Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

ACARIZAX 12 SQ-HDM sublingual lyophilisate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Standardised allergen extract from the house dust mites *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* 12 SQ-HDM* per sublingual lyophilizate.
For a full list of excipients, see section 6.1.
* [SQ-HDM is the dose unit for ACARIZAX. SQ is a method for standardisation on biological potency, major allergen content and complexity of the allergen extract. HDM is an abbreviation for house dust mite.]

3 PHARMACEUTICAL FORM

Sublingual lyophilisate.

White to off-white circular freeze-dried debossed sublingual lyophilisate.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ACARIZAX is indicated in adult patients (18-65 years) diagnosed by clinical history and a positive test of house dust mite sensitisation (skin prick test and/or specific IgE) with at least one of the following conditions:

- persistent moderate to severe house dust mite allergic rhinitis despite use of symptom-relieving medication
- house dust mite allergic asthma not well controlled by inhaled corticosteroids and associated with mild to severe house dust mite allergic rhinitis. Patients' asthma status should be carefully evaluated before the initiation of treatment (see section 4.3).

ACARIZAX is indicated in children (5-17 years) diagnosed by clinical history and a positive test of house dust mite sensitisation (skin prick test and/or specific IgE) with persistent moderate to severe house dust mite allergic rhinitis despite use of symptom-relieving medication.

4.2 Posology and method of administration

Posology
The recommended dose for children and adults (5-65 years) is one sublingual lyophilisate (12 SQ-HDM) daily.
Onset of the clinical effect is to be expected 8-14 weeks after initiation. International treatment guidelines refer to a treatment period of 3 years for allergy immunotherapy to achieve disease modification. Efficacy data is available for 18 months of treatment with ACARIZAX in adults; no data is available for 3 years of treatment (see section 5.1). If no improvement is observed during the first year of treatment with ACARIZAX there is no indication for continuing treatment.

Paediatric population
Allergic rhinitis: The posology to be used in children (5-17 years) is the same as in adults. Clinical experience in treatment of allergic rhinitis with ACARIZAX in children <5 years of age has not been established. ACARIZAX is not intended for treatment of allergic rhinitis in children <5 years of age. Currently available data are described in section 4.8 and 5.1.
Allergic asthma: The efficacy in treatment of allergic asthma with ACARIZAX in children <18 years of age has not been established. ACARIZAX is not intended for treatment of allergic asthma in children <18 years of age. Currently available data are described in section 4.8 and 5.1.

Elderly population
Clinical experience on immunotherapy with ACARIZAX in adults >65 years of age has not been established. ACARIZAX is not intended for use in adults >65 years of age (see section 5.1).

Method of administration

ACARIZAX treatment should be initiated by physicians with experience in treatment of allergic diseases.
The first sublingual lyophilisate should be taken under medical supervision and the patient should be monitored for at least half an hour, to enable discussion and possible treatment of any immediate side effects.
ACARIZAX is a sublingual lyophilisate. The sublingual lyophilisate should be taken with dry fingers from the blister unit immediately after opening the blister and placed under the tongue, where it will disperse. Swallowing should be avoided for approximately 1 minute. Food and beverage should not be taken for the following 5 minutes.
If treatment with ACARIZAX is interrupted for a period up to 7 days, treatment can be resumed by the patient. If the treatment is interrupted for more than 7 days it is recommended to contact a physician before resuming the treatment.

4.3 Contraindications

Hypersensitivity to any of the excipients(for a full list of excipients, see section 6.1).

Patients with FEV_1 < 70% of predicted value (after adequate pharmacological treatment) at initiation of treatment.

Patients who have experienced a severe asthma exacerbation within the last 3 months.

In patients with asthma and experiencing an acute respiratory tract infection, initiation of ACARIZAX treatment should be postponed until the infection has resolved.

Patients with active or poorly controlled autoimmune diseases, immune defects, immunodeficiencies, immunosuppression or malignant neoplastic diseases with current disease relevance.

Patients with acute severe oral inflammation or oral wounds (see section 4.4).

4.4 Special warnings and precautions for use

Asthma
Asthma is a known risk factor for severe systemic allergic reactions.
Patients should be advised that ACARIZAX is not intended to treat acute asthma exacerbations. In the event of an acute asthma exacerbation, a short-acting bronchodilator should be used. If patients find short-acting bronchodilator treatment ineffective or they need more inhalations than usual, medical attention must be sought.
Patients must be informed of the need to seek medical attention immediately if their asthma deteriorates suddenly.
ACARIZAX should initially be used as add on therapy and not as a substitute of pre-existing asthma medication. Abrupt discontinuation of asthma controller medication after initiation of ACARIZAX treatment is not recommended. Reductions in asthma controller medication should be performed gradually under the supervision of a physician according to asthma management guidelines.

Severe systemic allergic reactions
Treatment should be discontinued and a physician should be contacted immediatelyin case of severe systemic allergic reactions, severe asthma exacerbation, angioedema, difficulty in swallowing, difficulty in breathing, changes in voice, hypotension or feeling of fullness in the throat. The onset of systemic symptoms may include flushing, pruritus, sense of heat, general discomfort and agitation/anxiety.
One option for treating severe systemic allergic reactions is adrenaline. The effects of adrenaline may be potentiated in patients treated with tricyclic antidepressants, mono amino oxidase inhibitors (MAOIs) and/or COMT inhibitors with possible fatal consequences. The effects of adrenaline may be reduced in patients treated with beta-blockers.
Patients with cardiac disease may be at increased risk in case of systemic allergic reactions. Clinical experience in treatment with ACARIZAX of patients with cardiac disease is limited.
This should be taken into consideration prior to initiating allergy immunotherapy.
Initiation of ACARIZAX in patients who have previously had a systemic allergic reaction to subcutaneous house dust mite immunotherapy should be carefully considered, and measures to treat potential reactions should be available. This is based on post-marketing experience from a corresponding sublingual tablet product for grass pollen immunotherapy which indicates that the risk of a severe allergic reaction may be increased for patients who have previously experienced a systemic allergic reaction to subcutaneous grass pollen immunotherapy.

Oral inflammation
In patients with severe oral inflammation (e.g. oral lichen planus, mouth ulcers or thrush), oral wounds or following oral surgery, including dental extraction, or following tooth loss, initiation of ACARIZAX treatment should be postponed and ongoing treatment should be temporarily interrupted to allow healing of the oral cavity.

Local Allergic Reactions
When treated with ACARIZAX the patient is exposed to the allergen that causes the allergic symptoms. Therefore, local allergic reactions are to be expected during the treatment period. These reactions are usually mild or moderate; however, more severe oropharyngeal reactions mayoccur. If the patient experiences significant local adverse reactions from the treatment, anti-allergic medication (e.g. antihistamines) should be considered.

Eosinophilic oesophagitis
Cases of eosinophilic oesophagitis have been reported in association with ACARIZAX treatment. In patients with severe or persisting gastro-oesophageal symptoms such as dysphagia or dyspepsia, ACARIZAX should be interrupted and medical evaluation must be sought.

Autoimmune diseases in remission
Limited data is available on treatment with allergy immunotherapy in patients with autoimmune diseases in remission. ACARIZAX should therefore be prescribed with caution in these patients.

Food allergy
ACARIZAX may contain trace amounts of fish protein. Available data have not indicated an increased risk of allergic reactions in patients with fish allergy.

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction trials have been conducted in humans and no potential drug interactions have been identified from any source. Concomitant therapy with symptomatic anti-allergic medications may increase the tolerance level of the patient to immunotherapy. This should be considered at discontinuation of such medications.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is no data on the clinical experience for the use of ACARIZAX in pregnant women. Animal studies do not indicate increased risk to the foetus. Treatment with ACARIZAX should not be initiated during pregnancy. If pregnancy occurs during treatment, the treatment may continue after evaluation of the general condition (including lung function) of the patient and reactions to previous administration of ACARIZAX. In patients with pre-existing asthma close supervision during pregnancy is recommended.

Lactation
No clinical data are available for the use of ACARIZAX during lactation. No effects on the breastfed infants are anticipated.

Fertility
There is no clinical data with respect to fertility for the use of ACARIZAX. In a repeat dose toxicity study in mice no effects were observed in the reproductive organs of both genders.

4.7 Effects on ability to drive and use machines

Treatment with ACARIZAX has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile
Subjects taking ACARIZAX should primarily expect mild to moderate local allergic reactions to occur within the first few days and subsiding again with continued treatment (1-3 months) (see section 4.4). For the majority of events, the reaction should be expected to start within 5 minutes after intake of ACARIZAX on each day of occurrence and abate after minutes to hours. More severe oropharyngeal allergic reactions may occur (see section 4.4).
Isolated cases of severe acute worsening of asthma symptoms have been reported. Patients with known risk factors should not initiate treatment with ACARIZAX (see section 4.3).

Tabulated list of adverse reactions

The following table of adverse reactions is based on data from placebo-controlled clinical trials investigating ACARIZAX in adults and adolescents (more than 2100 patients treated with ACARIZAX) with house dust mite allergic rhinitis and/or allergic asthma and from spontaneous reporting.

Adverse reactions are divided into groups according to the MedDRA convention frequencies: 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).

System Organ Class	**Frequency**	**Adverse Drug Reaction**
Infections and infestations	***Very common***	Nasopharyngitis
	Common	Bronchitis, pharyngitis, rhinitis, sinusitis
	Uncommon	Laryngitis
Immune system disorders	***Uncommon***	Anaphylactic reaction
Nervous system disorders	***Common***	Dysgeusia
	Uncommon	Dizziness, paraesthesia
Eye Disorders	***Common***	Eye pruritus
	Uncommon	Conjunctivitis allergic
Ear and labyrinth disorders	***Very common***	Ear pruritus
	Uncommon	Ear discomfort
Cardiac disorders	***Uncommon***	Palpitations
Respiratory, thoracic and mediastinal disorders	***Very common***	Throat irritation
	Common	Asthma, cough*, dysphonia, dyspnoea, oropharyngeal pain, pharyngeal oedema
	Uncommon	Nasal congestion, nasal discomfort, nasal oedema, pharyngeal erythema, rhinorrhoea, sneezing, throat tightness, tonsillar hypertrophy
	Rare	Laryngeal oedema, nasal obstruction, tracheal oedema
Gastrointestinal disorders	***Very common***	Lip oedema, oedema mouth, oral pruritus
	Common	Abdominal pain, diarrhoea, dysphagia, dyspepsia, gastrooesophageal reflux disease, glossitis, glossodynia, lip pruritus, mouth ulceration, oral pain, tongue pruritus, nausea, oral discomfort, oral mucosal erythema, paraesthesia oral, stomatitis, tongue oedema, vomiting
	Uncommon	Dry mouth, lip pain, lip ulceration, oesophageal irritation, oral mucosal blistering, salivary gland enlargement, salivary hypersecretion
	Rare	Eosinophilic oesophagitis
Skin and subcutaneous tissue disorders	***Common***	Pruritus, urticaria
	Uncommon	Erythema
	Rare	Angioedema
General disorders and administration site conditions	***Common***	Chest discomfort, fatigue
	Uncommon	Malaise, sensation of foreign body

Description of selected adverse reactions

If the patient experiences significant adverse reactions from the treatment, anti-allergic medication should be considered.

Cases of serious systemic allergic reactions, including anaphylaxis have been reported post marketing. The medical supervision at first sublingual lyophilisate intake is therefore an important precaution (see section 4.2). However, cases of serious systemic allergic reaction have also occurred at doses subsequent to the initial dose.

In case of acute worsening in asthma symptoms or severe systemic allergic reactions, angioedema, difficulty in swallowing, difficulty in breathing, changes in voice, hypotension or feeling of fullness in the throat a physician should be contacted immediately. Hypertensive crisis has been reported following respiratory distress shortly after intake of ACARIZAX. In such cases treatment should be discontinued permanently or until otherwise advised by the physician.

*In clinical trials cough was observed with the same frequency for ACARIZAX and placebo.

Paediatric population

Adolescents 12-17 years of age

Reported adverse reactions in adolescents have been similar in frequency, type and severity as in adults.

Children 5-11 years of age
Overall, the safety profile in children treated with ACARIZAX was similar to that observed in adults and adolescents. The majority of adverse reactions were mild to moderate in severity and seen with a similar frequency category for children compared to adults/adolescents. The overall safety profile in children with asthma was similar to children without asthma. The safety profile of ACARIZAX in children is primarily based on data from double-blinded, placebo-controlled, multinational clinical trials (approximately 900 children treated with ACARIZAX) with active solicitation of predefined local adverse reactions the first 28 days of treatment.
The following adverse reactions were observed with a higher frequency in the children's studies compared to the adult and adolescent studies:
Abdominal pain, diarrhoea, dysgeusia, glossodynia, mouth ulceration, nausea, pharyngeal oedema and tongue oedema belonged to the frequency category very common (≥1/10). All of these were among the predefined solicited adverse reactions.
Symptoms of allergic conjunctivitis were reported with the frequency common (≥1/100 to <1/10).
Angioedema and eosinophilic oesophagitis were reported with the frequency uncommon (≥1/1,000 to <1/100).
Children <5 years of age
No data on treatment with ACARIZAX in children <5 years of age exist.

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:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

In phase I studies adult patients with house dust mite allergy were exposed to doses up to 32 SQ-HDM. No data are available in children (5-17 years) regarding exposure to doses above the recommended daily dose of 12 SQ-HDM.

If doses higher than the recommended daily dose are taken, the risk of side effects increases, including the risk of systemic allergic reactions or severe local allergic reactions. In case of severe reactions such as angioedema, difficulty in swallowing, difficulty in breathing, changes in voice, or feeling of fullness in the throat, immediate medical evaluation is needed. These reactions should be treated with relevant symptomatic medication.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Allergen extracts, house dust mite
ATC code: V01AA03

Mechanism of action
ACARIZAX is allergy immunotherapy. Allergy immunotherapy with allergen products is the repeated administration of allergens to allergic individuals with the purpose of modifying the immunological response to the allergen.
The immune system is the target for the pharmacodynamic effect of allergy immunotherapy, but the complete and exact mechanism of action regarding the clinical effect is not fully understood. Treatment with ACARIZAX has been demonstrated to induce an increase in house dust mite specific IgG_4 and to induce a systemic antibody response that can compete with IgE in the binding of house dust mite allergens. This effect is observed already after 4 weeks of treatment.
ACARIZAX works by addressing the cause of house dust mite respiratory allergic disease, and clinical effect during treatment has been demonstrated for both upper and lower airways. The underlying protection provided by ACARIZAX leads to improvement in disease control and improved quality of life demonstrated through symptom relief, reduced need for other medications and a reduced risk for exacerbation.

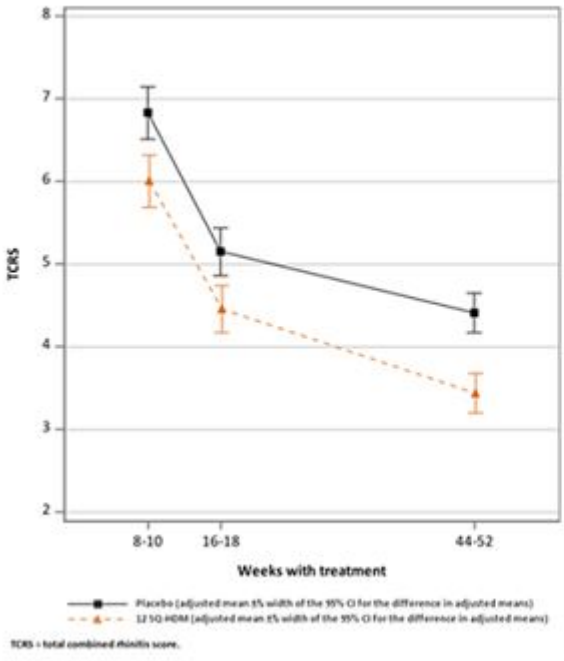
Clinical efficacy in adults
The efficacy of treatment with ACARIZAX 12 SQ-HDM in house dust mite respiratory allergic disease was investigated in two double-blind, randomised, placebo-controlled trials with different endpoints and in different patient populations. Two thirds of the trial subjects were sensitised to more allergens than just house dust mite. Being sensitised to house dust mite only or to

house dust mite and one or more other allergens did not impact the trial results. Supportive evidence from an allergen exposure chamber trial as well as a trial conducted with lower doses is also presented.

Allergic rhinitis

The MERIT trial (MT-06)

- The MERIT trial included 992 adults with moderate-to-severe house dust mite allergic rhinitis despite the use of rhinitis pharmacotherapy. Subjects were randomised to approximately 1 year of daily treatment with 12 SQ-HDM, 6 SQ-HDM or placebo and were given free access to standardised rhinitis pharmacotherapy. Subjects were seen by a specialist approximately every two months during the entire trial.
- The primary endpoint was the average daily total combined rhinitis score (TCRS) evaluated during the last 8 weeks of treatment.
    - The TCRS was the sum of the rhinitis symptoms score and the rhinitis medication score. The rhinitis symptoms score evaluated 4 nasal symptoms (runny nose, blocked nose, itching nose, sneezing) daily on a 0-3 scale (no, mild, moderate, severe symptoms), i.e. range of scale is 0-12. The rhinitis medication score was the sum of the score for nasal steroid intake (2 points per puff, max. 4 puffs/day) and oral antihistamine intake (4 points/tablet, max. 1 tablet/day), i.e. range: 0-12. Thus the TCRS range is: 0-24.
- Additional pre-defined key secondary endpoints were the total combined rhinoconjunctivitis score and rhinoconjunctivitis quality of life (RQLQ).
- Post-hoc analyses of the days with a rhinitis exacerbation were also conducted to further illustrate the clinical relevance of the results.
    - A rhinitis exacerbation was defined as a day where the subject returned to the high level of symptoms required for trial inclusion: a rhinitis symptom score of at least 6 or at least 5 with one symptom rated severe.



The MATIC trial: Development over time of the total combined rhinitis score

TCRS: total combined rhinitis score (symptoms + medication score).

TCRS measured as an average over 2 weeks of assessment beginning week 8 and week 16.

The primary endpoint was the average daily TCRS during the last approximately 8 weeks of treatment (weeks ~44-52).

Adjusted means of the average TCRS over time with error bars for the difference in adjusted means. Non-overlapping intervals indicate a statistically significant difference. between the groups.

MERIT results	**12 SQ-HDM**		**Placebo**		**Treatment effect**		
Primary endpoint	**N**	**Score**	**N**	**Score**	**Absolute difference**[c]	**Relative difference**[d]	**p-value**
Total combined rhinitis score							
FAS-MI[a] (adjusted mean)	318	5.71	338	6.81	1.09 [0.35;1.84]	-	**0.004**
FAS [b](adjusted mean)	284	5.53	298	6.76	1.22 [0.49;1.96]	18%	**0.001**
FAS [b] (median)	284	5.88	298	7.54	1.66	22%	**-**

Pre-defined key secondary endpoints	**N**	**Score**	**N**	**Score**	**Absolute difference** [c]	**Relative difference**[d]	**p-value**
Rhinitis symptoms score							
FAS [b](adjusted mean)	284	2.76	298	3.30	0.54 [0.18;0.89]	16%	**0.003**
FAS [b] (median)	284	2.98	298	3.98	1.00	25%	-
Rhinitis medication score							
FAS [b](adjusted mean)	284	2.22	298	2.83	0.60 [0.08;1.13]	21%	**0.024**
FAS [b] (median)	284	2.83	298	4.00	1.17	29%	-
Total combined rhinoconjunctivitis score							
FAS [b](adjusted mean)	241	7.91	257	9.12	1.21 [0.13;2.28]	13%	**0.029**
FAS [b] (median)	241	8.38	257	10.05	1.67	17%	-
Rhinoconjunctivitis quality of life questionnaire (RQLQ(S)) score							
FAS [b](adjusted mean)	229	1.38	240	1.58	0.19 [e] [0.02;0.37]	12%	**0.031**
FAS [b](median)	229	1.25	240	1.46	0.21	14%	-
Post-hoc endpoints	**N**	**Proportion**	**N**	**Proportion**	**Odds ratio**[f] **[95% CL]**		**p-value**
Probability of having a day with a rhinitis exacerbation							
FAS (estimate) [b]	284	5.33%	298	11.14%	0.45 [0.28;0.72]		**0.001**
Probability of having a day with a rhinitis exacerbation despite use of rhinitis pharmacotherapy							
FAS (estimate) [b]	284	3.43%	298	6.50%	0.51 [0.32;0.81]		**0.005**

N: number of subjects in treatment group with data available for the analysis. CL: confidence limits

[a] FAS-MI: full analysis set with multiple imputations. The analysis treats subjects who discontinued the trial before the efficacy assessment period as placebo subjects. For the primary analysis (FAS-MI) only the absolute difference was pre-specified.

[b] FAS: full analysis set. All available data used to its full extent, i.e. subjects who provided data during the efficacy assessment period.

[c] Absolute difference: placebo minus 12 SQ-HDM, 95% confidence limits.

[d] Relative difference to placebo: placebo minus 12 SQ-HDM divided by placebo.

[e] The difference between 12 SQ-HDM and placebo was primarily driven by differences in three domains: sleep problems, practical problems and nose symptoms.

[f] Odds ratio for having a rhinitis exacerbation: 12 SQ-HDM over placebo.

Supportive evidence – allergic rhinitis

A randomised, double-blind, placebo-controlled phase II trial was conducted in an allergen exposure chamber in 124 adults with house dust mite allergic rhinitis. Before each allergen challenge, subjects were washed out of all allergy pharmacotherapy. At the end-of-trial allergen challenge after 24 weeks of treatment with 12 SQ-HDM, 6 SQ-HDM or placebo, the mean rhinitis symptoms score was 7.45 [6.57;8.33] in the placebo group and 3.83 [2.94;4.72] in the 12 SQ-HDM group, corresponding to an absolute difference of 3.62 and a relative difference of 49% (95% confidence interval [35%;60%], p<0.001). The difference between 12 SQ-HDM and placebo was also statistically significant at 16 weeks (mean scores of 4.82 and 6.90, difference of 2.08 corresponding to 30%, 95% CI [17%;42%], p<0.001) and at 8 weeks (mean scores of 5.34 and 6.71, difference of 1.37 corresponding to 20%, 95% CI [7%;33%], p=0.007).

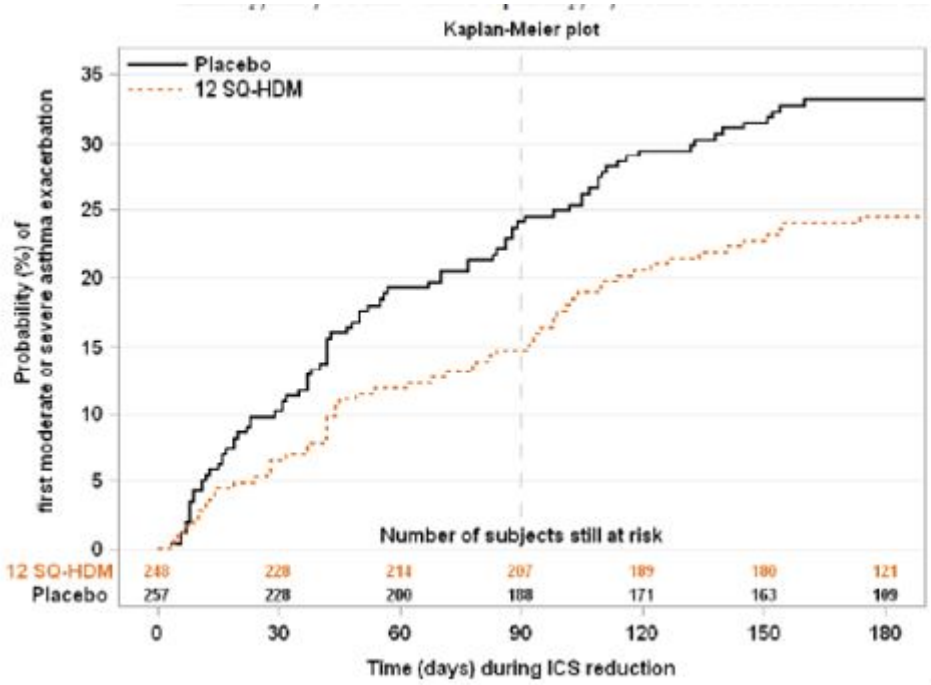
Allergic asthma

The MITRA trial (MT-04)

The MITRA trial included 834 adults with house dust mite allergic asthma not well-controlled by daily use of inhaled corticosteroid (ICS) corresponding to 400-1200 µg budesonide. All subjects received 7-12 months' treatment with 12 SQ-HDM,

6 SQ-HDM or placebo in addition to ICS and short-acting beta-agonist prior to ICS reduction. No titration phase to establish the lowest maintenance dose of ICS was conducted prior to randomisation. Efficacy was assessed by time to first moderate or severe asthma exacerbation under ICS reduction over the last 6 months of 13-18 months of treatment.

- The definition of a moderate asthma exacerbation was fulfilled if the subject experienced one or more of the 4 criteria below, and it led to change in treatment:
  - Nocturnal awakening or increase in symptoms: nocturnal awakening(s) due to asthma requiring short-acting β_2 agonist (SABA) for two consecutive nights or increase of ≥0.75 from baseline in daily symptom score on two consecutive days.
  - Increased SABA use: increase from baseline in occasions of SABA use on two consecutive days (minimum increase: 4 puffs/day).
  - Deterioration in lung function: ≥20% decrease in PEF from baseline on at least two consecutive mornings/evenings or ≥20% decrease in FEV1 from baseline.
  - Healthcare visit: visit to the emergency room / trial site for asthma treatment not requiring systemic corticosteroids.
- A severe asthma exacerbation was defined as experiencing at least one of the two following:
  - Need for systemic corticosteroids for ≥3 days
  - Emergency room visit requiring systemic corticosteroids or hospitalisation for ≥12h.



The MITRA trial – illustration of primary efficacy data: Development over time of the risk for experiencing a moderate or severe asthma exacerbation during ICS reduction/withdrawal.

On the graph time = 0 represents the time of the ICS reduction to 50%. After approximately 3 months, i.e. at time = 90 days, ICS was completely withdrawn for those subjects who had not exacerbated.

MITRA results	**12 SQ-HDM**		**Placebo**		**Efficacy 12 SQ-HDM over placebo**		**p-value**
	N	**n (%)**	**N**	**n (%)**	**Hazard ratio [95% CL]**	**Risk reduction**[a]	
Primary endpoint							
Any exacerbation, moderate or severe (FAS-MI) [b]	282	59 (21%)	277	83 (30%)	**0.69** [0.50;0.96]	31%	**0.027**

Any exacerbation, moderate or severe (FAS) [c]	248	59 (24%)	257	83 (32%)	**0.66** [0.47;0.93]	34%	**0.017**
Pre-defined analyses of components of the primary endpoint							
Nocturnal awakening or increase in symptoms [c]	248	39 (16%)	257	57 (22%)	**0.64** [0.42;0.96]	36%	**0.031**
Increased SABA use [c]	248	18 (7%)	257	32 (12%)	**0.52** [0.29;0.94]	48%	**0.029**
Deterioration in lung function [c]	248	30 (12%)	257	45 (18%)	**0.58** [0.36;0.93]	42%	**0.022**
Severe exacerbation [c]	248	10 (4%)	257	18 (7%)	0.49 [0.23;1.08]	51%	0.076

N: number of subjects in treatment group with data available for the analysis.
n (%): number and percentage of subjects in treatment group meeting criterion.
CL: confidence limits
[a] Estimated by hazard ratio
[b] FAS-MI: full analysis set with multiple imputations. The analysis treats subjects who discontinued the trial before the efficacy assessment period as placebo subjects.
[c] FAS: full analysis set. All available data used to its full extent, i.e. including all subjects who provided data during the efficacy assessment period.

Post-hoc analyses of the asthma symptoms and symptomatic medication use in the last 4 weeks of the treatment period prior to reduction of inhaled corticosteroids were also conducted to investigate the effect of ACARIZAX as add-on to inhaled corticosteroid. The analyses looked at asthma daytime and nocturnal symptom scores, nocturnal awakenings, and SABA intake. The post-hoc analyses showed numerical differences consistently in favour of 12 SQ-HDM over placebo for all parameters investigated during the last 4 weeks prior to inhaled corticosteroid reduction. The differences were only statistically significant for the asthma daytime symptom score (p=0.0450) and the odds for no nocturnal awakenings (p=0.0409).

Supportive evidence – allergic asthma
In a double-blind, randomised, placebo-controlled phase II trial, 604 subjects ≥14 years old with house dust mite allergic asthma controlled by inhaled corticosteroids (100-800µg budesonide) and a clinical history of house dust mite allergic rhinitis were randomised to approximately 1 year of treatment with 1, 3 or 6 SQ-HDM or placebo. At the 4-week end-of-trial efficacy evaluation period, the mean change from baseline in the daily ICS dose was 207.6 µg budesonide in the 6 SQ-HDM group and 126.3 µg in the placebo group corresponding to an absolute difference of 81 µg budesonide per day (95% confidence interval [27;136], p= 0.004. Relative mean and median ICS reductions from baseline were 42% and 50% for 6 SQ-HDM and 15% and 25% for placebo. In a post-hoc analysis of a subgroup (N=108) of subjects with lower asthma control and ICS ≥400 µg budesonide, the mean change from baseline in the daily ICS dose was 384.4 µg budesonide in the 6 SQ-HDM group and 57.8 µg in the placebo group corresponding to an absolute difference between 6 SQ-HDM and placebo of 327 µg budesonide per day (95% CI [182;471], p<0.0001, post-hoc analysis).

Paediatric population

Clinical efficacy in children
The efficacy of treatment with ACARIZAX 12 SQ-HDM in house dust mite respiratory allergic disease in children was investigated in two double-blind, randomised, placebo-controlled trials. The primary objective of the trials was to investigate efficacy in allergic rhinitis in the MT-12 trial and to investigate efficacy in allergic asthma in the MT-11 trial.

Allergic rhinitis:
Children 5-11 years of age

The MATIC trial (MT-12)

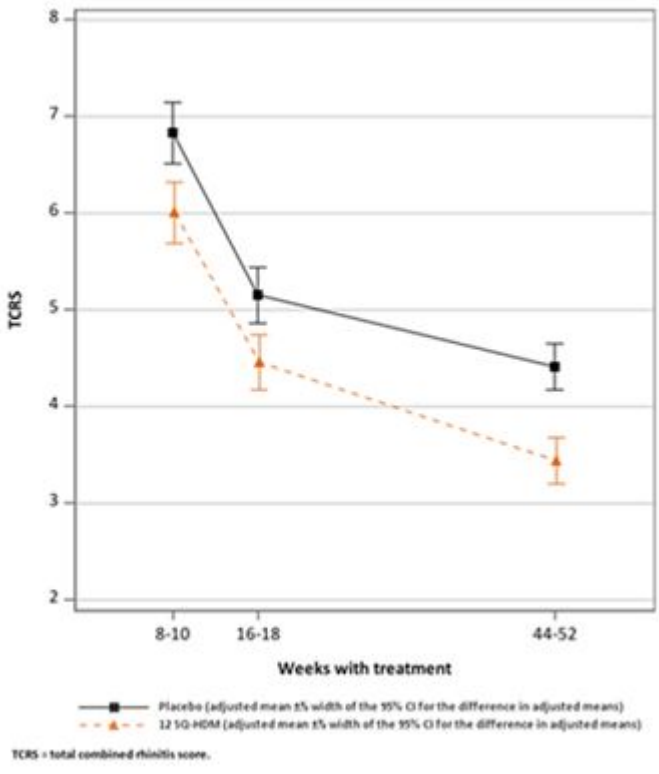
The efficacy of treatment with ACARIZAX 12 SQ-HDM in house dust mite allergic rhinitis in children 5-11 years was investigated in a double-blind, randomised, placebo-controlled trial (MATIC trial (MT-12)).

- The MATIC trial (MT-12) included 1458 children (5-11 years of age) with moderate to severe house dust mite allergic rhinitis/ rhinoconjunctivitis (baseline mean total combined rhinitis score (TCRS) 18.3). Approximately 40% of the trial population reported concomitant asthma at baseline. Subjects were randomised to approximately 1 year of daily treatment with 12 SQ-HDM or placebo and were given free access to standardised rhinitis and conjunctivitis pharmacotherapy.

- The primary endpoint was the average daily total combined rhinitis score (TCRS) evaluated during the last 8 weeks of treatment.

    - The daily TCRS is the sum of the rhinitis daily symptoms score (DSS) and the rhinitis daily medication score (DMS). The rhinitis symptoms score evaluated 4 nasal symptoms (runny nose, blocked nose, sneezing, itching nose) daily on a 0-3 scale (no, mild, moderate, severe symptoms), i.e. range of scale is 0-12. The rhinitis medication score was the sum of the score for nasal steroid intake (max. 8 points/day) and oral antihistamine intake (max. 4 points/day), i.e. range: 0-12. Thus the TCRS range is: 0-24.

- After 1 year of treatment with 12 SQ-HDM, an absolute difference in adjusted means of 0.97 (95% confidence interval [0.50;1.44]) and a relative difference of 22% ($p<0.0001$) compared to placebo was found. The treatment effect may vary between patients depending on their allergic disease status.
- Onset of the clinical effect was observed after 8 weeks of treatment ($p=0.01$).



The MATIC trial: Development over time of the total combined rhinitis score

TCRS: total combined rhinitis score (symptoms + medication score).

TCRS measured as an average over 2 weeks of assessment beginning week 8 and week 16.

The primary endpoint was the average daily TCRS during the last approximately 8 weeks of treatment (weeks ~44-52).

Adjusted means of the average TCRS over time with error bars for the difference in adjusted means. Non-overlapping intervals indicate a statistically significant difference. between the groups.

MATIC results	**12 SQ-HDM**		**Placebo**		**Treatment effect**		
Primary endpoint	**N**	**Score**	**N**	**Score**	**Absolute difference[b]**	**Relative difference[c]**	**p-value**
Total combined rhinitis score							
FAS[a] (adjusted mean)	693	3.44	706	4.41	0.97 [0.50; 1.44]	22.0%	**<0.0001**
Sensitivity estimator 1[e]	727[f]	3.45	731[f]	4.42	0.97 [0.49; 1.44]	21.9%	**<0.0001**

Pre-defined key secondary endpoints	**N**	**Score**	**N**	**Score**	**Absolute difference[b]**	**Relative difference[c]**	**p-value**
Rhinitis symptoms score							
FAS (adjusted mean)	693	1.50	706	1.92	0.43 [0.23; 0.62]	22.2%	**<0.0001**
Rhinitis medication score							
FAS (adjusted mean)	693	1.44	706	1.94	0.49 [0.18; 0.80]	25.3%	**0.0016**
Total combined rhinoconjunctivitis score							
FAS (adjusted mean)	693	4.01	706	5.16	1.15 [0.58; 1.71]	22.2	**<0.0001**
Pre-defined secondary endpoints	**N**	**Score**	**N**	**Score**	**Absolute difference[b]**	**Relative difference[c]**	**p-value**
Paediatric Rhinoconjunctivitis quality of life questionnaire (PRQLQ)							
FAS (adjusted mean)	695	0.84	690	1.01	0.17 [0.08; 0.25]	16.6%	**<0.0001**
Pre-defined secondary endpoints	**N**	**Propor-tion**	**N**	**Propor-tion**	**Odds ratio[d] [95%CL]**		**p-value**
Rhinitis exacerbation days							
FAS (estimate)	693	0.025	706	0.044	0.56 [0.42; 0.74]		**<0.0001**
Rhinitis mild days							
FAS (estimate)	693	0.318	706	0.209	1.77 [1.27; 2.47]		**0.0008**
Pre-defined explorative endpoints	**N**	**Propor-tion**	**N**	**Propor-tion**	**Odds ratio[d] [95%CL][d]**		**p-value**
Rhinitis symptom-free days							
FAS (estimate)	693	0.200	706	0.116	1.90 [1.37; 2.66]		**0.0002**

N: number of subjects with observations contributing to the analysis. CL: confidence limit

[a]FAS: full analysis set. All available data used to its full extent, i.e. subjects who provided data during the efficacy assessment period.

[b]Absolute difference: placebo minus 12 SQ-HDM, 95% confidence interval.

[c]Relative difference to placebo: placebo minus 12 SQ-HDM divided by placebo.

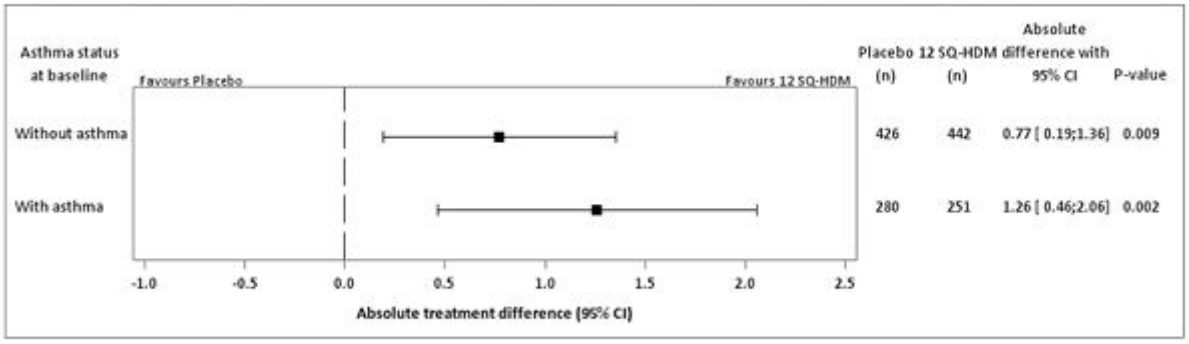
[d]Odds ratio for having a rhinitis exacerbation, rhinitis mild days and rhinitis symptom-free days: 12 SQ-HDM over placebo. Rhinitis exacerbation days (days with a rhinitis DSS of 6 or of 5 with one individual symptom scored 3 (symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping)).

[e]Trial product estimand: For subjects who discontinued treatment due to lack of efficacy or treatment-related adverse events, missing endpoints were imputed from the placebo group. For treatment discontinuations due to other reasons, missing endpoints were imputed from their own treatment group.

[f]For sensitivity estimator 1, N includes subjects with imputed observations.

Subgroup analysis of the primary endpoint (TCRS) by asthma status at baseline showed an absolute difference in adjusted means of 1.26 (95% confidence interval [0.46; 2.06]) in children with concomitant asthma and of 0.77 (95% confidence interval [0.19; 1.36]) in children without concomitant asthma. A pooled analysis of TCRS across 5 phase III trials in HDM allergic rhinitis patients treated with 12 SQ-HDM or placebo showed an absolute difference in adjusted means of 1.27 (95% confidence interval [0.82; 1.72]) in patients with concomitant asthma (N=1,450) and of 0.81 (95% confidence interval [0.49; 1.13]) in patients without concomitant asthma (N=2,595).

The MATIC trial: Forest plot of treatment difference of average daily TCRS in subgroups of asthma status at baseline - observed case (FAS)



CI = confidence interval, FAS = full analysis set, n = number of subjects with observations contributing to the analysis, TCRS = total combined rhinitis score

CI = confidence interval, FAS = full analysis set, n = number of subjects with observations contributing to the analysis, TCRS = total combined rhinitis score

Pre-specified analyses of asthma-related endpoints evaluated asthma daily symptom score, SABA use, SABA-free days, and nocturnal awakening requiring SABA use. The results showed numerical differences consistently in favour of 12 SQ-HDM over placebo for all 4 parameters. The differences were statistically significant for the asthma daily symptom score (p=0.0259) and nocturnal awakening requiring SABA use (p=0.0279).

Children 5-17 years of age

The MAPIT trial (MT-11)

The primary objective was to demonstrate efficacy of ACARIZAX 12 SQ-HDM versus placebo in children and adolescents (5-17 years) with house dust mite allergic asthma based on clinically relevant asthma exacerbations after at least 4 months of treatment. The ACARIZAX 12 SQ-HDM was administered as add-on treatment to asthma background treatment (low dose ICS plus long-acting β2-agonists [LABA] or high/medium dose ICS with or without LABA). The trial population also had a clinical history of house dust mite allergic rhinitis of any severity (total combined rhinitis score (TCRS) >0 at baseline; baseline mean TCRS 9.0). MT-11 was not designed to assess clinical effect in allergic rhinitis.

The results of the rhinitis endpoints TCRS, rhinitis DSS, and rhinitis DMS are presented in the table below.

MAPIT results	**12 SQ-HDM**		**Placebo**		**Treatment effect**		-
Pre-defined additional secondary endpoints[a]	**N**	**Score**	**N**	**Score**	**Absolute difference[b]**	**Relative difference[c]**	**p-value[d]**
Total combined rhinitis score							
FAS[e] (adjusted mean)	253	2.16	259	2.46	0.30 [-0.22; 0.81]	12.1%	**0.2597**
Rhinitis symptoms score							
FAS (adjusted mean)	253	0.55	259	0.67	0.12 [-0.04; 0.28]	18.2%	**0.1349**
Rhinitis medication score							
FAS (adjusted mean)	253	1.27	259	1.40	0.12 [-0.24; 0.48]	8.8%	**0.5071**

FAS: full analysis set. N: number of subjects with observations contributing to the analysis.
aRhinitis endpoints
bAbsolute difference: placebo minus 12 SQ-HDM, 95% confidence interval.
cRelative difference to placebo: placebo minus 12 SQ-HDM divided by placebo.
dThe p values were not adjusted for multiplicity. Therefore, the analyses are to be considered exploratory.
eAll available data used to their full extent, i.e. subjects who provided data during the efficacy assessment period.

Adolescents 12-17 years of age

The efficacy of treatment with ACARIZAX 12 SQ-HDM in house dust mite allergic rhinitis in adolescents was investigated in two double-blind, randomised, placebo-controlled trials (P001 and TO-203-3-2). In these studies a proportion of the subjects were adolescents.

- The P001 trial included 189 adolescents (of 1482 subjects randomised in total) with moderate-to-severe house dust mite allergic rhinitis/rhinoconjunctivitis with or without asthma. Subjects were randomised to approximately 1

year of daily treatment with 12 SQ-HDM or placebo and were given free access to standardised rhinitis pharmacotherapy.

The primary endpoint was the average daily total combined rhinitis score (TCRS) evaluated during the last 8 weeks of treatment.
After 1 year of treatment with 12 SQ-HDM, an absolute difference in medians of 1.0 (95% confidence interval [0.1; 2.0]) and a relative difference of 22% (p=0.024) compared to placebo was found in the adolescent group.

- The TO-203-3-2 trial included 278 adolescents (of 851 subjects randomised in total) with moderate-to-severe persistent house dust mite allergic rhinitis. Subjects were randomised to approximately 1 year of daily treatment with 12 SQ-HDM, 6 SQ-HDM, or placebo and were given free access to standardised rhinitis pharmacotherapy.

The primary endpoint was the average daily TCRS evaluated during the last 8 weeks of treatment.
At the end-of-trial after 1 year of treatment with 12 SQ-HDM, an absolute difference in means of 1.0 (95% confidence interval [0.1; 1.9], p=0.037) and a relative difference of 20% compared to placebo was found in the adolescent group.

Adolescent subgroups	**12 SQ-HDM**		**Placebo**		**Treatment effect**		
Primary endpoint: TCRS	**N**	**Score**	**N**	**Score**	**Absolute difference**	**Relative difference[d]**	**p-value**
P001							
FAS (adjusted mean)	76	3.6	84	4.8	1.2 [a] [0.1;2.3]	25%	**<0.05**
FAS (median)	76	3.3	84	4.3	1.0 [b] [0.1;2.0]	22%	**0.024**
TO-203-3-2							
FAS(adjusted mean)	99	4.1	92	5.1	1.0 [c] [0.1;1.9]	20%	**0.037**
FAS (median)	99	4.2	92	5.2	1.0	19%	-

TCRS: total combined rhinitis score
[a]: ANCOVA
[b]: Hodges-Lehmann estimate with 95% confidence intervals (primary analysis in the P001 trial)
[c]: Linear mixed-effects model (primary analysis in the TO-203-3-2 trial)
[d]: Relative difference to placebo: placebo minus 12 SQ-HDM divided by placebo

Allergic asthma:
Children 5-17 years of age
The MAPIT trial (MT-11) included 533 children and adolescents (5-17 years) with house dust mite allergic asthma. Subjects had a history of recent asthma exacerbations while being on asthma controller medication (low dose ICS plus LABA or medium/high dose ICS with or without LABA). Subjects were randomised to approximately 24-30 months of daily treatment with 12 SQ-HDM or placebo as add-on treatment to their asthma controller medication. The primary endpoint was the annualised rate of clinically relevant asthma exacerbations calculated as the number of exacerbations per year per subject during the efficacy evaluation period.
The adjusted rate ratio (12 SQ-HDM divided by placebo) was in favour of 12 SQ-HDM but there was no statistically significant difference in treatment effect between the treatment groups (rate ratio = 0.89, 95% CI [0.60; 1.31], p=0.54).
For subjects enrolled in the MAPIT trial (MT-11), the asthma exacerbation rate was generally low in both treatment groups during the trial and decreased by approximately 67% during the COVID-19 pandemic compared to the level prior to the COVID-19 pandemic, which may have had an influence on the fact that it was not possible to detect a statistically significant difference (see section 4.2 for information on paediatric use).
The European Medicines Agency has waived the obligation to submit the results of studies with ACARIZAX in children under the age of 5 in house dust mite respiratory allergy (treatment of allergic rhinitis, treatment of asthma).

Elderly population
ACARIZAX is not indicated in patients >65 years of age (see section 4.2). Limited safety and tolerability data exist for elderly patients >65 years of age.

Long-term treatment
International treatment guidelines refer to a treatment period of 3 years for allergy immunotherapy to achieve disease modification. Efficacy data is available for 18 months of treatment with ACARIZAX from the MITRA trial. Long-term efficacy has not been established.

5.2 Pharmacokinetic properties

No clinical studies investigating the pharmacokinetic profile and metabolism of ACARIZAX have been conducted. The effect of allergy immunotherapy is mediated through immunological mechanisms, and there is limited information available on the pharmacokinetic properties.

The active molecules of an allergen extract are composed primarily of proteins. For sublingually administered allergy immunotherapy products, studies have shown that no passive absorption of the allergen through the oral mucosa occurs. Evidence points towards the allergen being taken up through the oral mucosa by dendritic cells, in particular Langerhans cells. Allergen which is not absorbed in this manner is expected to be hydrolysed to amino acids and small polypeptides in the lumen of the gastrointestinal tract. There is no evidence to suggest that the allergens present in ACARIZAX are absorbed into the vascular system after sublingual administration to any significant extent.

5.3 Preclinical safety data

Conventional studies of general toxicology and toxicity to reproduction in mice have revealed no special hazards to humans.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Gelatine (fish source)
Mannitol
Sodium hydroxide (for pH adjustment)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium/aluminium blister cards in outer carton. Each blister card contains 10 sublingual lyophilisates.
Pack sizes: 10, 30 and 90.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7 MARKETING AUTHORISATION HOLDER

ALK-Abello A/S
Boge Alle 6-8
DK-2970 Horsholm
Denmark

8 MARKETING AUTHORISATION NUMBER

PA1255/010/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 29th November 2019
Date of last renewal: 30th August 2020

10 DATE OF REVISION OF THE TEXT

January 2025