

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

ACARIZAX 12 SQ-HDM oral lyophilisate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Standardised allergen extract from the house dust mites *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* 12 SQ-HDM* per oral lyophilisate

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

Oral lyophilisate

White to off-white freeze-dried debossed oral 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 adolescents (12-17 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 adults and adolescents (12-17 years) is one oral 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 is the same for adults and adolescents (12-17 years). Clinical experience in treatment of allergic rhinitis with ACARIZAX in children <12 years of age has not been established. ACARIZAX is not intended for treatment of allergic rhinitis in children <12 years of age. Currently available data are described in section 5.1.

Allergic asthma: Clinical experience 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.

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.

It is recommended that the first oral lyophilisate is taken under medical supervision and that the patient is monitored for at least half an hour, to enable discussion and possible treatment of any immediate side effects.

ACARIZAX is an oral lyophilisate. The oral 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 FEV₁ < 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 immediately in 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 may occur. If the patient experiences significant local adverse reactions from the treatment, anti-allergic medication (e.g. antihistamines) should be considered.

Eosinophilic esophagitis

Isolated cases of eosinophilic esophagitis have been reported in association with ACARIZAX treatment. In patients with severe or persisting gastro-esophageal symptoms such as dysphagia or dyspepsia, medical attention 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.

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 adult and adolescent patients with house dust mite allergic rhinitis and/or allergic asthma and spontaneous reporting.

Adverse reactions are divided into groups according to the MedDRA convention frequencies: Very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$).

System Organ Class	Frequency	Adverse Drug Reaction
Infections and infestations	<i>Very common</i>	Nasopharyngitis
	<i>Common</i>	Bronchitis, pharyngitis, rhinitis, sinusitis
	<i>Uncommon</i>	Laryngitis
Immune system disorders	<i>Uncommon</i>	Anaphylactic reaction
Nervous system disorders	<i>Common</i>	Dysgeusia
	<i>Uncommon</i>	Dizziness, paraesthesia
Eye Disorders	<i>Common</i>	Eye pruritus
	<i>Uncommon</i>	Conjunctivitis allergic
Ear and labyrinth disorders	<i>Very common</i>	Ear pruritus
	<i>Uncommon</i>	Ear discomfort
Cardiac disorders	<i>Uncommon</i>	Palpitations
Respiratory, thoracic and mediastinal disorders	<i>Very common</i>	Throat irritation
	<i>Common</i>	Asthma, dysphonia, dyspnoea, oropharyngeal pain, pharyngeal oedema
	<i>Uncommon</i>	Nasal congestion, nasal discomfort, nasal oedema, pharyngeal erythema, rhinorrhoea, sneezing, throat tightness, tonsillar hypertrophy
	<i>Rare</i>	Laryngeal oedema, nasal obstruction, tracheal oedema
Gastrointestinal disorders	<i>Very common</i>	Lip oedema, oedema mouth, oral pruritus
	<i>Common</i>	Abdominal pain, diarrhoea, dysphagia, dyspepsia, gastrooesophageal reflux disease, glossodynia, glossitis, lip pruritus, mouth ulceration, oral pain, tongue pruritus, nausea, oral discomfort, oral mucosal erythema, paraesthesia oral, stomatitis, tongue oedema, vomiting
	<i>Uncommon</i>	Dry mouth, lip pain, lip ulceration, oesophageal irritation, oral mucosal blistering, , salivary gland enlargement, salivary hypersecretion
Skin and subcutaneous tissue disorders	<i>Common</i>	Pruritus, urticaria
	<i>Uncommon</i>	Erythema
	<i>Rare</i>	Angioedema
General disorders and administration site conditions	<i>Common</i>	Chest discomfort, fatigue
	<i>Uncommon</i>	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 systemic allergic reactions, including anaphylactic reactions have been reported post marketing and are considered a class effect. The medical supervision at first oral lyophilisate intake is therefore an important precaution (see section 4.2). In some cases the serious systemic allergic reaction has 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.

Isolated cases of eosinophilic esophagitis have been reported (see section 4.4).

Paediatric population

ACARIZAX is not indicated in children <12 years of age (see section 4.2). Only limited data from children 5-11 years of age are available and no data on treatment with ACARIZAX in children <5 years of age exist. Reported adverse reactions in adolescents have been similar in frequency, type and severity as 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 listed in Appendix V*.

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 adolescents 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 IgG₄ 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.

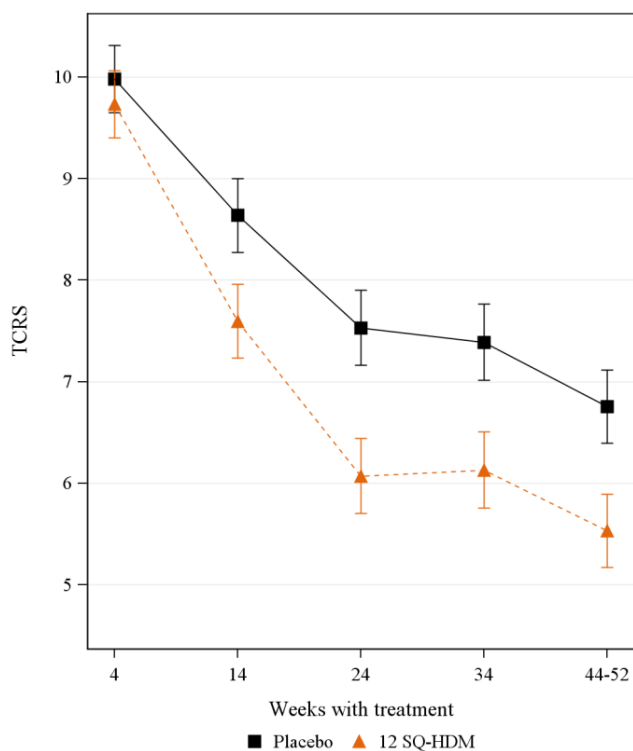
Clinical efficacy in adults

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 MERIT trial: Development over time of the total combined rhinitis score

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

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.

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							
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	20%	-
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%	-

MERIT results	12 SQ-HDM		Placebo		Treatment effect	
Post-hoc endpoints	N	Proportion	N	Proportion	Odds ratio ^f [95% CL]	P-value
<i>Probability of having a day with a rhinitis exacerbation</i>						
FAS (estimate) ^b	284	5.33%	298	11.14%	0.45 [0.28;0.72]	0.001
<i>Probability of having a day with a rhinitis exacerbation despite use of rhinitis pharmacotherapy</i>						
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%], $p = 0.007$).

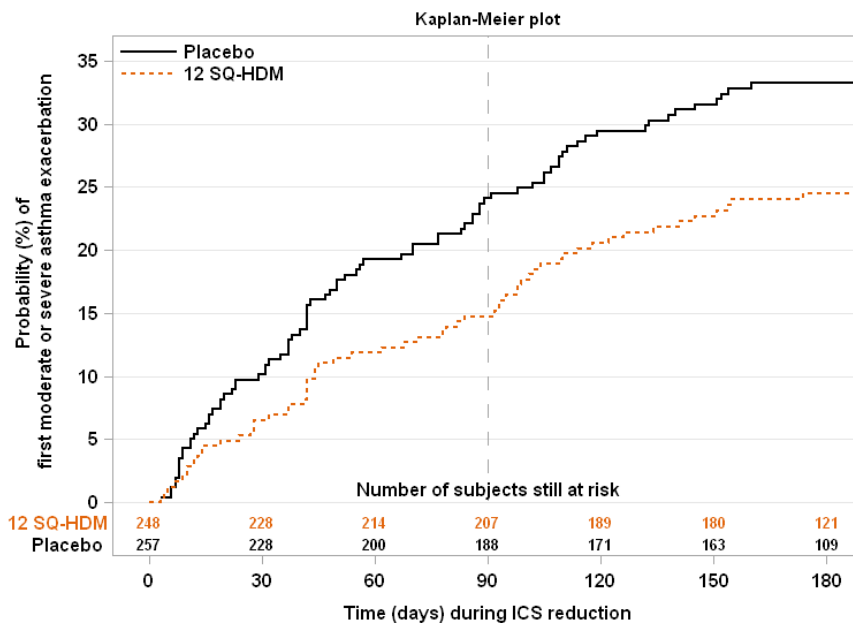
Allergic asthma

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 ACARIZAX 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:** $\geq 20\%$ decrease in PEF from baseline on at least two consecutive mornings/evenings or $\geq 20\%$ 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 ≥ 12 h.



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

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	
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 (100-800 μ g 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 μ g budesonide in the 6 SQ-HDM group and 126.3 μ g in the placebo group corresponding to an absolute difference of 81 μ g 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 μ g budesonide, the mean change from baseline in the daily ICS dose was 384.4 μ g budesonide in the 6 SQ-HDM group and 57.8 μ g in the placebo group corresponding to an absolute difference between 6 SQ-HDM and placebo of 327 μ g budesonide per day (95% CI [182;471], p<0.0001, post-hoc analysis).

Paediatric population

Allergic rhinitis:

Children 5-11 years of age

Clinical experience in treatment of allergic rhinitis with ACARIZAX in children <12 years of age has not been established.

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		
	N	Score	N	Score	Absolute difference	Relative difference ^d	p-value
<i>P001</i>							
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
<i>TO-203-3-2</i>							
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:

Paediatric population 5-17 years of age

Clinical experience in treatment of allergic asthma with ACARIZAX in children <18 years of age has not been established.

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, prevention of asthma, treatment of asthma).

The European Medicines Agency has deferred the obligation to submit the results of further studies with ACARIZAX in children 5 years or older in house dust mite respiratory allergy (treatment of allergic rhinitis, prevention of asthma, 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

3 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 oral 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-Abelló A/S

Bøge Alle 6-8

2970 Hørsholm

Denmark

8 MARKETING AUTHORISATION NUMBER(S)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT