1 NAME OF THE MEDICINE

12 SQ-HDM.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

ACARIZAX® is allergy immunotherapy.

ACARIZAX® oral lyophilisate tablets contain 12 SQ-HDM standardised allergen extract from the house dust mites (HDM) *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*.

The unit SQ-HDM has been defined to measure the potency of ACARIZAX® and is based on a standardised amount of allergens from each species. Each tablet contains 6 SQ-HDM of *D. pteronyssinus* and 6 SQ-HDM *D. farinae* for a total of 12 SQ-HDM.

ACARIZAX® oral lyophilisate tablets 12 SQ-HDM also contain gelatin (fish), mannitol and sodium hydroxide.

3 PHARMACEUTICAL FORM

ACARIZAX® 12 SQ-HDM is supplied as white to off-white freeze-dried debossed oral lyophilisate tablets.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Allergic rhinitis
ACARIZAX® is indicated for the treatment of house dust mite (HDM) allergic rhinitis not well controlled despite use of symptom relieving medication in adults and adolescents (≥ 12 years).

Allergic asthma
ACARIZAX® is indicated for the treatment of HDM allergic asthma not well controlled by inhaled corticosteroids and associated with HDM allergic rhinitis in adults. Patients' asthma status should be carefully evaluated before the initiation of treatment.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment with ACARIZAX® should be initiated by a clinician with experience in treatment of allergies. Patients should have a confirmed clinical history and a positive test of house dust mite sensitisation (specific IgE and/or skin prick test) prior to treatment.

The recommended dose for patients 12 years and above is one oral lyophilisate (12 SQ-HDM) daily.

It is recommended that the first oral lyophilisate is taken under medical supervision and that the patient is monitored for 30 minutes, to enable discussion and possible

treatment of any immediate side effects. See also **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**.

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 consumed for the following 5 minutes.

Onset of the clinical effect is to be expected 8-14 weeks after initiation of treatment. If no improvement is observed during the first year of treatment with ACARIZAX® there is no indication for continuing treatment.

Refer to treatment guidelines for recommendations on the duration of patient 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 clinical trial MT-04 (MITRA) conducted in adults with HDM allergic asthma. Long-term efficacy has not been established.

ACARIZAX® is not recommended for use in patients below 18 years of age for allergic asthma and below 12 years of age for allergic rhinitis due to insufficient data on safety and efficacy in these populations. See also **Clinical trials**.

If treatment with ACARIZAX® is interrupted for a period of up to 7 days, treatment can be resumed by the patient. If treatment is interrupted for more than 7 days, it is recommended to seek medical advice before continuing treatment.

4.3 CONTRAINDICATIONS

ACARIZAX® is contraindicated in patients:

- with a known hypersensitivity to any of the excipients
- with FEV_1 <70% of predicted value (after adequate pharmacological treatment) at initiation of treatment
- who have experienced a severe asthma exacerbation within the last 3 months
- with asthma and experiencing an acute respiratory tract infection, initiation of ACARIZAX® treatment should be postponed until the infection has resolved.
- with active or poorly controlled autoimmune diseases, immune defects, immunodeficiencies, immunosuppression or malignant neoplastic disease with current disease relevance.
- with acute severe oral inflammation or oral wounds (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Asthma

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 short-acting bronchodilator treatment is ineffective or there is a need for more inhalations than usual, medical attention must be sought.

ACARIZAX® should initially be used as add on therapy and not be used as a substitute of pre-existing asthma medication. Abrupt discontinuation of asthma controller medication after initiation of ACARIZAX® treatment is not recommended. Decreases in asthma controller medication should be gradual and performed under medical supervision.

Asthma is a known risk factor for severe systemic allergic reactions.

Patients must be advised to seek urgent medical attention should their asthma deteriorate suddenly.

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 (see **4.8 ADVERSE EFFECTS**). The use of anti-allergic medication (e.g. antihistamines) should be considered for any potential significant local adverse reactions to ACARIZAX®. These reactions are usually mild or moderate; however, more severe oropharyngeal reactions may occur.

Severe systemic allergic reactions
Treatment with ACARIZAX® should be discontinued immediately and urgent medical attention sought in cases 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.

Although side effects are more likely to occur within the first two months of commencing ACARIZAX®, they can occur at any time throughout the therapy.

Initiation of ACARIZAX® in patients who have previously had a systemic allergic reaction to subcutaneous HDM immunotherapy should be carefully considered, and measures to treat any potential adverse 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.

Severe systemic allergic reactions may be treated with adrenaline. The effects of adrenaline may be potentiated in patients treated with tricyclic antidepressants, mono amino oxidase inhibitors (MAOIs) and/or Catechol-O-methyl transferase inhibitors (COMT) with possible fatal consequences. The effects of adrenaline may be reduced in patients treated with beta-blockers.

Patients with cardiac disease who suffer a systemic allergic reaction may be at increased risk of a severe systemic allergic reaction. Clinical experience with the use of ACARIZAX® in patients with cardiac disease is limited.

This should be taken into consideration prior to initiating allergy 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 any ongoing treatment should be temporarily interrupted to allow healing of the oral cavity (see **4.2 DOSE AND METHOD OF ADMINISTRATION**).

Eosinophilic oesophagitis
Isolated cases of eosinophilic oesophagitis have been reported in ACARIZAX® clinical trials. Initiation of ACARIZAX® in patients with known eosinophilic oesophagitis should be carefully considered, and the possibility of exacerbating

existing disease should be assessed. In patients with severe or persisting gastro-esophageal symptoms such as dysphagia, abdominal pain or dyspepsia, ACARIZAX® should be interrupted and 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.

Use in the elderly
Special studies in the geriatric population have not been performed; however, ACARIZAX® has been administered to 13 subjects ≥ 65 years of age. No overall differences in safety and effectiveness were observed between these subjects and younger subjects.

Paediatric use
ACARIZAX® is not recommended for use in children below 12 years of age for allergic rhinitis. Clinical experience in treatment of allergic rhinitis with ACARIZAX® in children below 12 years of age has not been established.

ACARIZAX® is not recommended for use in patients below 18 years of age for allergic asthma. Clinical experience in treatment of allergic asthma with ACARIZAX® in children below 18 years of age has not been established.

Only limited data are available from patients 5-11 years of age (from the phase 1 trial MT-03 which investigated safety and tolerability in subjects 5-14 years of age with HDM allergic asthma). No data on treatment with ACARIZAX® in children below 5 years of age exist. See also **Clinical trials.**

Effect on laboratory tests
ACARIZAX® has no effect on laboratory tests.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction trials have been conducted in humans and no potential drug interactions have been identified from any source.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
There is no data available regarding fertility and use of ACARIZAX®. While dedicated fertility studies have not been conducted, histopathological assessment performed as part of the 26 week repeat dose toxicity study in mice showed no effects on the reproductive organs attributable to ACARIZAX®.

Use in pregnancy (Category B2)
There is no data available regarding use of ACARIZAX® during pregnancy. No adverse effects were observed in an embryo-fetal development study in mice with doses approximately 680 times greater than clinical doses.

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®.

Close supervision during pregnancy is recommended for patients with pre-existing asthma.

Use in lactation

No clinical data are available for the use of ACARIZAX® during lactation. Studies in animals to investigate excretion of ACARIZAX® into milk were not conducted. No effects on the breastfed infants are anticipated.

Initiation of allergy immunotherapy while breast feeding is not recommended. However if breast feeding is required during treatment, patients should be closely monitored.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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 **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**). For the majority of events, the reaction is 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 **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Isolated cases of severe acute worsening of asthma symptoms have been reported. Patients with known risk factors should not initiate treatment with ACARIZAX® (see **4.3 CONTRAINDICATIONS**).

In the pooled safety analysis of adult and adolescent subjects in the ACARIZAX® clinical development program, 85% of subjects administered ACARIZAX® reported at least 1 treatment emergent adverse event (TEAE). This was higher when compared with the placebo group (69%).

The majority of subjects in all treatment groups in the pooled analysis experienced TEAEs that were mild to moderate in intensity.

The most frequently reported TEAEs (defined as those occurring in ≥ 5% of subjects in any active group) are summarised by system organ class in Table 1.

The most common TEAEs included oral pruritus, throat irritation, ear pruritus and nasopharyngitis (reported by 34%, 33%, 23% and 20% of subjects (**Table 1**)).

No overall difference in safety was observed between the adult and adolescent population.

Table 1 – TEAEs in at least 5% of adult and adolescent subjects in the ACARIZAX® Phase I-III studies (safety population)[a]

System organ class/preferred term	Placebo (N=2210) n (%)	ACARIZAX® 12 SQ-HDM (N=2052) n (%)
Ear and labyrinth disorders		
Ear pruritus	96 (4%)	467 (23%)
Gastrointestinal disorders		
Abdominal pain	60 (3%)	119 (6%)
Glossodynia	27 (1%)	137 (7%)
Lip swelling	21 (<1%)	180 (9%)
Mouth swelling	14 (<1%)	140 (7%)
Nausea	67 (3%)	145 (7%)
Oedema mouth	2 (<1%)	115 (6%)
Oral discomfort	18 (<1%)	112 (5%)
Oral pruritus	139 (6%)	701 (34%)
Paraesthesia oral	30 (1%)	181 (9%)
Swollen tongue	18 (<1%)	150 (7%)
Tongue ulceration	21 (<1%)	94 (5%)
Infections and infestations		
Bronchitis	32 (4%)	30 (5%)
Nasopharyngitis	455 (21%)	415 (20%)
Pharyngitis	139 (6%)	169 (8%)
Respiratory, thoracic and mediastinal disorders		
Asthma	111 (5%)	103 (5%)
Pharyngeal oedema	25 (1%)	130 (6%)
Throat irritation	198 (9%)	686 (33%)

N: number of subjects in pool
n: number of subjects with event
[a] Includes clinical trials: MT-01, MT-02, MT-03, MT-04, MT-06, P001, P003, P008, TO-203-1-1, TO-203-3-1, TO-203-3-2

In the pooled Phase II/III adult studies, time to onset from first administration for oral pruritus, throat irritation and oedema mouth was typically fast (median onset 2 minutes, 2 minutes and 1 minute after first administration respectively). See also **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**.

Adverse reactions in adult and adolescent patients with HDM allergic rhinitis and/or allergic asthma reported in clinical trials with <5% frequencies are listed below.

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

Infections and infestations
Common: Rhinitis, sinusitis
Uncommon: Laryngitis

Immune system disorders
Uncommon: Anaphylactic reaction

Nervous system disorders
Common: Dysgeusia
Uncommon: Dizziness

Eye disorders
Common: Eye pruritus
Uncommon: Conjunctivitis allergic

Ear and labyrinth disorders
Uncommon: Ear discomfort

Cardiac disorders
Uncommon: Palpitations

Respiratory, thoracic and mediastinal disorders
Common: Dysphonia, dyspnoea, oropharyngeal pain
Uncommon: Nasal congestion, nasal discomfort, rhinorrhoea, sneezing, throat tightness
Rare: Laryngeal oedema

Gastrointestinal disorders
Common: Diarrhoea, dyspepsia, dysphagia, gastrooesophageal reflux disease, glossitis, lip pruritus, mouth ulceration, tongue pruritus, oral mucosal erythema, stomatitis, vomiting
Uncommon: Dry mouth, oesophageal irritation, oral mucosal blistering

Skin and subcutaneous tissue disorders
Common: Pruritus, urticaria
Rare: Angioedema

General disorders and administration site conditions
Common: Chest discomfort, fatigue
Uncommon: Malaise, sensation of foreign body

Post marketing experience
To date, there is limited post marketing data available for ACARIZAX®.

Cases of systemic allergic reactions, including anaphylactic reactions have been reported post marketing and are considered a class effect. Medical supervision at first oral lyophilisate intake is therefore recommended (see **4.2 DOSE AND METHOD OF ADMINISTRATION**). In some cases the serious systemic allergic reaction has occurred at doses subsequent to the initial dose (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**).

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration 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 at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There have been no cases of overdosage reported.

If doses higher than the recommended daily dose are taken, the risk of undesirable effects, including systemic allergic reactions or severe local allergic reactions, may increase. 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.

In the event of an overdose, the adverse effects should be treated symptomatically.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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 allergen to provide sustained underlying protection during subsequent allergen exposure. The immune system is the target for the pharmacodynamic effect of allergy immunotherapy, but the complete and exact mechanism of action is not fully understood.

ACARIZAX® is for the treatment of patients with specific IgE-mediated allergy symptoms induced by HDMs such as allergic rhinitis and/or allergic asthma. Treatment with ACARIZAX® has been shown to induce a systemic antibody response with an increase in HDM-specific IgG_4 that is likely to compete with IgE in the binding of HDM allergens. This effect is observed after 4 weeks of treatment.

ACARIZAX® works by modifying the immune response to HDM (*D. pteronyssinus and D. farinae*) allergens and provides specific desensitisation. Clinical effect during treatment has been demonstrated for both upper and lower airways (see **Clinical trials**). 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 trials

Adults

Allergic asthma

The efficacy and safety of ACARIZAX® in adults with partly controlled HDM allergic asthma despite daily use of inhaled corticosteroid (ICS) has been investigated in a Phase III randomised, double-blind, placebo-controlled, parallel-group, multicentre study (MT-04, MITRA)(n=834).

This trial comprised 2 phases. In the first phase (treatment maintenance), subjects were randomised to receive ACARIZAX® 12 SQ-HDM, 6 SQ-HDM or placebo once daily in addition to inhaled corticosteroids (ICS; corresponding to 400-1200 mcg budesonide) and short acting beta agonists (SABA; salbutamol 200 mcg/dose). The duration of the treatment maintenance period was 7-12 months (this varied as efficacy measurements were initiated outside of major pollen seasons to minimise confounding from other allergies). The second phase (ICS reduction/withdrawal) ran for a total of 6 months. Subjects continued to take ACARIZAX® 12 SQ-HDM, 6 SQ-HDM or placebo once daily throughout the ICS reduction/withdrawal period. In the first 3 months of the ICS reduction/withdrawal period, each subject's ICS dose was reduced by 50%, and in the last 3 months ICS was withdrawn completely. Use of SABA was permitted throughout the ICS reduction/withdrawal period if needed.

The primary endpoint was the time to the first moderate or severe asthma exacerbation during the reduction/withdrawal period. The definitions of moderate and severe asthma exacerbations are provided in **Table 2**.

The results for the primary endpoint are summarised in **Table 3**. Both ACARIZAX® 12 and 6 SQ-HDM demonstrated statistical significance compared to placebo for time to first asthma exacerbation (**Table 3**). The results for ACARIZAX® 12 SQ-HDM also met the pre-specified criterion for clinical relevance compared to placebo [i.e. Hazard ratio (HR) ≤0.70]. See also **Figure 1**.

Table 2 – Definitions of moderate and severe asthma exacerbations (clinical trial MT-04)

Asthma exacerbation	Definition
Moderate asthma exacerbation	Subject experienced one or more of the 4 following criteria and it led to change in treatment: • 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 • Increase from baseline in occasions of SABA use on two consecutive days (minimum increase: 4 puffs/day) • ≥ 20% decrease in PEF from baseline on at least two consecutive mornings/ evenings or ≥ 20% decrease in FEV_1 from baseline • Visit to the emergency room / trial site for asthma treatment not requiring systemic corticosteroids
Severe asthma exacerbation	Subject experienced at least one of the following criteria: • Need for systemic corticosteroids for ≥ 3 days • Emergency room visit requiring systemic corticosteroids or hospitalisation for ≥ 12h

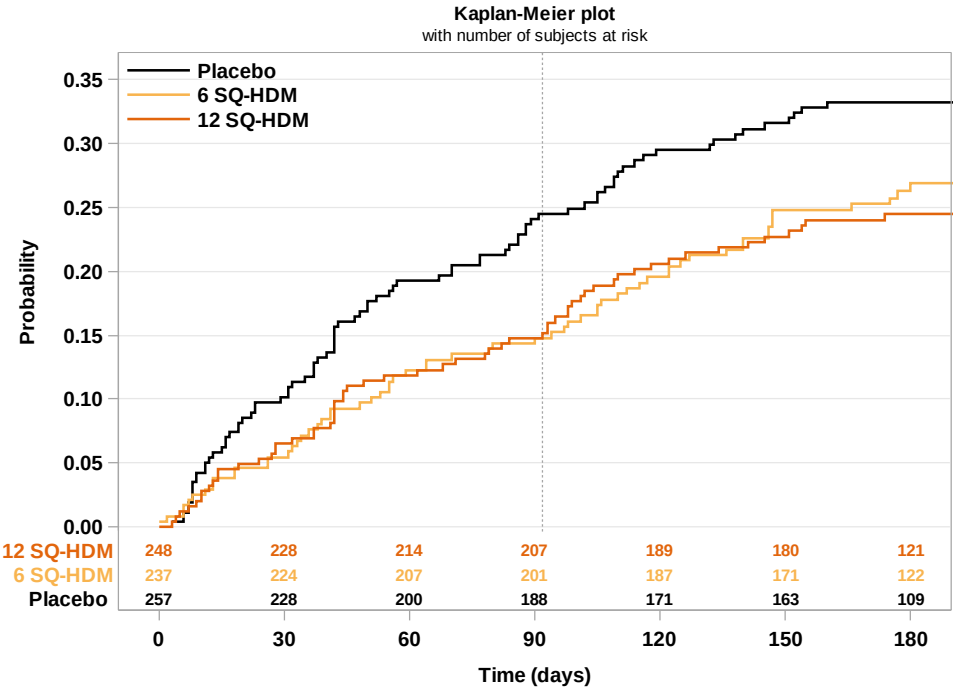
Table 3 – Efficacy outcomes for ACARIZAX® Phase III clinical trial MT-04 (MITRA)

	6 SQ-HDM vs placebo			12 SQ-HDM vs placebo		
Primary endpoint						
	HR [CI 95%]	**% risk reduction[a]**	**p-value**	**HR [CI 95%]**	**% risk reduction**	**p-value**
Time to first asthma exacerbation (FAS-MI)[a, b] (n=834)	0.72 [0.52, 0.99]	28%	0.0447	0.69 [0.50, 0.96]	31%	0.0271
Time to first asthma exacerbation (FAS)[c] (n=742)	0.69 [0.49, 0.96]	31%	0.0238	0.66 [0.47, 0.93]	34%	0.0170
Pre-defined analyses of components of the primary endpoint						
Time to first asthma exacerbation with deterioration in asthma symptoms[c, d]	0.72 [0.49, 1.07]	28%	0.1069	0.64 [0.42; 0.96]	36%	0.0312
Time to first asthma exacerbation with increased SABA use[c]	0.62 [0.36, 1.07]	38%	0.0857	0.52 [0.29; 0.94]	48%	0.0293
Time to first asthma exacerbation with deterioration in lung	0.60 [0.38, 0.95]	40%	0.0297	0.58 [0.36; 0.93]	42%	0.0221

function[c]						
Time to first severe exacerbation[c]	0.79 [0.40, 1.55]	21%	0.4887	0.49 [0.23; 1.08]	51%	0.076

a: Estimated by hazard ratio (HR). Clinical relevance pre-specified as HR ≤ 0.70.
b: Full analysis set (FAS) with multiple imputations (FAS-MI) - analysis treats all subjects who discontinued from the trial prior to ICS reduction as placebo subjects.
c: Full analysis set (FAS) – analysis uses all available data used to its full extent, i.e. subjects who provided data during the efficacy assessment period.
d: Criterion included daily asthma symptom score and nocturnal awakenings requiring SABA

Figure 1 – Kaplan-Meier plot of the probability of having a first moderate or severe asthma exacerbation (FAS)



Time=0 equals the time of ICS reduction, time=90 is the approximate time of ICS withdrawal. The numbers at the bottom are the numbers of subjects still at risk in each treatment group at each time point.

Allergic rhinitis

The efficacy and safety of ACARIZAX® in adults with persistent moderate-to-severe HDM-allergic rhinitis despite use of symptom-relieving medication has been investigated in a Phase III randomised, double-blind, placebo-controlled, parallel-group, multicentre study (MT-06, MERIT) (n=992). The definition of persistent and moderate to severe allergic rhinitis is provided in **Table 4**.

Table 4 – Definitions of persistent and moderate to severe allergic rhinitis (clinical trial MT-06)

Classification of allergic rhinitis	Definition
Persistent	Subject experienced at least one of the following criteria: • Clinical history of moderate to severe HDM allergic rhinitis for at least 1 year prior to the trial • Moderate to severe HDM allergic rhinitis symptoms during the baseline period defined as a daily total rhinitis score of at least 6 or a score of at least 5 with one symptom being severe, during at least 8 days of the 15 days baseline period • Use of symptomatic medication for treatment of HDM allergic rhinitis during at least 8 of the 15 days baseline period
Moderate to severe	Subject experienced at least one or more of the following items: • Use of symptomatic medication for treatment of HDM

	allergic rhinitis during at least 8 of the 15 days baseline period • Sleep disturbance • Impairment of daily activities, leisure and/or sport • Impairment of school or work

Subjects were randomised to receive ACARIZAX® 12 SQ-HDM, 6 SQ-HDM or placebo once daily for 12 months. Use of nasal steroids (budesonide 64 mcg/dose), oral antihistamines (desloratadine tablets, 5 mg), and antihistamine eye drops (azelastine 0.05%) was permitted as needed.

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 (maximum total possible score 24). 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) for a maximum total possible score of 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) for a maximum total possible score of 12.

The results for the primary endpoint are summarised in **Table 5**. Both ACARIZAX® 12 and 6 SQ-HDM demonstrated a statistically significant reduction in TCRS compared to placebo. The results for both ACARIZAX® 12 and 6 SQ-HDM also met the pre-specified criterion for clinical relevance compared to placebo (i.e. TCRS ≥ 1) commencing from 14 weeks of treatment and continuing for the duration of the trial.

Table 5 – Efficacy outcomes for ACARIZAX® Phase III clinical trial MT-06 (MERIT)

	Treatment group	Adjusted mean TCRS [95% CI]	Absolute difference to placebo[c] [95% CI]	p-value
FAS-MI[a] (n=992)	Placebo	6.81 [6.48, 7.13]	-	-
	6 SQ-HDM	5.74 [5.42, 6.05]	1.07 [0.34; 1.80]	0.004
	12 SQ-HDM	5.71 [5.40, 6.02]	1.09 [0.35; 1.84]	0.004
FAS with observations[b] (n=879)	Placebo	6.76 [5.94, 7.63]	-	-
	6 SQ-HDM	5.58 [4.81, 6.40]	1.18 [0.45; 1.91]	0.002
	12 SQ-HDM	5.53 [4.77, 6.35]	1.22 [0.49; 1.96]	0.001

a: Full analysis set with multiple imputations (FAS-MI) - analysis treats all subjects who discontinued from the trial prior to the efficacy evaluation period as placebo subjects
b: Full analysis set (FAS) with observations – all randomised subjects with observations of the endpoint of interest
c: Clinical relevance pre-specified as absolute difference in TCRS between active and placebo ≥ 1

Adolescents

Allergic rhinitis

The efficacy and safety of ACARIZAX® has been investigated in adolescents aged 12 to 17 years with persistent moderate-to-severe HDM allergic rhinitis with or without asthma despite the use of symptom relieving medication in two Phase III randomised, double blind, placebo controlled, parallel-group, multicentre trials (P001 and TO-203-3-2).

In P001, 189 adolescent subjects were randomised to receive ACARIZAX® 12 SQ-HDM or placebo once daily for 12 months. Use of nasal steroids (mometasone furoate 50mcg/dose), oral antihistamines (loratadine tablet 10 mg) and antihistamine eye drops (olopatadine hydrochloride 0.1%) was permitted as needed.

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 rhinitis symptom score and rhinitis medication score with a range of 0 to 24 points. The symptom scores used for evaluation were similar to the scores used in MT-06 (see also **Clinical trials** – **Adults** *Allergic rhinitis*).

The results for the primary endpoint are summarised in **Table 6**. ACARIZAX® 12 SQ-HDM demonstrated a statistically significant reduction in TCRS compared to placebo. The results met the criterion for clinical relevance (i.e. TCRS ≥ 1) compared to placebo as shown for adults in MT-06.

Table 6 – Efficacy outcomes for adolescents in Phase III clinical trial P001

	Treatment group	TCRS	Absolute difference to placebo [95% CI]	Relative effect[d]	p-value
FAS[a] (median) (n=160)	Placebo	4.25	-	-	-
	12 SQ-HDM	3.30	1.0[b] [0.1; 2.0]	22%	0.024
FAS (adjusted mean) (n=160)	Placebo	4.83	-	-	-
	12 SQ-HDM	3.64	1.2 [0.1; 2.3][c]	25%	<0.05

[a] Full analysis set (FAS) –subjects who provided data during the efficacy period
[b] The 95% confidence interval for median difference was based on the Hodges-Lehmann estimator
[c] The 95% confidence interval for mean difference was based on the analysis of covariance (ANCOVA)
[d] Treatment difference relative to placebo based on medians was calculated by (ACARIZAX® - placebo)/placebo*100

In TO-203-3-2, 278 adolescent subjects were randomised to receive ACARIZAX® 12 SQ-HDM, 6 SQ-HDM and placebo once daily for 12 months. Use of nasal steroids (fluticasone propionate 25-50mcg/dose), oral antihistamines (loratadine tablet 10 mg) and antihistamine eye drops (olopatadine hydrochloride 0.1%) were permitted as needed.

The primary endpoint was the TCRS during the efficacy evaluation period (defined as the last 8 weeks of treatment). The symptom scores used for evaluation were similar to the scores used in MT-06 (see also **Clinical trials** – **Adults** *Allergic rhinitis*).

The results for the primary endpoints for TO-203-3-2 are summarised in **Table 7**. The 12 SQ-HDM demonstrated a statistically significant reduction in TCRS compared to placebo. The results met the criterion for clinical relevance (i.e. TCRS ≥ 1) compared to placebo as shown for adults in MT-06.

Table 7 – Efficacy outcomes for adolescents in Phase III clinical trial TO-203-3-2

	Treatment group	TCRS	Absolute difference to placebo [95% CI]	Relative difference to placebo[c]	p-value
FAS[a] (median) (n=278)	Placebo	5.2	-	-	-
	12 SQ-HDM	4.2	1.0	19%	N/A
FAS (adjusted mean) (n=278)	Placebo	5.1	-	-	-
	12 SQ-HDM	4.1	1.0[b] [0.1; 1.9]	20%	0.037

[a] Full analysis set (FAS) –subjects who provided data during the efficacy period
[b] The 95% confidence interval for median difference was based on the linear mixed-effects model
[c] Treatment difference relative to placebo based on medians was calculated by (ACARIZAX® - placebo)/placebo * 100.
N/A – Data not available as the primary analysis was based on the mean and there were no pre-specified testing of the medians.

Paediatric population

The safety and tolerability of the SQ HDM SLIT-tablet has been investigated in a Phase 1 trial MT-03 with paediatric subjects aged 5-14 years with mild to moderate HDM allergic asthma. Only a limited number of subjects received ACARIZAX® 12 SQ-HDM.

The majority of subjects who received the SQ-HDM SLIT-tablet experienced TEAEs (treatment emergent adverse event) that were mild in severity. The most common TEAEs reported were oral pruritus, throat irritation and oedema mouth. These TEAEs were also reported for the pooled adult and adolescent patient population (see **Table 1**).

ACARIZAX® is not recommended for use in children below 12 years of age (see **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE** and **4.2 DOSE AND METHOD OF ADMINISTRATION**).

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 (SLIT) 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.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Results from genotoxicity testing indicate that ACARIZAX® does not pose any genotoxic risk to humans.

Carcinogenicity
Dedicated carcinogenicity studies with the ACARIZAX® tablet have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Refer to section **2. QUALITATIVE AND QUANTITATIVE COMPOSITION** for the complete list of excipients.

6.2 INCOMPATIBILITES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

ACARIZAX® 12 SQ-HDM oral lyophilisate has a shelf-life of 48 months when stored below 25°C. Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Packs contain 10, 30 and 90 oral lyophilisate tablets supplied in aluminium blister foils.

Not all pack sizes may be available.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure
No data available

CAS number
Not applicable

Pharmacotherapeutic group: Allergen extracts, house dust mite.

ATC Code: V01AA03

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine, S4

8 SPONSOR

Seqirus Pty Ltd ABN: 26 160 735 035
63 Poplar Road
Parkville VIC 3052
Telephone: +61 3 9389 2000
www.seqirus.com.au

9 DATE OF FIRST APPROVAL

01 August 2016

10 DATE OF REVISION

13 May 2019

ACARIZAX® is a registered trademark of ALK-Abelló A/S, used under licence.

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
N/A	Product information reformatted as per the current TGA Form for providing product information
4.1	Extension of indication for allergic rhinitis to include children ≥ 12 years
4.2	Dosing information updated for use in children ≥ 12 years
4.4	Special Warnings and Precautions for Use updated including Paediatric Use
4.8	Adverse Effects updated to include new clinical trial data
4.9	Overdose information updated
5.1	Clinical trial section updated with adolescent trial outcomes in allergic rhinitis. Paediatric population information updated.
5.1	Removal of incorrect section heading reference
6.1	Minor editorial change for clarity to the text
6.4	Section amended to reflect extended shelf life