PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

ACARIZAX®

Standardized Allergen Extract, House Dust Mites (*D. farinae and D. pteronyssinus*)

Sublingual Tablet, 12 SQ-HDM

Allergy Immunotherapy

Therapeutic classification: Allergen extracts, house dust mite

ATC code: V01AA03

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ACARIZAX® (Standardized Allergen Extract, House Dust Mites (*D. farinae* and *D. pteronyssinus*) Sublingual Tablet) is indicated as allergy immunotherapy for the treatment of moderate to severe house dust mite-induced allergic rhinitis, with or without conjunctivitis, in children and adults 5 to 65 years of age confirmed by a positive skin prick test and/or *in vitro* testing for *D. farinae* or *D. pteronyssinus* IgE antibodies.

Treatment with ACARIZAX® should only be prescribed and initiated by physicians with adequate training and experience in the treatment of respiratory allergic diseases.

1.1 Pediatrics

Pediatrics (<5 years of age): The safety and efficacy of immunotherapy with ACARIZAX® for house dust mite-induced allergic rhinitis, with or without conjunctivitis, have not been studied in patients under 5 years of age (see 7 WARNINGS AND PRECAUTIONS / 7.1.3 Pediatrics).

1.2 Geriatrics

Geriatrics (> 65 years of age): The safety and efficacy of immunotherapy with ACARIZAX® in patients over 65 years of age have not been well-established (see 7 WARNINGS AND PRECAUTIONS / 7.1.4 Geriatrics).

2 CONTRAINDICATIONS

ACARIZAX® is contraindicated in patients who:

- are hypersensitive to any of the excipients in the formulation or components of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- have previously had a severe systemic allergic reaction to house dust mite immunotherapy.
- have unstable, severe asthma (FEV1 <70% of predicted value after adequate pharmacologic treatment).
- are taking beta-blockers, as they can be non-responsive to beta-agonists that may be required to reverse a systemic reaction.
- have active inflammatory conditions in the oral cavity, e.g., oral lichen planus with ulcerations, severe oral candidiasis, dental extraction (see 7 WARNINGS AND PRECAUTIONS / Patients with Oral Conditions).
- have a history of eosinophilic esophagitis.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions
• Treatment with ACARIZAX® should only be prescribed and initiated by physicians with adequate training and experience in the treatment of respiratory allergic diseases. • Systemic allergic reactions, including severe local allergic reactions, have been observed in patients receiving ACARIZAX®, and may require emergency administration of epinephrine, antihistamines, bronchodilators or systemic corticosteroids (see 7 WARNINGS AND

PRECAUTIONS / Immune).
- The first tablet of ACARIZAX® must be taken at the physician's office under medical supervision and the patient must be monitored for 30 minutes.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- The first dose of ACARIZAX® should only be administered in a healthcare setting under the supervision of a physician with experience in the diagnosis and treatment of allergic diseases.
- After receiving the first dose, the patient should be kept under observation for 30 minutes to monitor for signs or symptoms of a severe systemic or a severe local allergic reaction. If the first dose is adequately tolerated, subsequent doses may be taken at home.
- Subsequent dose administration in children <12 years must be done under adult supervision and the child must be monitored for any signs of allergic reaction, including breathing difficulties. Observation should be for a minimum of 15 minutes.
- Treatment with ACARIZAX® can be initiated at any time during the year.
- Onset of the clinical effect is to be expected 8-14 weeks after initiation.
- In patients with history of house dust mite allergy, methods of determining the presence of house dust mite specific IgE should also include prick testing and/or serum testing for specific IgE against *D. farinae* or *D. pteronyssinus*.

4.2 Recommended Dose and Dosage Adjustment

For house dust mite-induced allergic rhinitis (with or without conjunctivitis), the recommended dose of ACARIZAX® is 1 sublingual tablet (12 SQ-HDM) daily.

Health Canada has not authorized an indication in patients under 5 years of age (see 7 WARNINGS AND PRECAUTIONS / 7.1.3 Pediatrics).

4.3 Administration

- ACARIZAX® is a sublingual tablet. The tablet should be taken from the blister unit after carefully removing the foil with dry hands.
- The tablet should be placed under the tongue immediately where it will rapidly dissolve within seconds.
- Do not take the tablet with food or beverage. Swallowing should be avoided for about 1 minute. Food and beverage should not be taken for the following 5 minutes.
- Wash hands after handling the tablet.

4.4 Missed Dose

Patients should not take more than one sublingual tablet daily. Advise patients who miss taking a dose of ACARIZAX® to return to their normal schedules the next day. If a treatment interruption is more than 15 days, advise patients to consult a physician before restarting treatment with ACARIZAX® (see 7 WARNINGS AND PRECAUTIONS / Immune).

5 OVERDOSAGE

The risk of side effects may increase with doses above 12 SQ-HDM. In the event of an overdose; any adverse effects should be treated symptomatically.

In clinical trials, local reactions such as oral pruritus, oral pain, throat irritation, and severe vomiting were observed with daily doses of 24 or 32 SQ-HDM.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Sublingual	Sublingual tablet / 12 SQ-HDM*	Gelatin (fish source) Mannitol Sodium hydroxide (for pH adjustment)

* SQ-HDM is the dose unit for ACARIZAX®. SQ is a method for standardization on biological potency, major allergen content and complexity of the allergen extract. HDM is an abbreviation for house dust mite.

ACARIZAX® is a white to off-white circular sublingual tablet with a debossed pentagon on one side. ACARIZAX® is a sublingual tablet designed to dissolve rapidly within seconds under the tongue.

Each ACARIZAX® tablet contains 12 SQ-HDM of standardized house dust mites allergen extract from *D. farinae* and *D. pteronyssinus*.

The active substance is a standardized allergen extract derived from house dust mites. ACARIZAX® contains the following inactive ingredients: gelatin NF (fish source), mannitol USP and sodium hydroxide NF. ACARIZAX® is free of lactose.

ACARIZAX® sublingual tablets are packaged in aluminum blister packs composed of a blister film and a lidding foil. The lidding foil has been designed to be peeled back from the blister film to allow the removal of the tablets.

The trade size is a box of 30 tablets (3 blisters packs with 10 tablets each).

ACARIZAX® (Standardized Allergen Extract, House Dust Mites (*D. farinae* and *D. pteronyssinus*) Sublingual Tablet) is an allergy immunotherapy tablet for the treatment of the signs and symptoms of house dust mite (HDM) allergy. It is formulated as an orally disintegrating tablet designed to rapidly dissolve within seconds under the tongue. The active substance is a standardized allergen extract derived from house dust mites. Each sublingual tablet has a strength of 12 SQ-HDM* [6 SQ-HDM *D.*

farinae and 6 SQ-HDM *D. pteronyssinus*]. Each tablet contains a 1:1:1:1 potency ratio of *D. farinae* group 1 allergen, *D. farinae* group 2 allergen, *D. pteronyssinus* group 1 allergen, and *D. pteronyssinus* group 2 allergen.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

No data are available regarding the effect of vaccination in patients with ACARIZAX® treatment. Vaccination may be given without interrupting treatment with ACARIZAX® after medical evaluation of the patient's general condition.

Patients previously administered epinephrine used to treat a severe systemic allergic reaction, including anaphylactic shock, were not studied in clinical trials with ACARIZAX®. Effects of epinephrine may be potentiated in patients treated with tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs) with possible fatal consequences; this should be taken into consideration prior to initiating specific immunotherapy.

ACARIZAX® should not be initiated in pregnant women.

ACARIZAX® should be used with caution in patients who have had severe local reactions to any house dust mite immunotherapy taken by mouth.

As with other immunotherapy treatments, patients treated with ACARIZAX® may have local swelling which is severe or which may increase in severity over time. Because of the risk of upper airway compromise, treatment with ACARIZAX® should be discontinued in these patients.

Carcinogenesis and Mutagenesis

No carcinogenicity studies were conducted in animals with *D. farinae* and *D. pteronyssinus* extracts. Based on *in vitro* assays for mutagenicity and an *in vivo* assay for DNA damage, no evidence of genotoxic risk was associated with *D. farinae* and *D. pteronyssinus* extracts.

Gastrointestinal

Eosinophilic esophagitis

Eosinophilic esophagitis has been reported in association with sublingual tablet immunotherapy. Discontinue ACARIZAX® and consider a diagnosis of eosinophilic esophagitis in patients who experience severe or persistent gastro-esophageal symptoms including dysphagia or chest pain.

Immune

Severe Allergic Reactions

ACARIZAX® can cause systemic allergic reactions including anaphylaxis which may be life-threatening. In addition, ACARIZAX® can cause severe local reactions, including laryngopharyngeal swelling which may compromise breathing and be life-threatening. Signs and symptoms that may be associated with a systemic allergic reaction include syncope, hypotension, tachycardia, rhinorrhea, sneezing, dyspnea, wheezing, bronchospasm, chest discomfort, abdominal pain, vomiting, diarrhea, rash, pruritus, flushing and urticaria.

Systemic allergic reactions, including anaphylactic reactions and severe local allergic reactions, have occurred in clinical trial patients treated with ACARIZAX® (see 8 ADVERSE REACTIONS). The majority of

these reactions occurred within minutes after receiving the first dose, but were also reported to occur after administration of subsequent doses. Rare cases of serious systemic allergic reactions have also been reported following the first reinitiated dose after a pause in treatment (see 8 ADVERSE REACTIONS / 8.4 Post-Market Adverse Drug Reactions, and 4 DOSAGE AND ADMINISTRATION / 4.4 Missed Dose). Treatment of severe allergic reactions may require the administration of epinephrine, antihistamines, inhaled bronchodilators and/or systemic corticosteroids.

The first dose of ACARIZAX® should only be administered in a healthcare setting under the supervision of a physician prepared to manage a severe systemic or a severe local allergic reaction. Patients should be observed for 30 minutes after first time administration of ACARIZAX®. Immediately discontinue ACARIZAX® in any patient developing clinical evidence of a severe systemic or severe local allergic reaction. In such cases, consider discontinuing treatment with ACARIZAX® permanently. Patients should be informed and educated about the symptoms of a severe allergic reaction, and instructed to discontinue ACARIZAX®, seek immediate medical care and contact their physician should any of these symptoms occur after taking ACARIZAX®.

The patient may also need to be adequately monitored when taking the first reinitiated dose after a pause of ACARIZAX® treatment of more than 15 days (see 8 ADVERSE REACTIONS / 8.4 Post-Market Adverse Drug Reactions).

Subsequent dose administration in children <12 years must be done under adult supervision and the child must be monitored for any signs of allergic reaction, including breathing difficulties. Observation should be for a minimum of 15 minutes.

Patients who are prescribed epinephrine while receiving immunotherapy should be instructed in the procedure of emergency self-administration of epinephrine (see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX). For children <12 years who are prescribed epinephrine, the parent/guardian should be instructed in the procedure of emergency administration of epinephrine. Instruct patients to seek immediate medical care upon use of epinephrine and to stop treatment with ACARIZAX®.

Patients with Oral Conditions

In patients with oral inflammation (e.g., oral lichen planus, mouth ulcers or thrush) or oral wounds, such as those following oral surgery, tooth loss or dental extraction, treatment with ACARIZAX® should be interrupted to allow healing of the oral cavity.

Respiratory

Patients with Asthma

Immunotherapy with ACARIZAX® is contraindicated in patients who have unstable or severe asthma. During treatment with ACARIZAX®, instruct patients to stop treatment with ACARIZAX® and contact their physician immediately if they have difficulty breathing or if asthma becomes inadequately controlled (see 2 CONTRAINDICATIONS).

Initiation of treatment with ACARIZAX® should be postponed in patients with uncontrolled asthma who are experiencing an acute respiratory tract infection until the infection has resolved.

7.1 Special Populations

7.1.1 Pregnant Women

Immunotherapy with ACARIZAX® should not be initiated during pregnancy because severe systemic reactions may be detrimental to the mother or fetus. No clinical data are available for the use of ACARIZAX® during pregnancy. For animal studies refer to 16 NON-CLINICAL TOXICOLOGY. Because ACARIZAX® is not expected to be absorbed systemically following sublingual administration, maternal use is not expected to result in fetal exposure to the drug.

7.1.2 Breast-feeding

No clinical data are available for the use of ACARIZAX® during lactation. It is not known whether ACARIZAX® is excreted in human milk.

7.1.3 Pediatrics

The safety and efficacy of immunotherapy with ACARIZAX® for house dust mite-induced allergic rhinitis, with or without conjunctivitis, have not been studied in patients under 5 years of age.

7.1.4 Geriatrics

The safety and efficacy of immunotherapy with ACARIZAX® in patients over 64 years of age have not been well-established.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Use of ACARIZAX® has been associated with systemic allergic reactions (see 7 WARNINGS AND PRECAUTIONS / Immune and 3 SERIOUS WARNINGS AND PRECAUTIONS BOX).

In 4 clinical trials (P001, MT-06, MT-04, P003) with ACARIZAX®, a treatment-related systemic allergic reaction was reported in 0.1% (1/1383) of patients treated with ACARIZAX®. Epinephrine was used in this incident. No death occurred in the clinical programme.

The percentage of patients who discontinued from the clinical trials because of a treatment-related adverse reaction while exposed to ACARIZAX® or placebo was 6.6% (91/1383) and 0.8% (11/1397), respectively. The most common treatment-related adverse reactions that led to trial discontinuation in patients who were exposed to ACARIZAX® were throat irritation (1.7%, 23/1383 patients), oral pruritus (1.2%, 17/1383 patients), mouth swelling (1.1%, 15/1383 patients), ear pruritus (1.1%, 15/1383 patients), and swollen tongue (1.0%, 14/1383 patients).

In the clinical trials, 0.3% (4/1383) of patients received epinephrine for treatment of ACARIZAX®-related allergic reactions.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be

useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety data described below are based on 4 clinical trials (P001, MT-06, MT-04, P003). In these trials, 95 adolescent patients 12 through 17 years of age and 1286 adult patients 18 years of age and older, with house dust mite-induced allergic rhinitis and with or without asthma, were exposed to at least one dose of ACARIZAX® (12 SQ-HDM). Of the patients treated with ACARIZAX®, approximately 50% had asthma and 71% were sensitized to other allergens in addition to house dust mites. The patient population was approximately 86% White and 46% male. The mean age of patients was about 34 years. Patient demographics in placebo treated patients were similar to the active group. (See 14 CLINICAL TRIALS / 14.1 Trial Design and Study Demographics for detailed demographics).

Trial P001 was a randomized, double-blind, placebo-controlled study conducted in the US and Canada in 1482 patients 12 years of age and older with mild or moderate house dust mite (HDM)-induced allergic rhinitis with or without conjunctivitis. Of the 1482 patients, 743 patients (94 adolescents and 649 adults) received at least one dose (12 SQ-HDM) of ACARIZAX® with a median treatment duration of 267 days (range 1 to 368 days). 738 patients (95 adolescents and 643 adults) received placebo. In addition to reporting any adverse event during the entire treatment period (up to 52 weeks), study patients were required to record solicited adverse reactions daily in the first 28 days of the treatment period. The solicited adverse reactions (see Table 1) are modified from the World Allergy Organization [WAO] list of local side effects of sublingual immunotherapy (SLIT).

In the study, one female adult experienced a systemic allergic reaction, which manifested as facial flushing, shortness of breath, pre-syncope, itchy palms and throat swelling, within minutes of administration of ACARIZAX® on Day 1 of treatment. The reaction was resolved after use of epinephrine.

As shown in Table 1. the solicited adverse reactions reported in ≥10% of patients treated with ACARIZAX® were: throat irritation (67.0% vs. 22% placebo), oral pruritus (62.3% vs. 14.2% placebo), ear pruritus (50.6% vs. 11.4% placebo), lip swelling (17.9% vs. 2.2% placebo), swollen tongue (16% vs. 2.2% placebo), pharyngeal edema (14.3% vs. 2.7% placebo), glossodynia (15.3% vs 3.4% placebo), nausea (13.2% vs. 4.5% placebo), tongue ulceration (12.7% vs. 2.2% placebo), abdominal pain upper (11% vs. 4.2% placebo), palatal swelling (10.6% vs. 1.4% placebo), and mouth ulceration (10.2% vs. 2.6% placebo).

During the first 28-day treatment, about 83% of ACARIZAX®-treated patients reported at least one solicited adverse reaction (Table 1). Patients typically reported more than one type of solicited adverse reaction occurring on the same day or on separate days. Most of the adverse reactions were transient and mild to moderate in intensity, where moderate was defined as an adverse reaction that interfered with usual activity. The median time to onset of solicited adverse reactions following initiation of treatment with ACARIZAX® varied from 1 to 7 days. The median duration of the reactions that occurred on the first day of treatment initiation ranged from 30 to 78 minutes. For many patients, these adverse reactions reoccurred with subsequent doses. The days of recurrence ranged from a median of 3 to 12 days. The number of reoccurrences of an adverse reaction varied among the patients. Some patients had daily reoccurring reactions. About 67%, 15% and 0.9% of ACARIZAX®-treated patients reported solicited adverse reactions with the highest severity level as mild, moderate and severe, respectively. 17% of ACARIZAX®-treated patients did not report solicited adverse reactions. When adverse reactions were solicited over the first 28 days of treatment, 53%, 44% and 38% of ACARIZAX®-treated patients

reported any of the solicited adverse reactions for a total of more than 10, 15 and 20 days, respectively. The frequency of reoccurrence of adverse reactions beyond the first 28 days of treatment was not attainable due to the difference in AE collection methods between the 28-day solicitation period and the remaining trial period.

In a pool of the other three clinical trials (MT-06, MT-04, and P003) that did not include active solicitation of pre-specified adverse reactions, 641 patients 17 years of age and older received at least one dose of ACARIZAX®. Table 1 presents the rates of treatment-related adverse reaction reported in ≥1% of patients treated with ACARIZAX® in these trials. For adverse reactions that were solicited in Study P001, the rate of these reactions reported in ACARIZAX®-treated patients in the pool of the three trials was significantly lower than that in Study P001 (See Table 1).

In 4 clinical trials (P001, MT-06, MT-04, P003), epinephrine was administered once in 4 of 1,383 patients (0.3%) for ACARIZAX®-related systemic allergic reactions (such as hypersensitivity, dyspnoea, throat tightness, laryngeal oedema and/or chest discomfort).

Analysis of reported adverse reactions of ACARIZAX® in adolescents did not identify material difference in type, frequency, recurrence and severity compared to adults.

Table 1 - Solicited* and Unsolicited Treatment-related Adverse Reactions Reported in ≥1% of Patients with House Dust Mite-Induced Allergic Rhinitis and/or Asthma Treated with ACARIZAX® and Occurring More Commonly than Placebo in One or More Trial Populations

	Trial Population: (P001)		**Trial Population: Three Pooled Trials (MT-06, MT-04, P003)**	
	ACARIZAX® N= 743 n (%)	**PLACEBO N= 738 n (%)**	**ACARIZAX® N= 642 n (%)**	**PLACEBO N= 656 n (%)**
Ear and Labyrinth Disorders	**380 (51.1)**	**84 (11.4)**	**30 (4.7)**	**3 (0.5)**
Ear pruritus	376 (50.6)*	84 (11.4)*	30 (4.7)	3 (0.5)
Eye Disorders	**20 (2.7)**	**15 (2.0)**	**10 (1.6)**	**9 (1.4)**
Eye pruritus	12 (1.6)	9 (1.2)	7 (1.1)	4 (0.6)
Gastrointestinal Disorders	**554 (74.6)**	**214 (29.0)**	**275 (42.8)**	**42 (6.4)**
Oral pruritus	463 (62.3)*	105 (14.2)*	127 (19.8)	16 (2.4)
Lip swelling	133 (17.9)*	16 (2.2)*	20 (3.1)	1 (0.2)
Swollen tongue	119 (16.0)*	16 (2.2)*	12 (1.9)	1 (0.2)
Glossodynia	114 (15.3)*	25 (3.4)*	14 (2.2)	1 (0.2)
Nausea	98 (13.2)*	33 (4.5)*	12 (1.9)	1 (0.2)
Tongue ulceration	94 (12.7)*	16 (2.2)*		
Abdominal pain upper	82 (11.0)*	31 (4.2)*		

	Trial Population: (P001)		Trial Population: Three Pooled Trials (MT-06, MT-04, P003)	
	ACARIZAX® N= 743 n (%)	**PLACEBO N= 738 n (%)**	**ACARIZAX® N= 642 n (%)**	**PLACEBO N= 656 n (%)**
Palatal swelling	79 (10.6)*	10 (1.4)*		
Mouth ulceration	76 (10.2)*	19 (2.6)*		
Mouth swelling	71 (9.6)*	12 (1.6)*	10 (1.6)	0 (0.0)
Paresthesia oral	68 (9.2)	21 (2.8)	35 (5.5)	2 (0.3)
Tongue pruritus	35 (4.7)	7 (0.9)	30 (4.7)	6 (0.9)
Diarrhea	34 (4.6)*	13 (1.8)*		
Stomatitis	22 (3.0)	11 (1.5)	7 (1.1)	2 (0.3)
Oral pain	22 (3.0)	5 (0.7)		
Oral mucosal erythema	16 (2.2)	4 (0.5)		
Vomiting	15 (2.0)*	4 (0.5)*		
Dyspepsia	14 (1.9)	0 (0.0)	7 (1.1)	0 (0.0)
Lip edema	12 (1.6)*	1 (0.1)*	16 (2.5)	2 (0.3)
Tongue edema	12 (1.6)*	0 (0.0)*	11 (1.7)	0 (0.0)
Enlarged uvula	12 (1.6)*	0 (0.0)*		
Dysphagia	11 (1.5)	0 (0.0)		
Abdominal pain	10 (1.3)*	4 (0.5)*		
Lip pruritus	10 (1.3)	2 (0.3)	11 (1.7)	0 (0.0)
Hypoesthesia oral	8 (1.1)	6 (0.8)		
Gastrooesophageal reflux disease	8 (1.1)	0 (0.0)		
Palatal edema	8 (1.1)*	0 (0.0)*		
Mouth edema			57 (8.9)	1 (0.2)
Oral discomfort			13 (2.0)	2 (0.3)
General Disorders and Administration Site Conditions	**20 (2.7)**	**9 (1.2)**	**12 (1.9)**	**4 (0.6)**
Chest discomfort	9 (1.2)	2 (0.3)		

	Trial Population: (P001)		Trial Population: Three Pooled Trials (MT-06, MT-04, P003)	
	ACARIZAX® N= 743 n (%)	**PLACEBO N= 738 n (%)**	**ACARIZAX® N= 642 n (%)**	**PLACEBO N= 656 n (%)**
Injury, Poisoning and Procedural Complications			**18 (2.8)**	**11 (1.7)**
Accidental overdose			18 (2.8)	11 (1.7)
Nervous System Disorders	**83 (11.2)**	**40 (5.4)**	**9 (1.4)**	**2 (0.3)**
Dysgeusia	67 (9.0)*	27 (3.7)*		
Paresthesia	9 (1.2)	2 (0.3)		
Respiratory, Thoracic and Mediastinal Disorders	**516 (69.4)**	**176 (23.8)**	**137 (21.3)**	**40 (6.1)**
Throat irritation	498 (67.0)*	162 (22.0)*	96 (15.0)	16 (2.4)
Pharyngeal edema	106 (14.3)*	20 (2.7)*	14 (2.2)	0 (0.0)
Pharyngeal erythema	16 (2.2)	3 (0.4)		
Dry throat	9 (1.2)	2 (0.3)		
Oropharyngeal pain	9 (1.2)	2 (0.3)		
Sneezing	9 (1.2)	1 (0.1)		
Skin and Subcutaneous Tissue Disorders	**25 (3.4)**	**16 (2.2)**	**11 (1.7)**	**10 (1.5)**
Urticaria	12 (1.6)	3 (0.4)		
Pruritus	10 (1.3)	9 (1.2)		

Percentage reported in the table reflects the data collected over the entire trial duration.
*P001 solicited adverse reactions (modified from World Allergy Organization [WAO] list of local side effects of sublingual immunotherapy) were those reported by subjects within approximately 28 days of treatment initiation.

8.2.1 Clinical trial adverse reactions - pediatrics

Children 5-11 years of age

The safety data described below are based on children 5 through 11 years of age from 3 clinical trials (MT-03, MT-11, and MT-12)). In these trials, 895 patients 5 through 11 years of age with house dust mite-induced allergic rhinitis/rhinoconjunctivitis with or without asthma, were exposed to at least one dose of ACARIZAX® (12 SQ-HDM). Of the patients treated with ACARIZAX®, 49% had asthma and 57% were sensitized to other allergens in addition to house dust mites. The patient population was 99% White and 66% male. The mean age of patients was about 8 years. Patient demographics in placebo

treated patients were similar to the active group. (See 14 CLINICAL TRIALS / 14.1 Trial Design and Study Demographics for detailed demographics).

In addition to reporting any adverse event during the entire treatment period (up to 52 weeks), study patients were required to record solicited adverse reactions daily in the first 28 days of the treatment period. The solicited adverse reactions are modified from the World Allergy Organization [WAO] list of local side effects of sublingual immunotherapy (SLIT).

The safety profile in children 5 to 11 years of age was largely similar to that previously observed in adult and adolescent clinical trials. The overall safety profile in children with asthma was similar to children without asthma.

In children 5-11 years of age the most frequent treatment-related adverse reactions occurred at or near the administration site. Most treatment-related adverse reactions were seen with a similar frequency as in adults. However, the following treatment-related adverse reactions reported in ≥1% pediatric patients were observed more frequently in pediatric patients than in adult and adolescent patients (P001, Table 2): abdominal pain upper (29.5% vs. 11.0%), lip swelling (20.2% vs 17.9%), glossodynia (20.2% vs. 15.3%), nausea (17.3% vs. 13.2%), dysgeusia (15.9% vs. 9.0%), mouth swelling (13.9% vs. 9.6%), diarrhea (8.2% vs. 4.6%), vomiting (5.5% vs. 2.0%).

No study patients experienced ACARIZAX® related anaphylactic reactions and no adverse events were treated with epinephrine.

Table 2 - Solicited* and Unsolicited Treatment-Related Adverse Reactions Reported in ≥1% of Pediatric Patients (5-11 years) with House Dust Mite-Induced Allergic Rhinitis and/or Asthma Treated with ACARIZAX® and Occurring More Commonly than in the Placebo Group

	ACARIZAX® N= 895 n (%)	**PLACEBO N= 900 n (%)**
Ear and Labyrinth Disorders	**296 (31.1)**	**149 (16.6)**
Ear pruritus	296 (31.1)*	149 (16.6)*
Gastrointestinal Disorders	**629 (70.3)**	**364 (40.4)**
Oral pruritus	517 (57.8%)*	210 (23.3%)*
Abdominal pain upper	264 (29.5%)*	150 (16.7%)*
Glossodynia	181 (20.2%)*	47 (5.2%)*
Lip swelling	181 (20.2%)*	43 (4.8%)*
Nausea	155 (17.3%)*	82 (9.1%)*
Mouth swelling	124 (13.9%)*	28 (3.1%)*
Swollen tongue	124 (13.9%)*	22 (2.4%)*
Mouth ulceration	85 (9.5%)*	53 (5.9%)*
Diarrhoea	73 (8.2%)*	54 (6.0%)*
Tongue ulceration	55 (6.1%)*	30 (3.3%)*

	ACARIZAX® N= 895 n (%)	PLACEBO N= 900 n (%)
Vomiting	49 (5.5%)*	22 (2.4%)*
Tongue pruritus	10 (1.1%)	1 (0.1%)
Nervous System Disorders	**142 (15.9)**	**121 (13.4)**
Dysgeusia	142 (15.9%)*	121 (13.4%)*
Respiratory, Thoracic and Mediastinal Disorders	**503 (56.2)**	**280 (31.1)**
Throat irritation	498 (55.6%)*	273 (30.3%)*
Pharyngeal swelling	93 (10.4%)*	31 (3.4%)*

Percentage reported in the table reflects the data collected over the entire trial duration.
*Solicited adverse reactions (modified from World Allergy Organization [WAO] list of local side effects of sublingual immunotherapy) were those reported by subjects within approximately 28 days of treatment initiation.

8.3 Less Common Clinical Trial Adverse Reactions

The following adverse reactions occurred less common (<1%):
Blood and Lymphatic System Disorders: lymphadenitis
Cardiac Disorders: palpitations
Ear and Labyrinth disorders: ear congestion, ear discomfort, tinnitus
Eye Disorders: eye irritation, eyelids pruritus, ocular hyperaemia, scintillating scotoma
Gastrointestinal Disorders: abdominal discomfort, abdominal distension, cheilitis, erosive duodenitis, gastritis, gingival edema, gingival pruritus, gingival swelling, glossitis, hypertrophy of tongue papillae, lip blister, lip disorder, lip pain, noninfective sialoadenitis, odynophagia, esophageal irritation, esophageal pain, esophageal spasm, esophagitis, oral disorder, oral mucosal erosion, oral mucosal blistering, oral mucosal discoloration, oral papule, palatal disorder, rectal hemorrhage, salivary gland enlargement, salivary hypersecretion, sensitivity of teeth, submaxillary gland enlargement, tongue blistering
General Disorders and Administration Site Conditions: asthenia, chest pain, fatigue, feeling hot, local swelling, malaise, mucosal dryness, sensation of foreign body, thirst
Immune System Disorders: hypersensitivity, oral allergy syndrome
Infections and Infestations: abscess oral, acute sinusitis, nasopharyngitis, oral candidiasis, sinusitis, upper respiratory tract infection, viral upper respiratory tract infection
Injury, Poisoning and Procedural Complications: tongue injury
Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, body temperature increased, forced expiratory volume decreased
Musculoskeletal and Connective Tissue Disorders: back pain, musculoskeletal pain, neck pain
Nervous System Disorders: aphonia, hypoesthesia, somnolence, tremor
Psychiatric Disorders: anxiety
Renal and Urinary Disorders: micturition urgency
Respiratory, Thoracic and Mediastinal Disorders: bronchospasm, dry throat, dysphonia, dyspnea, laryngeal discomfort, laryngeal edema, nasal congestion, nasal obstruction, nasal edema, nasal pruritus, nasal ulcer, oropharyngeal discomfort, oropharyngeal swelling, pharyngeal disorder,

pharyngeal hypoesthesia, pharyngeal ulceration, rhinorrhea, sinus congestion, sneezing, snoring, throat tightness, tonsillar hypertrophy, upper-airway cough syndrome
Skin and Subcutaneous Tissue Disorders: alopecia, eczema, rash, rash papular
Vascular Disorders: hot flush

Adverse Drug Reactions of Special Interest in Controlled Clinical Trials

- Hypersensitivity Reactions (systemic reactions): There were 4 patients (1 adolescent, 3 adult) with systemic allergic reactions who were exposed to ACARIZAX®. In 3 of the 4 patients, the systemic allergic reaction was attributed to triggers unrelated to ACARIZAX® use.
- Serious and Severe Local Reactions and progression of oral reactions to the throat: There were no patients exposed to ACARIZAX® who developed serious local allergic swellings or airway compromise. Severe reactions that affected the throat included mouth edema (n=2), throat tightness (n=1), pharyngeal edema (n=1), and tongue edema (n=1).
- Acute Asthma: There was 1 adult patient with a serious treatment-related asthma exacerbation who was exposed to ACARIZAX® in the clinical development program.

8.3.1 Less common clinical trial adverse reactions - pediatrics

The following treatment-related adverse reactions occurred less common (<1%) in children (5-11 years):
Eye Disorders: conjunctival hyperaemia, conjunctival irritation, conjunctivitis allergic, lacrimation increased, periorbital edema
Gastrointestinal Disorders: abdominal discomfort, dry mouth, dyspepsia, dysphagia, enlarged uvula, eosinophilic esophagitis, eructation, glossitis, lip oedema, lip pain, lip pruritus, edema mouth, esophageal irritation, oral discomfort, oral mucosal erythema, paresthesia oral, salivary gland enlargement, salivary hypersecretion, tongue discomfort, tongue erythema, tongue edema
General disorders and administration site conditions: application site pain, chest discomfort, chest pain, edema mucosal, swelling face
Immune system disorders: hypersensitivity
Infections and infestations: conjunctivitis, gastroenteritis
Injury, poisoning and procedural complications: accidental overdose
Metabolism and nutrition disorders: decreased appetite
Psychiatric disorders: dissociation
Respiratory, thoracic and mediastinal disorders: cough, dyspnea, oropharyngeal pain, pharyngeal oedema, pharyngeal paresthesia, rhinorrhea, throat tightness, tonsillar hypertrophy
Skin and Subcutaneous Tissue Disorders: dermatitis allergic, pruritus, skin edema

8.4 Post-Market Adverse Reactions

In post-marketing experience with ACARIZAX® (adult and adolescent patients), rare cases of serious systemic allergic reactions, including anaphylactic shock, have been reported shortly after the first initial dose or following the first reinitiated dose after a prolonged pause in treatment (more than 15 days). See 7 WARNINGS AND PRECAUTIONS / Immune and 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

In addition, in post-marketing experience with ACARIZAX®, rare cases of eosinophilic esophagitis have been reported (see 7 WARNINGS AND PRECAUTIONS / Gastrointestinal).

There is limited post-marketing experience in treatment with ACARIZAX® in children <12 years of age.

9 DRUG INTERACTIONS

9.1 Drug Interactions Overview

No potential drug interactions have been identified, and no drug interaction studies have been conducted in humans.

Co-administration with other immunotherapy has not been studied.

9.2 Drug-Behavioural Interactions

If dizziness or fatigue is experienced by the patient they should be advised not to drive or operate machinery until these effects have passed.

9.3 Drug-Drug Interactions

Interactions with other drugs have not been established.

- See 2 CONTRAINDICATIONS for potential drug-drug interactions with beta-blockers.
- See 7 WARNINGS AND PRECAUTIONS / General for potential drug-drug interactions with MAOIs or tricyclic antidepressants.

9.4 Drug-Food Interactions

Interactions with food have not been studied.

9.5 Drug-Herb Interactions

Interactions with herbal products have not been studied.

9.6 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been studied.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The immune system is the target of immunotherapy. The aim is to prevent or suppress allergic symptoms through repeated administration of the allergen. The effect of sublingual immunotherapy is thought to be mediated through local and systemic immunomodulatory mechanisms (immune deviation) including changes in allergen specific antibodies and regulatory T-cells leading to long-term tolerance development.

10.2 Pharmacodynamics

The immune system is the target for the pharmacodynamic effect. The aim is to induce an immune response against the allergen with which the patient is treated. ACARIZAX® administered daily via the sublingual route induces a time and dose-dependent immune response in both house dust mites specific IgG_4 and IgE. Data from studies of up to 52 weeks demonstrate that these immunological changes can be observed as early as approximately 28 days after treatment initiation and continue during treatment. The clinical significance of these findings has not been established.

10.3 Pharmacokinetics

No pharmacokinetic studies in animals or clinical studies investigating the pharmacokinetic profile and metabolism of *D. farina*e and *D. pteronyssinus* extracts have been conducted.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (do not store above 25°C). Store in the original package until use to protect from moisture.

12 SPECIAL HANDLING INSTRUCTIONS

There are no special handling instructions for ACARIZAX®.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

The potency of the two drug substances in SQ-HDM is based on the total allergenic activity and the content of two major allergens (group 1 and group 2).

Proper name: Standardized Allergen Extract, House Dust Mites (*D. farinae* and *D. pteronyssinus*

Molecular formula and molecular mass: Contains two drug substances, each of which consists of a complex mixture of proteins and other biologically derived substances extracted from two cultivated house dust mite species. Therefore, there is no molecular formula and no detailed structural information available.

Physicochemical properties: Light to dark brown non-sterile, non-adhesive frozen droplets that are soluble in a range of buffers and water.

Product Characteristics:

The drug substances (DS) are prepared by extraction of house dust mites, which are then purified by filtration and stabilized into frozen droplets before incorporation in the final dosage form. The characterization of the major allergenic components includes identification of the relevant allergen. Each tablet contains a 1:1:1:1 potency ratio of *D. farinae* group 1 allergen, *D. farinae* group 2 allergen, *D. pteronyssinus* group 1 allergen, and *D. pteronyssinus* group 2 allergen.

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The efficacy of ACARIZAX® for the treatment of HDM-induced allergic rhinitis was investigated in three double-blind, placebo-controlled, randomized clinical field efficacy trials (Trials P001, MT-06 and MT-12). Collectively, the trials were conducted with initiation of treatment throughout the year. Subjects received ACARIZAX® or placebo as a sublingual tablet daily for a duration of approximately 12 months.

Table 3 - Summary of patient demographics for clinical trials in Allergic Rhinitis

Trial #	Trial design	Dosage and duration	Number of subjects N = total	Subject Population • **Age Range (mean)** • *Male (%) / Female (%)*
P001	Phase III R, MC, DB, PG, PC	12 SQ-HDM QD placebo *Up to approximately* *12 months*	741 741 N = 1482	12 – 85 years (35) *608 (41) / 875 (59)*
MT-06	Phase III R, MC, DB, PG, PC	12 SQ-HDM QD 6 SQ-HDM QD placebo *Approximately 12 months*	318 336 338 N = 992	18 - 66 years (32) *494 (50) / 498 (50)*
MT-12	Phase III R, MC, DB, PG, PC	12 SQ-HDM QD placebo *Up to approximately* *12 months*	729 731 N=1460	5-11 years (8) *963 (66)/495(34)*

R = randomized; MC = multi-center; DB = double-blind; PG = parallel-group; PC = placebo-controlled
HDM = house dust mite; SQ-HDM = dose unit of the HDM SLIT-tablet; QD = once a day

Trial P001 (North American Field Efficacy Trial)

P001 was a double-blind, placebo-controlled, randomized field efficacy trial conducted in the United States and Canada for a duration of up to 12 months, that compared the efficacy of ACARIZAX® (N=741) compared to placebo (N=741) in the treatment of HDM-induced allergic rhinitis. Subjects 12 through 85 years of age were enrolled if they had a history of symptomatic allergic rhinitis and were sensitized to *D. farinae* and/or *D. pteronyssinus* as determined by house dust mite specific IgE. Subjects were required to be symptomatic and were not taking symptom-relieving allergy medications at enrollment.

Subjects with mild to moderate asthma, defined as asthma of a severity that required, at most, a daily medium dose of an inhaled corticosteroid, were enrolled in the trial.

In this trial, 31% of subjects had asthma, 48% had conjunctivitis, and 76% were polysensitized to other allergens in addition to HDM, including trees, grasses, weeds, animal danders and molds. The subject population was 76% White, 11% African American, 7% Asian, and 59% female. The mean age of subjects was 35 years.

The efficacy of ACARIZAX® in the treatment of HDM-induced allergic rhinitis was assessed through self-reporting of symptoms and medication use. Based on these self-assessments, the total combined rhinitis score (TCRS), daily symptom scores (DSS) and daily medication scores (DMS) for rhinoconjunctivitis were calculated. Daily symptoms included four nasal symptoms (runny nose, stuffy nose, sneezing, and itchy nose) and two ocular symptoms (gritty/itchy eyes and watery eyes). Each of these rhinoconjunctivitis symptoms was individually graded by subjects daily on a scale of 0 (none) to 3 (severe) and then summed. Subjects in active and placebo arms of this trial were allowed to take symptom-relieving allergy medications (including oral and ocular antihistamines and nasal

corticosteroids) during the trial as needed. The DMS measured the use of these standard symptom-relieving allergy medications. Predefined daily maximum scores were assigned to each class of rhinitis and conjunctivitis medication as 0=none, 6=oral antihistamine, 6=ocular antihistamine, and 8=nasal corticosteroid.

The primary endpoint was the average TCRS during approximately the last 8 weeks of treatment. The TCRS represents the sum of the daily rhinitis DSS and the rhinitis DMS. Other secondary endpoints in this trial included the average rhinitis DSS, the average rhinitis DMS, and the total combined score (TCS). The TCS represents the sum of the rhinoconjunctivitis DSS and the rhinoconjunctivitis DMS, which was then averaged during approximately the last 8 weeks of treatment.

Subjects in this trial were required to stop taking symptom-relieving allergy medication during the baseline period. The mean rhinitis DSS at baseline was 7.94 out of 12 total points in both the treatment arm and in the placebo arm.

Trial MT-06 (European Field Efficacy Trial)

This double-blind, placebo-controlled, randomized field efficacy trial evaluated adult subjects 18 through 66 years of age comparing ACARIZAX® (N=318) and placebo (N=338) administered as a sublingual tablet daily for a duration of approximately 12 months. Subjects in this trial had a history of symptomatic allergic rhinitis when exposed to house dust and were sensitized to *D. farinae* and/or *D. pteronyssinus* as determined by house dust mite specific IgE testing. At trial entry, subjects were required to be symptomatic despite taking symptom-relieving allergy medications during the baseline period.

In this trial, 46% of subjects had asthma, 97% had conjunctivitis and 67% were polysensitized to other allergens in addition to HDM, including trees, grass, weeds, animal danders and molds. The trial population was 98% White, <1% African American, and <1% Asian; 50% of subjects were female. The mean age of subjects in this trial was 32 years. The primary efficacy endpoint was the average TCRS during the last 8 weeks of treatment. The mean Rhinitis DSS at baseline was 7.95 out of 12 for the treatment arm and 8.00 out of 12 total points for the placebo arm.

Trial P003 (House Dust Mite Environmental Exposure Chamber (EEC) Trial)

A double-blind, placebo-controlled, phase IIb, dose-finding, randomized environmental exposure chamber (EEC) trial evaluated adult subjects 18 through 58 years of age comparing ACARIZAX® (N=42) and placebo (N=41) administered as a sublingual tablet daily for approximately 24 weeks. Subjects had a history of symptomatic allergic rhinitis with and without conjunctivitis and were sensitized to *D. farinae* and/or *D. pteronyssinus* as determined by HDM specific IgE.

In this trial, 23% of subjects had asthma, 87% had conjunctivitis, and 84% were polysensitized to other allergens in addition to HDM, including tree, grass, weeds, animal danders and molds. The subject population was 90% White, <1% African American, 8% Asian, and 43% female. The mean age of subjects was 27 years.

The primary endpoint was the average TNSS at Week 24. The Total Nasal Symptom Score (TNSS) represents the sum of 4 nasal symptoms (runny nose, stuffy nose, sneezing, and itchy nose). Secondary endpoints were the average TNSS at Weeks 8 and 16, and Total Symptom Score (TSS) at Week 24. Baseline TNSS following house dust mite EEC challenge prior to treatment was 7.74 out of 12 total points for ACARIZAX® and 7.32 out of 12 total points for placebo.

Trial MT-12 (European and North American Field Efficacy Trial)

This double-blind, placebo-controlled, randomized field efficacy trial evaluated pediatric subjects 5

through 11 years of age comparing ACARIZAX® (N=729) and placebo (N=731) administered as a sublingual tablet daily for a duration of approximately 12 months. Subjects in this trial were given free access to sponsor-provided rhinoconjunctivitis and asthma rescue medication. Subjects had a history of moderate to severe rhinitis or rhinoconjunctivitis (with or without asthma) when exposed to house dust mite and were sensitized to *D. farinae* and/or *D. pteronyssinus* as determined by house dust mite specific IgE testing.

At trial entry, subjects were required to be symptomatic despite taking symptom-relieving allergy medications during the previous year prior to screening.

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

In this trial the mean age of subjects was 8 years and 34% of subjects were female. The trial population was 98% White, <1% Asian, <1% Black or African American. 39% of subjects had house dust mite-induced allergic conjunctivitis. Sensitisation to other allergens in addition to house dust mite was demonstrated for 52% of subjects and 38% of subjects reported asthma at baseline. The baseline mean TCRS was approximately 18 in both treatment groups (on a scale of 0-24), rhinitis DSS and rhinitis DMS were approximately 8 and 10, respectively, in both treatment groups (on a scale of 0-12) and the mean asthma DSS at baseline was approximately 2 in both treatment groups (on a scale of 0-12).

14.2 Study Results

Trial P001 (North American Field Efficacy Trial)

Based on the primary analysis, patients treated with ACARIZAX® had significant relief of nasal symptoms and reduction in standard allergy medication use as measured by a decrease in TCRS compared to placebo-treated subjects. Similar improvement was observed in patients treated with ACARIZAX® for other key secondary endpoints. The results of this trial are shown in Table 4.

Table 4 - Total Combined Rhinitis Score (TCRS), Rhinitis Daily Symptom Score (DSS), Rhinitis Daily Medication Score (DMS), and Total Combined Score (TCS) During the Last 8 Weeks of Treatment (P001)

Endpoint	ACARIZAX® (n)† Score‡	Placebo (n)† Score‡	Treatment Difference (ACARIZAX® - Placebo)		Difference Relative to Placebo§	
			Estimate	p-value	Estimate	(95% CI)
Primary Endpoint						
TCRS*	(566) 4.10	(620) 4.95	-0.80	<0.001	-17.2%	(-25.0%, -9.7%)

TCRS[+]	(566) 3.16	(620) 3.87	-0.71	<0.001	-18.4%	(-31.0%, -6.5%)
Secondary Endpoints						
Rhinitis DSS*	(566) 3.55	(620) 4.20	-0.60	<0.001	-15.5%	(-24.4%, -7.3%)
Rhinitis DMS[#]	(566) 0.65	(620) 0.79	-0.15	0.154[¶]	-18.4%	(-41%, 4.3%)
TCS*	(566) 5.50	(620) 6.60	-1.10	<0.001[¤]	-16.7%	(-24.6%, -4.0%)

TCRS=Total Combined Rhinitis Score (Rhinitis DSS + Rhinitis DMS); TCS=Total Combined Score (Rhinoconjunctivitis DSS + Rhinoconjunctivitis DMS); CI=Confidence Interval

* Non-parametric analysis for TCRS, Rhinitis DSS, and TCS endpoints using the Wilcoxon Rank Sum test.

[+] Longitudinal Data Analysis (LDA) model for TCRS.

[#] Parametric analysis using a zero-inflated log-normal model for Rhinitis DMS endpoint. 337 (59.5%) and 336 (54.2%) subjects in the ACARIZAX® and placebo treatment groups, respectively, did not utilize rescue medications.

[†] Number of subjects in analyses; subjects not evaluable for diary-based endpoints were not included in the analyses (ACARIZAX® 23.5%; placebo 16.3%).

[‡] For the non-parametric analyses, the estimated group medians are reported and treatment difference is the Hodges-Lehmann estimate. For the LDA and zero-inflated log-normal models, the estimated group means are reported and treatment difference is the difference in estimated group means.

[§] Difference relative to placebo was calculated based on the estimated group medians (for non-parametric analyses) or means (for LDA and zero-inflated log-normal model) as: (ACARIZAX® – placebo)/placebo x 100%.

[¶] Not statistically significant.

[¤] This result cannot be considered confirmatory due to the pre-specified multiplicity control strategy, which involved a sequential testing procedure (order: TCRS, rhinitis DSS, rhinitis DMS, TCS).

Trial MT-06 (European Field Efficacy Trial)

Based on the primary analysis, patients treated with ACARIZAX® had significant relief of nasal symptoms and reduction in standard allergy medication use as measured by a decrease in TCRS compared to placebo-treated subjects. Similar improvement was observed in patients treated with ACARIZAX® for other key secondary endpoints. The results of this trial are shown in Table 5.

Table 5 – Total Combined Rhinitis Score (TCRS), Rhinitis Daily Symptom Score (DSS), Rhinitis Daily Medication Score (DMS), and Total Combined Score (TCS) During the Last 8 Weeks of Treatment (MT-06)

Endpoint	ACARIZAX® (n)[†] Score[‡]	Placebo (n)[†] Score[‡]	Treatment Difference (ACARIZAX® - Placebo)	Difference Relative to Placebo[§]

			Estimate	p-value	Estimate	(95% CI)
Primary Endpoint						
TCRS*	(318) 5.71	(338) 6.81	-1.09	0.004	-16.1%	(-25.8%, -5.7%)
TCRS[+]	(284) 4.92	(298) 6.23	-1.31	<0.001	-21.0%	(-31.2%, -9.4%)
Secondary Endpoints						
Rhinitis DSS*	(318) 2.84	(338) 3.31	-0.47	0.01	-14.1%	(-23.8%, -3.9%)
Rhinitis DMS*[#]	(318) 2.32	(338) 2.86	-0.54	0.045	-18.9%	(-34.7%, -1.3%)
TCS*[¶]	(241) 7.91	(257) 9.12	-1.21	0.029	-13.2%	(-23.7%, -1.5%)

TCRS=Total Combined Rhinitis Score (Rhinitis DSS + Rhinitis DMS); TCS=Total Combined Score (Rhinoconjunctivitis DSS + Rhinoconjunctivitis DMS); CI=Confidence Interval

* Linear mixed effect (LME) model. Multiple imputation was performed for TCRS, rhinitis DSS, and rhinitis DMS.

[+] Longitudinal Data Analysis (LDA) model for TCRS analysed post hoc.

[†] Number of subjects in analyses; all randomized subjects were included in the LME analyses of TCRS, rhinitis DSS, and rhinitis DMS. All randomized subjects evaluable for diary-based endpoints were included in the LDA model for TCRS and in the LME analysis of TCS.

[‡] Estimated group means are reported. Treatment difference is difference in estimated group means.

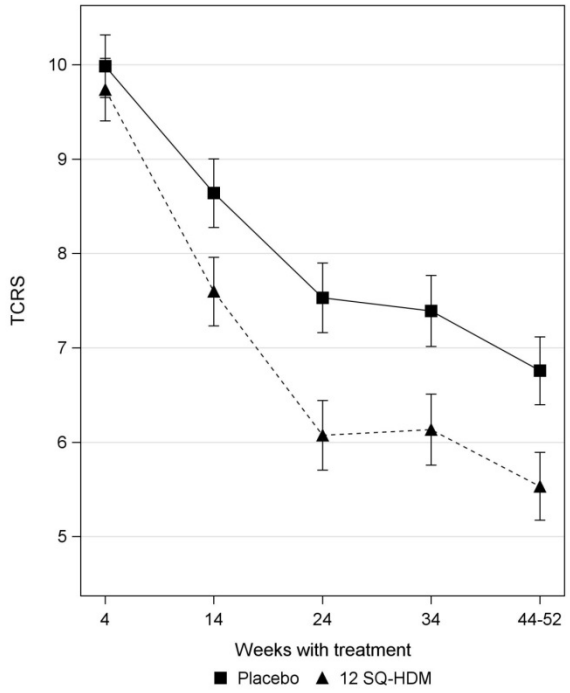
[¤] The pre-specified multiplicity control strategy involved a sequential testing procedure (order: TCRS, rhinitis DSS, rhinitis DMS, TCS).

[§] Difference relative to placebo was calculated based on the estimated group means as: (ACARIZAX® – placebo)/placebo x 100%.

[#] 45 (15.8%) and 29 (9.7%) subjects in the ACARIZAX® and placebo treatment groups, respectively, did not utilize rescue medications.

[¶] Subjects from Serbia and Croatia (48 [15.1%] and 46 [13.6%] subjects in the ACARIZAX® and placebo treatment groups, respectively) were not included in the analysis of TCS because the preferred formulations of antihistamine eye drops were not available in these countries at the time the trial was conducted.

Efficacy was assessed at pre-defined intervals throughout the treatment period at weeks 4, 14, 24 and 34 in addition to during the last 8 weeks of treatment (see Figure 1).



Error bars: 95% confidence interval for the difference in adjusted means based on analysis of covariance model.

Figure 1 – Adjusted Means of the Total Combined Rhinitis Score (TCRS) Over Time (MT-06)

Trial P003 (House Dust Mite Environmental Exposure Chamber (EEC) Trial)

The results of the trial are shown in Table 6.

Table 6 – Total Nasal Symptom Score (TNSS) and Total Symptom Score (TSS) During HDM-Allergen Challenge (EEC Trial)

Endpoint*	ACARIZAX® (n)† Score‡	Placebo (n)† Score‡	Treatment Difference (ACARIZAX®- Placebo)		Difference Relative to Placebo§	
			Estimate	p-value	Estimate	(95% CI)
Primary endpoint						
TNSS – Week 24	(36) 3.83	(34) 7.45	-3.62	<0.001	-48.6%	(-60.2%, -35.3%)
Secondary endpoints						
TNSS – Week 8	(40) 5.34	(39) 6.71	-1.37		-20.4%	(-33.3%, -6.8%)
TNSS – Week 16	(39) 4.82	(38) 6.90	-2.08		-30.1%	(-42.3%, -16.8%)
TSS –	(36)	(34)	-4.84		-52.2%	(-65.0%, -37.0%)

Week 24	4.43	9.27				

TNSS=Total Nasal Symptom Score, endpoint score range: 0-12.; TSS=Total Symptom Score (TNSS + total ocular symptom score), endpoint score range 0-18; CI=Confidence Interval

* Parametric analysis using analysis of covariance for all endpoints: analysis via ANCOVA with treatment and baseline endpoint score as fixed effects. The endpoint was calculated based on diary entries over the last 4 hours of the chamber session. Baseline endpoint value was calculated based on the screening.

† Number of subjects in analyses. Subjects who discontinued the trial prior to the given time point were not included in the analyses.

‡ For all endpoints, the estimated group least squares mean is reported. Treatment difference was the difference between least squares means.

§ Difference relative to placebo was calculated based on the estimated group least squares means as: (ACARIZAX®-placebo)/placebo x 100%.

Trial MT-12 (European and North American Field Efficacy Trial)

After 12 months of treatment with ACARIZAX® an absolute difference in adjusted means of 0.97 (95% confidence interval [0.50;1.44], (p<0.0001)) and a relative difference of 22% compared to placebo was found for the primary endpoint (TCRS). 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), (see Figure 2).

The results of this trial are shown in Table 7.

Table 7 – Total Combined Rhinitis Score (TCRS), Rhinitis Daily Symptom Score (DSS), Rhinitis Daily Medication Score (DMS), Total Combined Rhinoconjunctivitis Score (TCS) During the Last 8 Weeks of Treatment (MT-12)

Endpoint	**ACARIZAX® (n) Score**	**Placebo (n) Score**	**Treatment Difference in Adjusted Means (ACARIZAX® - Placebo)**		**Difference Relative to Placebo**	
	Adjusted Mean	Adjusted Mean	Estimate	p-value	Estimate	95% CI
Primary endpoint						
TCRS	(693) 3.44	(706) 4.41	-0.97	<0.0001	-22.0%	[-31.1; -12.0]
Secondary Endpoints (Pre-defined key secondary endpoints)						
Rhinitis DSS	(693) 1.50	(706) 1.92	-0.43	<0.0001	-22.2%	[-30.8;-12.8]
Rhinitis DMS	(693) 1.44	(706) 1.94	-0.49	0.0016	-25.3%	[-38.3; -10.5]
Rhinoconjunctivitis TCS	(693) 4.01	(706) 5.16	-1.15	<0.0001	-22.2%	[-31.5; -12.0]
Pre-defined secondary endpoints						
PRQLQ	(695) 0.84	(690) 1.01	-0.17	<0.0001	-16.6%	[-24.0; -8.8]
	Proportion	Proportion	Odds ratio			

Rhinitis exacerbation days	(693) 0.025	(706) 0.044	0.56			
Rhinitis mild days	(693) 0.318	(706) 0.209	1.77			
Pre-defined explorative endpoints						
Rhinitis symptom-free days	(693) 0.200	(706) 0.116	1.90			

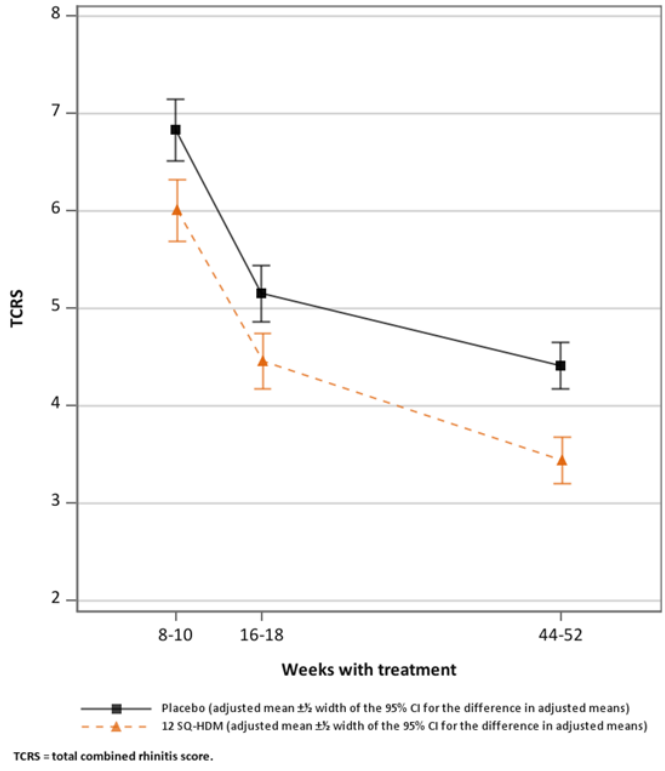
CI=confidence interval; DMS=daily medication score; DSS=daily symptom score; n=number of subjects with observations contributing to the analysis; PRQLQ=paediatric rhinoconjunctivitis quality of life questionnaire; TCRS=total combined rhinitis score (=rhinitis DSS + rhinitis DMS); TCS=total combined rhinoconjunctivitis score (=rhinoconjunctivitis DSS + rhinoconjunctivitis DMS).

Estimated group means are reported. Treatment difference is difference in estimated group means. Absolute difference=ACARIZAX® - placebo, 95% CI. Relative difference to placebo was calculated based on the estimated group least squares means as: (ACARIZAX® - placebo) / placebo x 100%, 95 CI.

Odds ratio for having a rhinitis exacerbation, rhinitis mild days and rhinitis symptom-free days: 12 SQ-HDM / placebo.

A rhinitis exacerbation day was defined as a day with a rhinitis DSS of 6 or of 5 with 1 individual symptom scored 3 (symptom that is hard to tolerate or causes interference with activities of daily living and/or sleeping).

Efficacy was assessed at pre-defined intervals during the treatment period from week 8 and 16 in addition to during the last 8 weeks of treatment (see Figure 2)



The MT-12 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.

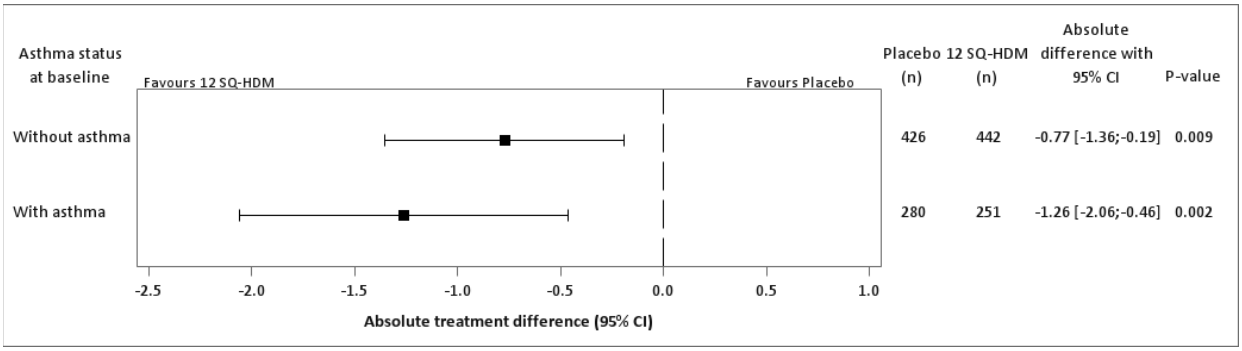
The primary endpoint was the average daily TCRS during the last approximately 8 weeks of treatment (weeks ~44-52).

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.

Figure 2 – Adjusted Means of the Total Combined Rhinitis Score (TCRS) Over Time (MT-12)

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).

Figure 3 - 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; SQ-HDM=dose unit of the HDM SLIT-tablet; TCRS=total combined rhinitis score.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: A general toxicity study in mice dosing HDM allergen extract (the active substance of ACARIZAX®) up to 14 SQ-HDM/day for 6 months did not reveal any significant treatment-related effects.

No dedicated animal safety pharmacology studies were conducted with ACARIZAX® (*D. farinae* and *D. pteronyssinus*). However, there were no overt central nervous system or respiratory effects noted for up to 6-months of dosing in the mouse based on routine clinical observations.

Carcinogenicity: The carcinogenic potential of ACARIZAX® has not been evaluated.

Genotoxicity: There were no clinically relevant positive findings in in vitro chromosome aberration assays, an in vitro bacterial mutagenesis assay and a combined Comet and micronucleus assay for mutagenicity in rats using HDM allergen extract (*D. farinae and D. pteronyssinus*).

Reproductive and Developmental Toxicology: Mice administered HDM allergen extract by daily subcutaneous injections from the time of implantation through late gestation (gestational days 6 to 17) revealed no significant treatment related effects on post-implantation loss or prenatal development up to five times the human sublingual dose.

Fertility studies have not been performed with HDM allergen extract.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

ACARIZAX®

Standardized Allergen Extract, House Dust Mites (*D. farinae* and *D. pteronyssinus*)

Sublingual Tablet, 12 SQ-HDM

Read this carefully before you start taking **ACARIZAX®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **ACARIZAX®**.

Serious Warnings and Precautions

- ACARIZAX® is intended for use only by physicians with adequate training and experienced in the treatment of allergic diseases.
- It is common for patients to experience mild or moderate local allergic reactions with ACARIZAX® (for example, an itchy mouth or a sore throat). Serious life-threatening allergic reactions which require immediate medical attention may occur in patients treated with ACARIZAX®. If you experience stronger allergic reactions with a feeling of swelling in the throat, difficulty swallowing or breathing and voice changes, contact your physician immediately. The treatment has to be stopped immediately until your physician advises otherwise.
- The first tablet of ACARIZAX® must be taken at the doctor's office. Your doctor will also tell you to stay on site for 30 minutes to check out for possible side effects to the treatment you may have.

What is ACARIZAX® used for?

ACARIZAX® is for children and adults aged 5 to 65 who are allergic to house dust mites and have allergic rhinitis (with or without conjunctivitis). Symptoms of allergic rhinitis include sneezing, runny or itchy nose, stuffed up nose (with or without symptoms of conjunctivitis such as itchy, burning, red, or watery eyes).

Before you begin treatment with ACARIZAX®, your allergy to house dust mites will be confirmed by a doctor who will perform skin and/or blood tests.

ACARIZAX® is NOT a medication that gives immediate relief for symptoms of house dust mite allergy.

ACARIZAX® has not been tested in subjects under 5 years old, and the efficacy and safety of ACARIZAX® have not been well established in subjects over 64.

How does ACARIZAX® work?

ACARIZAX® is a tablet that treats your allergy caused by house dust mites. It contains an allergen extract that helps to make you less sensitive to the house dust mites you are allergic to.

What are the ingredients in ACARIZAX®?

Medicinal ingredients: standardized allergen extract from the house dust mites *D. farinae* and *D. pteronyssinus*

Non-medicinal ingredients: fish gelatin, mannitol, and sodium hydroxide. ACARIZAX® does not contain lactose.

ACARIZAX® comes in the following dosage forms:

ACARIZAX® is a prescription tablet that you take once a day by placing it under your tongue.

Each tablet contains 12 SQ-HDM of a Standardized Allergen Extract, House Dust Mites (*D. farinae and D. pteronyssinus*).

Do not use ACARIZAX® if:

- you are allergic (hypersensitive) to any of the non-medicinal ingredients of ACARIZAX® (see **What are the ingredients in ACARIZAX?**)
- you have had a serious allergic reaction to house dust mite allergy shots, tablets or drops;
- you have severe or unstable asthma.
- are taking beta-blockers (a medicine prescribed for heart conditions, such as high blood pressure).
- you have any swelling or sores in your mouth or have recently had any mouth injury or mouth surgery (such as a tooth removal) or tooth loss. Your doctor may delay the start of your treatment until you are better.
- you have been diagnosed with a rare condition called eosinophilic esophagitis.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ACARIZAX®. Talk about any health conditions or problems you may have, including if you:

- have ever had a serious allergic reaction to allergy shots, tablets or drops
- have worsening asthma symptoms or breathing problems
- have an airway infection, such as common cold, sore throat or pneumonia
- are pregnant or plan to become pregnant
- are breastfeeding or plan to breastfeed. It is not known if ACARIZAX® will pass into breast milk
- have diseases affecting the immune system e.g. autoimmune diseases, immune complex diseases or (severe) immune deficiency diseases.
- have malignant diseases (e.g. cancer).

Other warnings you should know about:

There is limited experience with ACARIZAX® in patients younger than 5 or older than 64. Therefore, the use of ACARIZAX® is not recommended in these age groups.

<u>Stop treatment and get emergency medical treatment right away if you have any of the following</u>

symptoms after taking ACARIZAX®:

- dizziness, fainting, fast or weak heartbeat, feeling nervous or feeling of "impending doom"
- throat tightness or swelling of the tongue or throat that causes trouble speaking, breathing or swallowing
- wheezing, shortness of breath, cough, chest tightness or trouble breathing
- stomach cramps, vomiting or diarrhea
- skin rash, itching, flushing or hives

Children must be watched by an adult for any signs of allergic reactions, including breathing difficulties, for a minimum of 15 minutes after taking each tablet. The need for an epinephrine device should be decided on a case-by-case basis and discussed with your doctor.

Stop treatment with ACARIZAX® if you have any of the following symptoms that do not go away or that worsen:

- heartburn, difficulty swallowing, pain with swallowing, or chest pain

Tell your healthcare professional or pharmacist about all the medicines you take, including any prescription and non-prescription medicines, vitamins, minerals, natural supplements or alternative medicines. Your doctor will tell you if it is safe to take other medicines while you are using ACARIZAX®. **No drug interaction studies have been done in patients taking** ACARIZAX®**.**

How to take ACARIZAX®:

The first dose of ACARIZAX® should only be taken in the doctor's office. After taking the first dose, you will be watched for 30 minutes by a healthcare professional for symptoms of a serious allergic reaction.

Your doctor may prescribe medicines for you to take in case you have a serious allergic reaction.

After the first dose, you may take ACARIZAX® at home.

Usual dose:

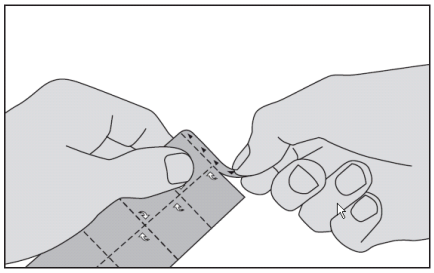
Take ACARIZAX® once daily for as long as your doctor tells you to take it. ACARIZAX® treatment can begin at any time during the year.

How should I take ACARIZAX®?

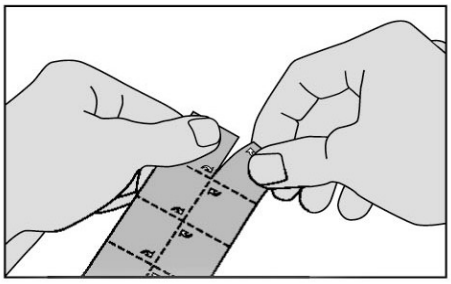
1. Do not use food or water to take the tablet.
2. Remove the tablet from the package with dry hands by carefully removing the foil. (If your hands are wet or damp, the tablet will break or dissolve too soon.)
3. Place the tablet under the tongue right away. It will rapidly dissolve.
4. Do not swallow for about 1 minute.
5. Do not drink or eat for 5 minutes after taking the tablet.
6. Wash your hands after handling the tablet.

Detailed Instructions

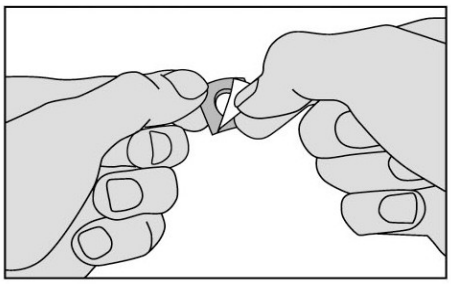
1. Tear off the strip marked with triangles at the top of the blister pack.

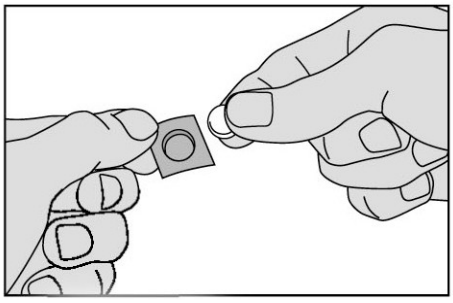


2. Tear a square off the blister pack along the perforated lines.

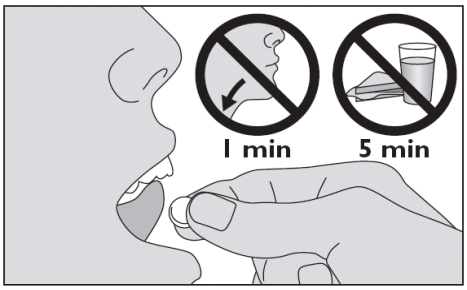


3. Remove the tablet carefully from the foil (do not force the tablet through the foil. It may become damaged as it easily breaks. Instead, fold back the marked corner of the foil and then pull it off). Take it immediately.





4. Place the tablet under the tongue. Allow it to remain there for a few seconds until it dissolves. Do not swallow during the first minute. Do not eat or drink for 5 minutes. Wash hands after handling the tablet. Children must be watched for signs of allergic reactions including breathing difficulties for a minimum of 15 minutes after taking each tablet.



General information about the safe and effective use of ACARIZAX®

This medicine has been prescribed for you. Do not give it to anyone else. It may harm them, even if their symptoms are the same as yours.

Your doctor may also prescribe medications to treat possible allergic reactions from ACARIZAX® treatment.

Overdose:

Taking more than one ACARIZAX® tablet in one day can cause severe allergic reactions.

If you think you, or a person you are caring for, have taken too much ACARIZAX®, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

Do not take more than one ACARIZAX® tablet daily. If you miss a dose, return to your normal schedule the next day. Do not take a double dose to make up for the forgotten dose.

If temporarily stopping treatment for more than 15 days consult your doctor before restarting treatment with ACARIZAX®.

What are possible side effects from using ACARIZAX®?

These are not all the possible side effects you may have when taking ACARIZAX®. If you experience any side effects not listed here, tell your healthcare professional.

Side effects caused by ACARIZAX® usually happen early in treatment, but can happen even if you have been taking ACARIZAX® for months.

The most common side effects of ACARIZAX® include:

- throat irritation
- itching of the ears and/or mouth
- tingling and/or burning of the mouth
- swelling of the mouth including lips and/or tongue

Stronger allergic reactions to ACARIZAX® include:

- swelling of the throat, mouth or tongue
- difficulty swallowing or breathing
- asthma attack/wheezing
- hives/itchy rash
- voice changes (hoarse voice or trouble speaking)
- rapid heart rate
- low blood pressure
- fainting

If you experience these symptoms, contact your doctor immediately and get emergency treatment. Do not take any more doses until your doctor tells you to.

Very common [in more than 10% of patients (1 in 10)]:
Mouth: itching, burning, ulcer; swelling on the roof of the mouth
Tongue: swelling, ulcer
Lips: swelling
Throat: irritation, swelling
Ears: itching
Other: nausea, pain in the stomach

Common [in 1-10% of patients (more than 1 in 100 but less than 1 in 10)]:
Mouth: discomfort, swelling, tingling, pain, numbness, soreness, unpleasant taste; redness on the inside of the mouth
Tongue: itching, swelling
Lips: itching, swelling
Throat: trouble swallowing; redness, dryness, pain; swelling in the back of the throat
Eyes: itching
Other: heart burn, diarrhea, vomiting, indigestion, chest discomfort, tingling, sneezing, itching all over the body, hives all over the body

Uncommon [between 0.1% and 1% of patients (more than 1 in 1000 but less than 1 in 100)]:
Mouth: inflammation, swelling, dryness, decreased sensation, blister, pain and swelling of the gums, salivary gland enlargement, excessive salivating
Tongue: inflammation, blister, redness
Lips: inflammation, blister, ulcer
Throat: inflammation, tightness, discomfort, pain, swelling, dryness, swelling of the tonsils
Ears: discomfort, pain
Eyes: inflammation, irritation, redness, eyelid swelling, tearing

Nose: inflammation, itching, swelling, discomfort, congestion, runny nose, sneezing, nose bleeding
Other: shortness of breath, asthma, cough, difficulty or inability speaking, sensation of foreign body, stomach pain and discomfort, constipation, heartburn, chest pain and discomfort, tiredness, dizziness, headache, itching, rash, flushing, redness of the skin, eczema, tingling or prickling sensation, respiratory tract infection, feeling nervous

Rare [less than 0.1% of patients (less than 1 in 1000)]:
Other: Eosinophilic esophagitis which may present as any of the following symptoms that do not go away or worsen: heartburn, difficulty swallowing, pain with swallowing, or chest pain.

The side effects observed in children were similar to those in adults. The following side effects were reported in addition or more often in children compared to adults:

Mouth: swelling (very common), unpleasant taste (very common)

Eyes: allergic inflammation (redness, irritation, tearing) (common)

Other: Eosinophilic esophagitis which may present as any of the following symptoms that do not go away or worsen: heartburn, difficulty swallowing, pain with swallowing, or chest pain (uncommon), rapid swelling of the face (uncommon)

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
VERY COMMON			
Swelling in the mouth	√		
Swelling in the throat	√		
Swollen tongue	√		
COMMON			
Trouble swallowing			√
Chest discomfort	√		
Itching all over the body	√		
Hives all over the body	√		
UNCOMMON			
Throat tightness			√
Severe allergic reactions			Seek emergency help immediately
Shortness of breath			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store at room temperature (do not store above 25°C).
- Store in the original package and protect from moisture.
- Keep out of reach and sight of children.

If you want more information about ACARIZAX®:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html.
- Contact regarding reporting of Side Effects to ALK Inc.:
  Telephone (toll-free): 1-800-325-7354 (for English) or 1-800-663-0972 (for French)
  Fax (toll-free): 1-866-255-2244

This leaflet was prepared by ALK-Abelló A/S.

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