standardised allergen extract from the house dust mites *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* sublingual lyophilisate (Acarizax®)

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

standardised allergen extract from the house dust mites *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* (Acarizax®) is accepted for restricted use within NHSScotland.

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

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

SMC restriction: persistent moderate to severe house dust mite allergic rhinitis despite use of symptom-relieving medication.

In three double-blind phase III studies, one year's treatment with Acarizax®, in combination with standard care, significantly improved a combined measure of rhinitis symptom severity and medication use (total combined rhinitis score) compared with placebo.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Standardised allergen extract from the house dust mites *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* (hereafter referred to by its brand name, Acarizax®) is an allergy immunotherapy that repeatedly administers allergens to allergic individuals to modify their immunological response to the allergen. The mechanism of action is not fully understood but may involve an increase in house dust mite specific immunoglobulin G4 (IgG4) and a systemic antibody response that competes with immunoglobulin E (IgE) in the binding of house dust mite allergens. It is a sublingual immunotherapy (SLIT) administered as one (12 standardised quality units of house dust mite [SQ-HDM]) lyophilisate once daily. Onset of clinical effect is expected 8 to 14 weeks after initiation. If no improvement is observed during the first year, there is no indication for continuing treatment. The first dose should be taken under medical supervision, and the patient should be monitored for at least half an hour. International guidelines refer to a treatment period of three years. See summary of product characteristics (SPC) for further information.[1]

1.2. Disease background

Allergic rhinitis is IgE-mediated inflammation of the upper respiratory tract due to allergen exposure in an allergic individual that is characterised by nasal pruritus, sneezing, rhinorrhoea, and nasal congestion. It may be associated with symptoms throughout the year, that include palate, throat, ear, and eye itching plus eye redness, puffiness, and watery discharge. It may exacerbate asthma, disturb sleep and substantially impact quality of life, with secondary effects on concentration, mood and behaviour, leading to fatigue and difficulties with work and other daily activities. It can affect all ages, with about 80% developing symptoms before 20 years of age.[2, 3]

1.3. Company proposed position

The submitting company has requested that Acarizax® is restricted for use in adult patients (18 to 65 years) with house dust mite sensitisation and persistent moderate to severe house dust mite allergic rhinitis despite use of symptom-relieving medication.

1.4. Treatment pathway and relevant comparators

Allergen avoidance may be challenging for patients with house dust mite-sensitive allergic rhinitis due to difficulties reducing exposure to mites in the home. The British Society for Allergy and Clinical Immunology (BSACI) guideline recommends intranasal corticosteroids for initial treatment for moderate to severe allergic rhinitis and, if an inadequate response is achieved, they may be combined with antihistamines. Depending on response and symptoms, further treatment options (which may not be licensed specifically for house dust mite allergic rhinitis) include topical ipratropium bromide, leukotriene receptor antagonist, and short course of intranasal decongestant. Allergen immunotherapy is noted as an option for patients with an allergy to house dust mite who respond inadequately to anti-allergic medicines and where the allergen is not easily avoided.[3] The submitting company considers standard of care described above (excluding allergen immunotherapy) to be the relevant comparator. Clinical experts consulted by SMC confirmed this and noted that there is an unmet need for additional treatment options for patients with symptoms inadequately controlled by the current standard of care.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence is from the MT-06 (MERIT), P001 and TO-203-32, as detailed in Table 2.1.[4-9]

Table 2.1. Overview of relevant studies.[4-9]

Criteria	MT-06 (MERIT); P001; TO-203-32
Study design	Double-blind, multicentre, phase III.
Eligible patients	Patients (aged 18 to 65 years in MT-06, ≥12 years in P001, and 12 to 64 years in TO-203-32) with moderate to severe HDM-induced allergic rhinitis ≥ 1 year. Positive skin prick test response and positive IgE for *D. pteronyssinus, D. farinae*, or both. Moderate to severe symptoms based on baseline total rhinitis symptom score (≥6 or ≥5 plus one severe symptom for ≥8 of 15 days in MT-06 and ≥5 of 7 days in P001; ≥7 for ≥7 of 14 days in TO-203-32). Disturbance of sleep, daily activities, or productivity except in P001. No seasonal allergic asthma or rhinoconjunctivitis.
Treatments	Acarizax® 12 SQ-HDM or placebo sublingual once daily for 12 months (MT-06 and TO-203-32 also included groups treated with Acarizax® 6 SQ-HDM, which is unlicensed). Corticosteroid nasally (budesonide 64 microgram in MT-06, mometasone 50 microgram in P001, and fluticasone 50 microgram in TO-203-32), antihistamine orally (loratadine 10 mg except MT-06, desloratadine 5 mg) and antihistamine eye drops (olopatadine 0.1 %, except MT-06, azelastine 0.05%) could be used as needed during the studies, including the assessment period (last 8 weeks of treatment).
Randomisation	Assigned equally. Stratified by asthma (yes or no) and age (<18 or ≥18 years) in P001.
Primary outcome	Average daily TCRS over last 8 weeks of treatment.
Key secondary outcomes	Over the last 8 weeks of treatment: allergic rhinitis symptom score, first in all studies; allergic rhinitis medication score, second in all studies except in TO-203-32. RQLQ third in MT-06; total combined allergic rhinoconjunctivitis score, fourth in MT-06 and third in P001; and allergic rhinitis/rhinoconjunctivitis symptoms on visual analogue scale fourth in P001.
Statistical analysis	Multiplicity of key secondary end points controlled by hierarchical testing in the orders listed above. Analyses of efficacy were in all randomised patients in MT-06, in all treated patients in P001; and in all treated patients who recorded ≥80% of the symptom and medication scores in last 8 weeks of treatment period in TO-203-32.

Abbreviations: HDM = house dust mite; RQLQ = rhinitis quality of life questionnaire; SQ-HDM = standardised quality units of house dust mite; TCRS = total combined rhinitis score, which ranges from 0 to 24 and is the sum of allergic rhinitis symptom score (runny nose, blocked nose, sneezing and itchy nose each scored from 0 [no symptom] to 3 [severe]; range 0 to 12) and allergic rhinitis medication score (oral antihistamine scored 0 to 4 [score of 4 per tablet] and nasal corticosteroid scored 0 to 8 [scored 2 per puff]; range 0 to 12).

In all studies, Acarizax® 12 SQ-HDM, compared with placebo, significantly improved the primary outcome, total combined rhinitis score (TCRS), and the key secondary outcome, allergic rhinitis symptom score over the last 8 weeks of treatment. In MT-06, there was significant improvement with Acarizax® 12 SQ-HDM for the other key secondary outcomes: allergic rhinitis medication score, rhinitis quality of life questionnaire (RQLQ) and combined rhinoconjunctivitis score over the last 8 weeks of treatment. The latter was the third key secondary outcome in P001 and was not significant, thereby ending formal testing in that study. Results are detailed in Table 2.2, omitting those for the unlicensed dose of Acarizax® 6 SQ-HDM.[4-9] In MT-06, the number of symptom-free days increased with Acarizax®, and in post hoc analyses the number of days with rhinitis exacerbation (allergic rhinitis symptom score 6 or 5 with one symptom being severe) halved.[5, 10]

Table 2.2: Results for Acarizax® 12 SQ-HDM in MT-06 (MERIT), P001 and TO-203-32 studies.[4-9]

Over last 8 weeks of treatment:	MT-06		P001		TO-203-32	
	Acarizax® N=318	Placebo N=338	Acarizax® N=566	Placebo N=620	Acarizax® N=281	Placebo N=285
Primary outcome: Total combined rhinitis score (TCRS)						
Mean	5.53	6.76	4.67	5.49	4.14	5.14
Difference (95% CI)	1.22 (0.49, 1.96)[A]		0.8 (0.40, 1.20)[A]		1.0 (0.48, 1.50)[A]	
Secondary outcome: Allergic rhinitis symptom score						
Mean	2.76	3.30	3.83	4.46	3.87	4.75
Difference (95% CI)	0.54 (0.18, 0.89)[B]		0.60 (0.30, 1.00)[A]		0.87 (0.43, 1.32)[A]	
Secondary outcome: Allergic rhinitis medicines score						
Mean	2.22	2.83	0.84	1.03	0.10	0.15
Difference (95% CI)	0.60 (0.08, 1.13)[B]		0.15 (0.05, 0.35)[C]		0.05 (*)	
Secondary outcome: Change from baseline in Rhinitis Quality of Life Questionnaire (RQLQ)						
Mean	1.38	1.58	*	*	-	-
Difference (95% CI)	0.19 (0.02, 0.37)[B]		0.28 (*)			
Secondary outcome: Combined rhinoconjunctivitis score						
Mean	7.91	9.12	6.40	7.62	5.30	6.64
Difference (95% CI)	1.21 (0.13, 2.28)[B]		1.10 (0.60, 1.70)		1.34 (*)	
Secondary outcome: Allergic rhinitis on visual analogue scale						
Mean	-	-	42	48	-	-
Difference (95% CI)	-		6.1 (3.1, 9.1)		-	

Abbreviations: CI = confidence interval; SQ-HDM = standardised quality units of house dust mite. A p≤0.001, B p<0.05, C p=0.154. * = results considered commercial in confidence by the company.

2.2. Evidence to support the positioning proposed by the submitting company

MT-06 provides evidence to support the positioning in adult patients (18 to 65 years) with house dust mite sensitisation and persistent moderate to severe house dust mite allergic rhinitis despite use of symptom-relieving medication.[4] In TO-203-32 and P001 subgroup analyses of the primary outcome were performed by age but the results are considered commercial in confidence.

2.3. Health-related quality of life outcomes

Acarizax® compared with placebo significantly improved RQLQ in MT-06 and appeared to be associated with improvement that was not formally tested in P001. The RQLQ assesses patients' experiences during the previous week of the impact of rhinoconjunctivitis on their quality of life, where the overall score is the mean of 28 questions assessed on a 7-point (0 [no impairment] to 6 [maximum impairment]) scale within seven domains: activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional. Results, detailed in Table 2.2, indicate improvements over placebo of 0.19 and 0.28 on a score that can range from 0 to 6.[5, 6] The clinical relevance of these is unknown. In TO-203-32, Acarizax® compared with placebo appeared to be associated with improvement that was not formally tested in Japanese Rhinoconjunctivitis Quality of Life Questionnaire (JRQLQ) general state, which ranges from 0 [fine] to 4 [crying].[8, 9]

2.4. Supportive studies

In a retrospective observational study (RELY) of 3,584 patients in Denmark and Sweden who received sublingual allergy immunotherapy for house dust mite allergic rhinitis, there were

reductions in the use of allergic rhinitis medications after three to five years follow-up compared with an untreated control group.[11]

In a retrospective observational study (REACT) of 47,440 patients in Germany who received allergy immunotherapy for allergic rhinitis between 2008 to 2016, compared with an untreated control patients, had greater reductions in allergic rhinitis prescriptions from the pre-index year of -0.46 versus -0.38 at year 3, -0.57 versus -0.45 at year 5, and -0.65 versus -0.52 at year 9.[12]

*Other data were also assessed but remain confidential.**

3. Summary of Safety Evidence

Mild to moderate local allergic reactions occur within 5 minutes of each Acarizax® administration and abate after minutes to hours during the first few days of treatment. These subside with continued treatment over 1 to 3 months. More severe oropharyngeal allergic reactions may occur. The SPC recommends that if the patient experiences significant local adverse reactions from the treatment, anti-allergic medication (e.g. antihistamines) should be considered. [1]

In MT-06, within the Acarizax® 12 SQ-HDM and placebo groups, adverse events were reported by 67% (213/318) and 46% (154/338) and were considered possibly treatment-related in 53% and 15%, respectively. Serious adverse events occurred in 0 and 2.4% patients in the respective groups and there were 4.1% and 2.1% patients who discontinued treatment due to adverse events. Frequently reported treatment-related adverse events included oral pruritus (21% and 2.4%), throat irritation (15% and 3.6%), mouth oedema (9.1% and 0.3%), and oral paraesthesia (7.2% and 0.6%), respectively.[4, 5]

In P001, within the Acarizax® 12 SQ-HDM and placebo groups, adverse events assessed proactively through questionnaires were reported by 91% (676/743) and 73% (539/738) and were considered possibly treatment-related in 84% and 41%, respectively. Serious adverse events occurred in 1.5% and 1.0% patients in the respective groups and there were 9.8% and 2.6% of patients who discontinued treatment due to adverse events. Frequently reported treatment-related adverse events included throat irritation (67% and 22%), oral pruritus (62% and 14%), ear pruritus (51% and 11%), lip swelling (18% and 2%), swollen tongue (16% and 2%), glossodynia (15% and 3%), pharyngeal oedema (14% and 3%), nausea (13% and 4.5%), tongue ulceration (13% and 2%), upper abdominal pain (11% and 4%), palatal swelling (11% and 1%) and mouth ulceration (10% and 3%), respectively.[6, 7]

In TO-203-32, within the Acarizax® 12 SQ-HDM and placebo groups, adverse events were reported by 90% (284/314) and 80% (256/319) and were considered possibly treated-related in 64% and 17%, respectively. Serious adverse events occurred in 1.6% and 0.9% patients in the respective groups and there were 1.3% and 1.9% patients who discontinued treatment due to adverse events. Frequently reported treatment-related adverse events included throat irritation (12% and 0.9%), oral pruritus (18% and 1.3%), mouth oedema (18% and 0), oral paraesthesia (10% and 1.3%), oral discomfort (9.9% and 0.9%), and ear pruritus (8.6% and 0.3%), respectively.[9]

Overall, the adverse events associated with Acarizax® were generally mild to moderate and the number of patients discontinuing treatment due to adverse events was small.

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In three double-blind studies, over the last 8 weeks of a years' treatment, Acarizax® was associated with reductions over placebo in total combined rhinitis score (allergic rhinitis symptoms and medication use) of 0.8 to 1.2 on a scale that ranges from 0 to 24. There appeared to be improvements over placebo with Acarizax® for the symptom severity component, ranging from 0.5 to 0.9 on a scale of 0 to 12 and in medication use component, ranging from 0.05 to 0.6 on a scale of 0 to 12. These were supported by responder analyses.[4-10]
- Acarizax® is the first allergen immunotherapy licensed for house dust mite associated allergic rhinitis.

4.2. Key uncertainties

- In the submission, the primary outcome (TCRS), is expressed as a percentage of the mean in the placebo group during the last 8 weeks of treatment, giving values around 17% to 18% in P001 and MT-06. However, if the placebo effect is measured as a percent change from baseline to the last 8 weeks, the benefit of Acarizax® over it can be estimated to be around 10% to 13% in these studies.[4, 6]
- The clinical relevance of the improvements in allergic rhinitis symptoms and medication use with Acarizax® is unknown. The responder analyses that supported these indicated a small decrease over placebo in the number of days with exacerbations of allergic rhinitis in MT-06 and a small increase in the proportion of patients with minimal symptom days during the last 8 weeks of treatment in P001.[5, 7] The clinical relevance of the improvements in quality of life assessed via RQLQ and JRQLQ is also unknown.[5, 7, 9]
- The SPC notes that guidelines refer to a treatment period of three years for allergy immunotherapy to achieve disease modification.[1] This is supported by a literature review.[13] Efficacy data for Acarizax® are available for 18 months of treatment, with no data available for three years of treatment.[1] Real world data from RELY and REACT, which were not conducted in the UK and are limited by retrospective observational design, suggest small reductions compared with control patients in the number of prescriptions for allergic rhinitis medication several years after immunotherapy use.[11, 14] There are no data to characterise and quantify the long-term effects of Acarizax® on symptoms of allergic rhinitis, and it is not clear whether it has a disease modifying effect after three years of treatment.
- Some clinical experts consulted by SMC suggested that Acarizax® may not be used in practice in patients who are sensitive to other allergens, in addition to house dust mites. The majority of patients in MT-06, P001, and TO-203-32 were polysensitised, 68%, 76% and 79%, respectively.[4, 6, 8] Subgroup analyses, considered confidential by the company, do not support definitive conclusions or estimates of treatment benefit in the patients that Acarizax® may be given to in practice.

4.3. Clinical expert input

Clinical experts consulted by SMC considered that Acarizax® fills an unmet need in this therapeutic area, namely it provides a treatment option for patients with symptoms inadequately controlled by current standard of care. They note that it is a therapeutic advance for this reason and that it would be added to current standard of care. However, they advise that it may be of limited use for patients who are polysensitised to several different allergens.

4.4. Service implications

Clinical experts consulted by SMC considered that the introduction of this medicine may impact on service delivery due to the additional clinic visits for monitoring and follow-up requirements associated with Acarizax® therapy, which is expected to be given as a three-year course.

*Other data were also assessed but remain confidential.**

5. Summary of Patient and Carer Involvement

No patient group submission was received.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

An economic case was presented and is summarised in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime
Population	Acarizax® for the treatment of adult (18-65 years) patients with persistent moderate to severe HDM allergic rhinitis (HDM AR) despite the use of symptom-relieving medication.
Comparators	Established clinical management (ECM) alone. ECM included oral antihistamines, nasal corticosteroids and antihistamine eye drops. Patients in the Acarizax® arm could also receive ECM.
Model description	A Markov state transition model was used with four-health states according to disease severity: mild AR, moderate AR, severe AR and death. Health states were based on a modified version of Allergic Rhinitis and its impact on Asthma (ARIA) guidelines from literature that differentiated moderate and severe AR.[15] AR severity status was determined by the presence of impairment in the ARIA health-related quality of life questionnaire (HRQoL) which included four HRQoL items: sleep, daily activities/sport, work/school and troublesome symptoms. Whether troublesome symptoms were present was based on another questionnaire, the rhinitis daily symptom score (DSS), which included runny nose, blocked nose, sneezing and itchy nose with each rated between 0 (no symptoms) to 3 (severe symptoms); a DSS score of 4 or more was considered to constitute troublesome symptoms. Health states were defined as: • Mild AR: no affected ARIA HRQoL items. • Moderate AR: 1 to 3 affected items. • Severe AR: all 4 affected items.

	The model cycle length was 1-year.
Clinical data	Data from the MT-06 study informed baseline patient characteristics, health state occupancy at baseline and 1-year (model cycle 2), and adverse events (AEs) with Acarizax® and ECM. Patients could discontinue Acarizax® due to AEs or for other reasons at rates for each observed in the Acarizax® arm of MT-06 (4.09% and 5.03%, respectively).
Extrapolation	From cycle 2 onwards, patients in the ECM arm were assumed to remain in the health state they occupied at the end of the MT-06 observation period. A proportion of patients in the Acarizax® arm were assumed to improve each year with the rate of improvement being 5% for years 2 – 5, then 2.5% from years 5 – 10. From years 10 – 20 treatment waning was assumed whereby a proportion of patients in the Acarizax® arm were assumed to worsen per year at a rate of 2.5%. From year 20 onwards there were no further health state transitions. The transition rates over time in the Acarizax® were based on assumptions but the company did provide studies that supported the continued improvement in AR in terms of symptomatic medication use and self-report of AR symptoms up to 7-years for other allergen immunotherapies or sublingual immunotherapies in patients with AR with and without HDM sensitivity.[12, 16] The maximum treatment duration with Acarizax® was assumed to be 3 years. AE discontinuations were assumed to occur in the first model cycle and so these patients reverted to ECM health state distributions and modelling assumptions from cycle 2 onwards. Patients who discontinued for other reasons were assumed to retain the full modelled treatment effect for Acarizax®. Discontinuation for other reasons was held constant over years 2 and 3.
Quality of life	Treatment arm specific utilities were assigned based on analysis of EQ-5D-3L data collected during the MT-06 study. This resulted in a utility value of 0.919 in the Acarizax® treatment arm and 0.898 in the ECM alone arm. No disutilities were included for AEs.
Costs and resource use	Costs were included for Acarizax® acquisition, ECM medication-use costs, the first administration of Acarizax® in a secondary care setting, AEs and health care resource use. ECM medication-use costs varied by health state and treatment arm. Health care resource use included annual GP visits and annual secondary care visits. Annual GP visits in the ECM arm (1.7) were according to expert opinion sought by the company and a relative reduction was applied in the Acarizax® arm based on the reduction in GP and specialist care visits observed in the MT-06 study (4.92%), which the company assumed were entirely GP visits. Annual secondary care visits in the ECM arm (2.66) were according to an analysis of hospital registry data for a generic allergy population, and a relative reduction was applied in the Acarizax® arm (73.53%) from a before and after study of patients with AR and asthma with HDM sensitivity treated with a subcutaneous allergen immunotherapy.[17]
PAS/contract price	A Patient Access Scheme (PAS) was not proposed by the submitting company.

6.2. Results

The base case results are presented in Table 6.2. Acarizax® was dominant compared to ECM alone meaning it was estimated as resulting in lower costs and better health outcomes for patients.

Table 6.2 Base case results

Technology	Total		Incremental		ICER (£/QALY)
	Costs (£)	QALYs	Costs (£)	QALYs	
ECM	16,273	18.53	-	-	Dominant
Acarizax®	12,577	18.79	-3,696	0.26	

Abbreviations: ECM = established clinical management; ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life year.

Dominant: The assessed medicine was estimated as having lower costs and greater health outcomes than the comparator.

The key cost driver was a reduction in secondary care costs with Acarizax® which were partially offset by the acquisition cost of Acarizax®.

The incremental quality adjusted life year (QALY) gain with Acarizax® was driven by the difference in utility values across the treatment arms of the model.

6.3. Sensitivity analyses

The company presented a range of sensitivity analyses. Key scenario analyses are shown in Table 6.3.

Table 6.3: Key scenario analyses

#	Parameter	Base case	Scenario	Incr. costs (£)	Incr. QALYs	ICER (£/QALY)
Base case				-3,696	0.26	Dominant
1a	Time horizon	Lifetime	5-years	691	0.09	7,928
1b			10-years	-1,016	0.16	Dominant
2	Annual number of GP visits	Primary care Delphi = 1.70	MT-06 = 0.1037	-3,675	0.26	Dominant
3	Annual number of secondary care visits	HES data analysis = 2.66	Demoly et al.,[18] 2016 = 1.70	-1,384	0.26	Dominant
4	Acarizax® transitions from year 2 to year 20	Year 2 – 5: 5% annual improvement Year 5 – 10: 2.5% annual improvement	Patients remain in health state at end of year 1 for remainder of time horizon	-3,697	0.26	Dominant

		Years 10 – 20: 2.5% annual waning				
5	HRQoL	Treatment specific utility values: Acarizax® = 0.919 ECM = 0.898	Health state-specific utility values: Mild AR = 0.953 Moderate AR = 0.892 Severe AR = 0.884	-3,696	0.12	Dominant
6	Acarizax® treatment duration	3-years	4-years	-2,860	0.26	Dominant
7			5-years	-2,100	0.25	Dominant
8	Secondary care visit reduction with Acarizax®	El-Qutob[17] 73.53%	Equal to reduction in GP visits per year observed in MT-06 = 4.92%	2,281	0.26	8,747
9	Treatment waning	Year 10 – 20: 2.5% annual waning	Year 7 – 10, at year 10 all patients in Acarizax arm are equal to ECM patients	-221	0.12	Dominant
C1	Combined scenarios	Scenarios 5 + 8 Health-state specific utility values + secondary care visit reduction with Acarizax® equal to reduction in GP visits per year observed in MT-06 = 4.92%		2,281	0.12	18,502
C2		C1 (Scenarios 5 + 8) + scenario 4 Health-state specific utility values + secondary care visit reduction with Acarizax® equal to reduction in GP visits per year observed in MT-06 = 4.92% + Patients remain in health state at end of year 1 for remainder of time horizon		2,287	0.09	24,410
C3		C1 (Scenarios 5 + 8) + 1b		2,499	0.08	31,909

		Health-state specific utility values + secondary care visit reduction with Acarizax® equal to reduction in GP visits per year observed in MT-06 = 4.92% + time horizon = 10-years			
C4		C2 (Scenarios 5 + 8 + 4) + 1b Health-state specific utility values + secondary care visit reduction with Acarizax® equal to reduction in GP visits per year observed in MT-06 = 4.92% + Patients remain in health state at end of year 1 for remainder of time horizon + time horizon = 10-years	2,503	0.05	47,729

Abbreviations: C = combined scenario; ECM = established clinical management; GP = general practitioner; HES = hospital episode statistics; HRQoL = health-related quality of life; ICER = incremental cost-effectiveness ratio Incr. = incremental; QALY = quality adjusted life year.

Dominant: The assessed medicine was estimated as having lower costs and greater health outcomes than the comparator.

6.4. Key strengths

- The choice of comparator reflects Scottish clinical practice according to clinical experts consulted by SMC.
- The sources used to value health care resources were appropriate.

6.5. Key uncertainties

- The lifetime time horizon with a starting age of 32-years led to uncertainty regarding the face validity of longer-term costs and health effects projected by the model relative to the availability of 12-months of clinical data comparing Acarizax® to placebo from the pivotal study. Data from the MT-06 study only provided evidence of improvement in allergic rhinitis (AR) severity with Acarizax® compared to ECM alone up to 1-year but the economic model assumed continued improvement in AR severity up to 10-years prior to treatment waning and adopted a lifetime time horizon. The company based this assumption on expert opinion and evidence from published literature. The literature cited by the company was based on different formulations of sublingual immunotherapy (SLIT) in house dust mite sensitised AR patients and so there was some uncertainty around the generalisability of these results to patients treated with Acarizax®.[12, 16] Additionally, the studies cited by the company suggested treatment waning as early as 7-years and that waning depended on the duration of treatment with Acarizax®. One of these studies also observed that

retreatment with Acarizax® was required at around 10-years to sustain treatment effectiveness.[16] Scenarios that explored earlier treatment waning (Scenario 9) and a 10-year time horizon (Scenario 1b) were considered relevant to explore the uncertainty around the duration of treatment waning and retreatment. Scenario 4 also highlighted the importance of the benefit of Acarizax® beyond the available data from the comparative evidence, however this was only impactful when combined with varying utility by health state rather than by treatment arm (Scenario C2).

- The company's approach to adopting treatment arm specific utility in the model was highly uncertain. This approach meant that health-related quality of life was dependent on whether patients received Acarizax® or ECM alone and was independent of the treatment effect on AR severity. Analyses that used treatment arm independent health state utility values resulted in a much lower QALY gain compared with the base case approach (Scenario 5 and Scenarios C1 – C4).
- A key driver of the cost-effectiveness results was a reduction in secondary care visits for patients treated with Acarizax®, but this was associated with several uncertainties. Firstly, the study that the relative effectiveness of Acarizax® was based upon did not report the frequency of secondary care visits and so a baseline rate (with ECM alone) of secondary care visits was based on an unpublished data analysis of secondary care visits for patients in England for a generic allergy population (2.66 visits per year). This may have overestimated the frequency of secondary care visits compared to the population in the economic evaluation. Alternative sources were presented by the company that seemed to more closely match the target population for treatment with Acarizax® which provided lower estimates of annual secondary care visits. Secondly, the relative reduction in the rate of secondary care visits (73.53%) was from a study of subcutaneous SLIT in patients with AR and asthma.[17] It wasn't clear that this relative reduction would be generalisable to the population in the economic analysis and its magnitude, relative to the improvement in the MT-06 primary outcome of TCRS with Acarizax®, presented a face validity concern. A scenario that assumed the relative reduction in annual secondary care visits was equal to the relative reduction in annual GP and specialist care visits observed in MT-06 for patients treated with Acarizax® compared to ECM alone (4.92%) resulted in much higher estimate of cost-effectiveness (Scenario 8). Thirdly, the baseline rate of secondary care visits and relative reduction in secondary care visits were applied to the ECM alone and Acarizax® arms independent of AR severity, implying a treatment effect independent of AR severity which presented a further face validity concern.
- There was some uncertainty around the duration of treatment with Acarizax® in the model. The base case assumed a treatment duration of 3-years which the company highlighted is supported by international guidelines and referred to in the SPC, it was uncertain what the duration of treatment with Acarizax® would be in routine clinical practice in Scotland. Scenario analyses that explored treatment durations of 4- and 5-years increased incremental costs associated with Acarizax® (Scenarios 6 and 7, respectively). SMC clinical

experts did agree that the expected typical treatment duration of Acarizax® would be 3-years.

7. Conclusion

After considering all the available evidence, the Committee accepted Acarizax® for restricted use in NHSScotland.

8. Guidelines and Protocols

In July 2017, the British Society for Allergy and Clinical Immunology (BSACI) updated the BSACI guideline for the diagnosis and management of allergic and non-allergic rhinitis (Revised Edition 2017; First edition 2007).[3]

9. Additional Information

9.1. Product availability date

September 2021

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Standardised allergen extract from the house dust mites *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* (Acarizax®)	one (12 SQ-HDM) sublingual lyophilisate once daily	**972**

Costs from BNF online on 30 March 2026.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated that there would be 1,960 patients eligible for treatment with Acarizax® per year. The estimated uptake rate was 5% in year 1 rising to 15% in year 3 with a discontinuation rate applied of 9.12% in year 1 and 5.03% in year 2 and year 3. This resulted in 89 patients estimated to receive treatment in year 1 rising to 279 patients in year 3.

The gross impact on the medicines budget was estimated to be £87k in year 1 rising to £272k in year 3. As no medicines were assumed to be displaced the net budget impact is equivalent to the gross medicines budget impact.

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This assessment is based on data submitted by the applicant company up to and including **29 May 2026.**

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC includes Scottish national contract prices in its decision-making. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document.

Patient Access Schemes (PAS): A PAS is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. The Patient Access Scheme Assessment Group (PASAG), established under the auspices of Public Services Delivery Scotland, reviews and advises NHS Scotland on the feasibility and acceptability on implementing proposed schemes. PASAG operates separately from SMC to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a PAS that has been considered acceptable for implementation by PASAG, a set of guidance notes on the operation of the scheme will be circulated to health boards' Area Drugs and Therapeutics Committees prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.