-dose toxicity, genotoxicity, toxicity to reproduction and development

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Sodium chloride, glycerol, mannitol, water for injections.

6.2. Incompatibilities

Not applicable

6.3. Shelf life

36 months before opening (except for STALORAL 10 IR/ml weed pollen species group: 18 months before opening).
30 days after opening.

6.4. Special precautions for storage

Store in a refrigerator (2°C – 8°C).
In any case when vials are transferred, keep them in an upright position.
Staloral 300 vials to which the metered pump has already been adjusted may only be transferred in the packaging with the safety ring in place.

Staloral 300 vials to which the metered pump has already been adjusted may not be transported in plane cargo compartment.

6.5. Nature and contents of container

Primary packaging is an amber glass vial type I, rubber stopper, aluminium "Tear-off" closure with colour differentiated plastic cover:

- Blue for 10 IR/ml
- Purple for 300 IR/ml

The packaging contains dosing pumps (one for each vial), package leaflet.

Pack size:

Initial treatment:

1 vial with blue closure (10 IR/ml)
2 vials with violet closure (300 IR/ml)
3x1 dosing pump

Maintenance treatment:

2 vials with violet closure (300 IR/ml)
2x1 dosing pump.

Not all pack sizes may be marketed

6.6. Special precautions for disposal

No special requirements.

7. MARKETING AUTHORIZATION HOLDER

Stallergenes
6, Rue Alexis de Tocqueville
92160 Antony
France

8. MARKETING AUTHORIZATION NUMBER(S)

59/334/03-C

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORIZATION

Date of first authorization: 30.10.2003 / 4.2.2015

10. DATE OF REVISION OF THE TEXT

23.7.2024