NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

12 SQ-HDM SLIT for treating allergic rhinitis and allergic asthma caused by house dust mites (review of TA834)

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using 12 SQ-HDM SLIT in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: [June 2024]

Note that this document is not NICE's final guidance on 12 SQ-HDM SLIT. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using 12 SQ-HDM SLIT in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 17 July 2024
- Second evaluation committee meeting: 12 November 2024
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 12 standard quality house dust mite sublingual lyophilisate (SQ-HDM SLIT) is not recommended, within its marketing authorisation, for treating the following conditions diagnosed by clinical history and a positive test of house dust mite sensitisation (skin prick test or specific IgE):

- persistent moderate to severe house dust mite allergic rhinitis in people aged 12 to 65 years despite using symptom-relieving treatment
- house dust mite allergic asthma in adults that:
  - is not well controlled by inhaled corticosteroids and
  - is associated with mild to severe house dust mite allergic rhinitis.

1.2 This recommendation is not intended to affect treatment with 12 SQ-HDM SLIT that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop. For children or young people, this decision should be made jointly by the healthcare professional, the child or young person, and their parents or carers.

Why the committee made these recommendations

Standard care for moderate to severe house dust mite allergic rhinitis for people aged 12 to 65 years includes treatments to relieve symptoms such as intranasal corticosteroids and antihistamines. Standard care for house dust mite allergic asthma in adults includes inhaled corticosteroids and short-acting beta agonists. It may also include additional long-acting beta agonists and leukotriene receptor antagonists.

Clinical trial evidence suggests that 12 SQ-HDM SLIT plus standard care may reduce rhinitis symptoms and medicine use compared with placebo plus standard care in people with house dust mite allergic rhinitis. For people with house dust mite

allergic asthma, clinical trial evidence suggests that 12 SQ-HDM SLIT plus standard care may reduce asthma exacerbations compared with placebo plus standard care. But these results are uncertain. It is unclear how the treatment would benefit people in clinical practice because the trial populations and the way the trials were done does not reflect NHS clinical practice.

There are uncertainties in the economic modelling. This is because of uncertainties in the clinical evidence and the model structures do not reflect how people would have treatment in NHS clinical practice.

More evidence is needed to determine the clinical and cost effectiveness of 12 SQ-HDM SLIT in NHS clinical practice. So, it is not recommended.

2 Information about 12 SQ-HDM SLIT

Marketing authorisation indication

2.1 12 standard quality house dust mite sublingual lyophilisate (SQ-HDM SLIT; Acarizax, ALK-Abello) is indicated 'in adult patients (18-65 years) diagnosed by clinical history and a positive test of house dust mite sensitisation (skin prick test and/or specific IgE) with at least one of the following conditions:

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

12 SQ-HDM SLIT is also indicated 'in adolescents (12-17 years) diagnosed by clinical history and a positive test of house dust mite sensitisation (skin prick test and/or specific IgE) with persistent moderate to severe house dust mite allergic rhinitis despite use of symptom-relieving medication'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for 12 SQ-HDM SLIT.

Price

2.3 The list price of 12 SQ-HDM SLIT is £80.12 (excluding VAT; BNF accessed April 2024) per pack of 30 tablets. Costs may vary in different settings because of negotiated procurement discounts.

3 Committee discussion

The evaluation committee considered evidence submitted by ALK-Abello, a review of this submission by the external assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

Details of the condition

3.1 Allergic respiratory disease (ARD) is a group of respiratory conditions that are triggered by allergens, which can include house dust mites. An inflammatory response occurs when people who are sensitised to house dust mites are exposed to house dust mite-derived allergens. This can create an allergic reaction in the upper or lower respiratory tract that can lead to symptoms of rhinitis, such as nasal congestion, and asthma, such as wheezing, chest tightness and coughing. It may also cause red, itchy or watery eyes. The patient experts explained the challenges associated with the condition. Experiencing these symptoms can impact physical and mental health. Sleeping difficulties can cause significant fatigue. Allergic rhinitis and allergic asthma can impact all aspects of daily life. It can affect the ability to attend a workplace or school, and limit employment opportunities. Avoiding house dust mites is almost impossible, and there is a high burden of trying to eliminate house dust mites by cleaning. The patient experts explained that family members can have feelings of guilt when they cannot successfully remove house dust mites and their relative

continues to have symptoms. One patient expert explained that while symptom-relieving medicine is available, for some people this does not fully control the symptoms and most people would prefer to avoid prolonged use of corticosteroids. The patient experts stated that people would welcome a treatment option such as 12 standard quality house dust mite sublingual lyophilisate (SQ-HDM SLIT). This treatment aims to target the root cause of their condition by desensitising them to house dust mites, which may potentially reduce their corticosteroid burden. The committee concluded that allergic rhinitis and allergic asthma caused by house dust mites can impact people's quality of life and day-to-day activities. There is an unmet need for an additional treatment to symptom-relieving medicine, which does not adequately control rhinitis and asthma in everyone.

Clinical management

Allergic rhinitis

3.2 Allergic rhinitis is treated in line with the British Society for Allergy & Clinical Immunology (BSACI) rhinitis guideline and the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline in secondary care. Oral or intranasal antihistamines are the first-line treatment for mild to moderate, intermittent, or mild persistent symptoms. Intranasal corticosteroids are recommended for moderate to severe persistent symptoms, or if initial treatment is not effective. Combinations of oral antihistamines and intranasal corticosteroids can be used if symptoms continue. Further add-on treatments can be considered. These can include intranasal anticholinergics, oral antihistamines, intranasal decongestants and leukotriene receptor antagonists (LTRAs), depending on symptoms. The company considered that 12 SQ-HDM SLIT would be an additional treatment for allergic rhinitis to be taken alongside symptom-relieving medicine. The committee recognised that the BSACI guideline positioned allergy immunotherapy, if symptoms are mainly because of 1 allergen, after all other treatment options had been considered. The clinical experts

stated that this would be the most appropriate positioning. The committee concluded that for people with house dust mite allergic rhinitis, 12 SQ-HDM SLIT would be used in addition to symptom-relieving medicine, after all appropriate symptom-relieving medicine had been tried and symptoms continued.

Allergic asthma

3.3 In clinical practice asthma treatment follows the NICE guideline on asthma: diagnosis, monitoring and chronic asthma management, the Global Initiative for Asthma (GINA) guidelines (Redell et al. 2021) and the British Thoracic Society (BTS) and Scottish Intercollegiate Guideline Network (SIGN) British guideline on the management of asthma. These guidelines involve a stepwise approach to assessing, treating and monitoring asthma control, in which additional treatments are added if symptoms are not controlled. If asthma becomes uncontrolled despite inhaled corticosteroids (usually offered with another treatment such as long-acting beta 2 agonists or LTRAs), then low-dose oral corticosteroids or biological treatments are added. Biological treatments may be offered if asthma is not controlled well enough by maintenance treatment with high-dose inhaled corticosteroids plus a long-acting beta 2 agonist or another treatment. The committee noted the current BTS and SIGN guideline does not define when to use allergy immunotherapy for treating allergic asthma. The company stated that 12 SQ-HDM SLIT was expected to be an addition to the existing treatment options for asthma. The marketing authorisation for 12 SQ-HDM SLIT states that people would be eligible for the treatment if their asthma is categorised as 'not well controlled by inhaled corticosteroids'. The company considered that the positioning of 12 SQ-HDM SLIT would align with steps 2, 3 and 4 of the GINA guidance. The company considered that 12 SQ-HDM SLIT was not an alternative option for severe asthma as an alternative to biological treatments, because this would be beyond the marketing authorisation.

12 SQ-HDM SLIT would be expected to be used before biological treatments and was not expected to replace them. The clinical experts

considered that 12 SQ-HDM SLIT would be best positioned within steps 2 to 3 of the BTS and SIGN guideline. That is, it would be used at the same position as existing treatments for asthma control. The committee concluded that for people with allergic asthma not well controlled by inhaled corticosteroids and associated with allergic rhinitis, 12 SQ-HDM SLIT would be used in addition to symptom-relieving medicine, but before biological treatments.

Setting for prescribing 12 SQ-HDM SLIT

3.4 The marketing authorisation for 12 SQ-HDM SLIT states that house dust mite allergy must be confirmed. ARD is mostly diagnosed in primary care and some tests of sensitisation such as a radioallergosorbent test may be done by GPs. But further testing such as skin prick testing and taking a clinical history to determine house dust mites as the allergen would be done in secondary care. 12 SQ-HDM SLIT is a sublingual immunotherapy (SLIT) that contains a standardised allergen extract from the house dust mites Dermatophagoides pteronyssinus and Dermatophagoides farina. The committee noted that the marketing authorisation states that 'treatment should be initiated by physicians with experience in treatment of allergic diseases'. The clinical experts explained that they expected 12 SQ-HDM SLIT would be prescribed in secondary care. A patient expert who was also a GP agreed, but noted that some GPs would have enough experience to prescribe. The committee concluded that 12 SQ-HDM SLIT would be prescribed in secondary care.

Eligibility criteria for people with allergic asthma

3.5 A clinical expert stated that they expected a minority of people with ARD caused by house dust mites would need 12 SQ-HDM SLIT. The committee noted that the marketing authorisation indication is for 'house dust mite allergic asthma not well controlled by inhaled corticosteroids'. But, the clinical trial assessing 12 SQ-HDM SLIT for asthma (see section 3.7) included people with asthma that could be considered controlled. It was unclear how 'asthma not well controlled by inhaled

corticosteroids' would be defined in clinical practice. A clinical expert stated that they would expect to start 12 SQ-HDM SLIT when a person with uncontrolled asthma was having fewer exacerbations. The committee concluded that it remained uncertain about the eligibility criteria for 12 SQ-HDM SLIT for people with allergic asthma with allergic rhinitis in clinical practice. This uncertainty included whether people would start treatment when their asthma was not well controlled, or whether they would need to wait for a reduction in exacerbations before starting treatment.

Clinical evidence

3.6 Two multi-centre placebo-controlled randomised controlled trials (RCTs) informed the company's modelling of the clinical and cost effectiveness of 12 SQ-HDM SLIT for allergic rhinitis and allergic asthma with allergic rhinitis:

- MT-04 (n=834) was a European double-blind multicentre RCT of house dust mite allergic asthma with an asthma control questionnaire (ACQ) score between 1.0 and 1.5. Adults (aged at least 18 years) had daily treatment with 6 SQ-HDM SLIT (a lower dose of SQ-HDM that is not included in the marketing authorisation), 12 SQ-HDM SLIT or placebo for 13 to 18 months. People in MT-04 were allowed to have budesonide (an inhaled corticosteroid) and short-acting beta 2 agonists (SABAs), in addition to the investigational product. The trial had a maintenance phase and a phase in which inhaled corticosteroids were stopped in both arms over a 6-month period. The primary efficacy assessment was made during this 6-month inhaled corticosteroid withdrawal period, which was timed to fall outside of the pollen season.
- MT-06 (n=992) was a European double-blind, multi-centre RCT that included people who had moderate to severe persistent house dust mite allergic rhinitis (with or without asthma). Adults (aged 18 to 65) had daily treatment with placebo, 6 SQ-HDM SLIT or 12 SQ-HDM SLIT for about 12 months. People in MT-06 were allowed to use nasal

corticosteroids, oral antihistamines and antihistamine eye drops, in addition to the investigational product. The trial had 2 phases: a maintenance phase, which was up to 10 months, and a 2-month efficacy assessment phase that was timed to fall outside of the pollen season.

A further trial, P001 (n=1,482), was a randomised, double-blind, multicentre trial done in the US and Canada. People (aged 12 years or older) with symptoms of allergic rhinitis or allergic rhinoconjunctivitis caused by exposure to house dust mites had daily treatment with placebo or 12 SQ-HDM SLIT for about 12 months. This trial was not used to inform the economic model. Two further trials done in Japan in people with allergic rhinitis and allergic asthma did not inform the economic model.

Applicability of trial data to NHS clinical practice

3.7 The EAG identified many methodological limitations across the trials that it considered to have important implications on the applicability of the trial results to the NHS. These included specifically for MT-04:

- People had to report that their asthma symptoms were partially controlled (ACQ score between 1.0 and 1.5) before randomisation. People with an ACQ score of more than 1.5 at randomisation (suggesting asthma was not well controlled) were not eligible to take part in MT-04. The EAG considered that this meant that there was limited data for people whose asthma was not well controlled with inhaled corticosteroids.
- People in MT-04 had a mandated reduction of inhaled corticosteroids by 50% over the first 3 months of the efficacy period and these were stopped completely for the second 3 months of the efficacy period. This would not reflect clinical practice if 12 SQ-HDM SLIT was used.
- Part of the MT-04 protocol required people who had more than 3 asthma exacerbations to withdraw from the trial in the assessment

phase. The EAG considered this restricted outcome data for people who might have had multiple exacerbations.

In all the 12 SQ-HDM SLIT trials:

- The primary efficacy assessment was done outside of the major pollen season. The EAG considered that this restricted approach to evaluating outcomes was especially problematic in MT-04 because asthma exacerbations were only evaluated outside of the major pollen season. The EAG's clinical adviser would have preferred to have seen efficacy data from timepoints including the pollen season.
- The trials prohibited taking some medicines alongside 12 SQ-HDM SLIT. The clinical experts confirmed that in UK clinical practice, people can access alternative treatments to control their asthma, such as higher-dose SABAs, long-acting muscarinic antagonists or LTRAs, which were not allowed in the trials.
- The trials typically lasted between 12 to 18 months. This was shorter than the recommended immunotherapy duration in the ARIA guideline and in the marketing authorisation for 12 SQ-HDM SLIT. The EAG considered that this meant that the studies did not evaluate the effects of having 3 years of treatment, or whether the effects of having 12 SQ-HDM SLIT would continue after treatment had stopped.

The company explained the rationale behind the trials' designs. In MT-04, the company clarified that the ACQ scores were set at these levels to ensure that people in the trials did not have uncontrolled symptoms at the start of the trial. This was for safety reasons. The reduction in inhaled corticosteroids was to induce an exacerbation in a controlled way to assess the efficacy of SQ-HDM SLIT for reducing asthma exacerbations. A clinical expert stated that in clinical practice they would want to start treatment when a person's asthma was well controlled but with exacerbations in the last 12 months. The clinical experts explained that assessing asthma symptoms every 12 months is expected in clinical practice. The patient experts noted that some of the treatments which

were prohibited in the trials would not be used long term. The company explained that prohibiting some symptom-relieving medicine was to allow for more consistency in the concomitant treatments that people had in the trials. The company clarified that house dust mite allergens are more prevalent during the autumn and winter periods. So setting the trial when the major pollen season had ended ensured that the allergic symptoms were assessed when exposure to the allergen was at its peak and less likely to be caused by another allergen such as pollen. The company recognised the trial durations did not fulfil 3 years of allergy immunotherapy. But, it considered the trials were adequately powered to address their primary outcomes during a 12-month assessment period. The committee recognised that the trials were bound by their investigational objective. But it concluded that the protocol requirements meant that the submitted clinical evidence was limited in showing how effective 12 SQ-HDM SLIT would be if it is used as intended in the NHS. In the NHS, 12 SQ-HDM SLIT would be used for allergic asthma that is not controlled by inhaled corticosteroids and the inhaled corticosteroids would not be stopped. For people with allergic rhinitis and allergic asthma it would be used throughout the year and alongside a broader potential range of symptom-relieving medicines than allowed in the trials.

Clinical efficacy estimates

Allergic rhinitis

3.8 The allergic rhinitis trials reported rhinitis symptoms using the total combined rhinitis score (TCRS):

- In MT-06 a statistically significant mean difference in TCRS was seen between the groups during period 2 (visit 5: -1.41, 95% confidence interval [CI] -2.14 to -0.68; visit 6: -1.22, 95% CI -1.99 to -0.46) and in period 3 (visit 7 to 8: -1.09, 95% CI -1.84 to -0.35). This suggested the placebo group reported worse symptoms and more medicine use compared with the 12 SQ-HDM SLIT group. Since analysis of data in

period 3 was adjusted to account for missing data, the EAG considered this data had better internal validity.

- In P001 the placebo group reported statistically significantly higher on the TCRS (5.49) compared with the 12 SQ-HDM SLIT group (4.67), mean difference -0.82 (95% CI -1.24 to -0.40), which suggested worse symptoms. Because this analysis only included the full analysis set, in which many people had stopped having treatment, the EAG considered that the results were biased.

The committee considered whether any change in outcomes from having 12 SQ-HDM SLIT compared with placebo could be considered to have a meaningful impact for people with allergic rhinitis. The World Allergy Organization's recommendations for standardisation of clinical trials with allergen-specific immunotherapy for respiratory allergy has suggested that a minimal clinically relevant result should be at least 20% more than a placebo. The EAG noted that for several outcomes for the allergic rhinitis trials, the relative difference between 12 SQ-HDM SLIT compared with placebo was less than 20%. In MT-06, the period 3 TCRS (adjusted for missing data), suggested there was a difference between groups of 16%. The EAG considered that this did not suggest results were clinically meaningful according to this cut off. Results for people completing the rhinitis quality of life questionnaire reported a -0.21 absolute difference (95% CI -0.39 to -0.02) between scoring for people in the 12 SQ-HDM SLIT and placebo groups. The committee noted that Juniper et al. (1999) had reported that an absolute difference of 0.5 was considered clinically meaningful. So the committee was uncertain whether treatment with 12 SQ-HDM SLIT would be clinically meaningful. The committee further noted that in MT-06, up to 40% of people had improved rhinitis outcomes in the placebo arm compared with baseline. The reasons for this were unresolved and this added to the uncertainty around the relative treatment effect of 12 SQ-HDM SLIT. The committee noted that although some outcomes had statistically significant results, the

differences between 12 SQ-HDM SLIT and placebo did not meet published cut-offs for a clinically meaningful effect. However, it questioned whether the 20% cut off was too high. Also, the committee noted its uncertainty about the clinical effectiveness of 12 SQ-HDM SLIT if it was used in the way it would be expected to be used in the NHS. This is because the trials had not been designed to determine this. Overall, the committee concluded that, based on the trial evidence, it was not possible to conclude that 12 SQ-HDM SLIT would show a clinical benefit for allergic rhinitis compared with established clinical management in the NHS.

Allergic asthma

3.9 The primary outcome in MT-04 was time to first moderate or severe asthma exacerbation during the efficacy assessment phase. MT-04 reported a statistically significant (31%) risk reduction of a moderate or severe asthma exacerbation compared with placebo (hazard ratio [HR] 0.69, 95% CI 0.50 to 0.96, p=0.027), in the full analysis set with multiple imputation (to adjust for missing data). Asthma symptoms were also reported using ACQ scores. At visit 13, which happened during the mandated withdrawal phase of the trial, there was no statistically significant difference in ACQ score between the 12 SQ-HDM SLIT arm and the placebo arm (mean difference -0.12, 95% CI -0.25 to 0.01). One clinical expert explained that if there was no difference seen in clinical practice for an asthma treatment, then the asthma treatment would be stopped.

There was no presented published estimate of a clinically relevant reduction in exacerbations, but the clinical expert stated that a 30% reduction seen in MT-04 would be clinically meaningful. The EAG noted that Juniper et al. (2005) had reported a clinically relevant result as 0.5 for the ACQ. Because the ACQ score for 12 SQ-HDM SLIT was lower than and not statistically significantly different to placebo, the EAG did not consider this to be clinically meaningful. The committee concluded that

there was uncertainty in whether 12 SQ-HDM SLIT had a clinically meaningful effect compared with placebo in the trial. It was also uncertain about the clinical effectiveness of 12 SQ-HDM SLIT if it was used in the way it was expected to be used in the NHS. This is because the trial had not been designed to determine this. Overall, the committee concluded that, based on the trial evidence, it was not possible to conclude that 12 SQ-HDM SLIT would show a clinical benefit for allergic asthma with allergic rhinitis compared with established clinical management in the NHS.

Real-world evidence

3.10 The clinical experts and patient experts reported that there have been benefits seen in people who have had immunotherapies for allergic rhinitis and allergic asthma in NHS clinical practice, including 12 SQ-HDM SLIT. The experts also said that benefits of 12 SQ-HDM SLIT, such as its impact on reducing fatigue and corticosteroid burden, would not have been captured by the trials The clinical experts noted that the 22-item Sino-Nasal Outcome Test (SNOT-22) was an important outcome for allergic rhinitis. They explained that this tool can capture self-reported outcomes such as fatigue. The company had provided additional observational data from several studies on allergy immunotherapy as supporting evidence on using house dust mite allergy immunotherapy. Both the company and EAG noted that there were limitations with the observational evidence provided. These limitations included lack of comparator treatment arms, that the studies included allergy immunotherapy for sensitisation to other allergens, and immunotherapy administered either subcutaneously or sublingually. The committee suggested that the clinical evidence the company had provided could be supplemented by further patient-reported outcomes or real-world evidence. Such data should:

- align with the NICE real-world evidence framework for conducting, reporting, analysing and interpreting real world evidence

- include patient-reported outcomes on potential benefits of 12 SQ-HDM SLIT, which may include SNOT-22 to assess the impact of fatigue upon allergic rhinitis and impact on corticosteroid use
- present supporting clinical and economic evidence if an argument is made for a class effect of immunotherapy (either for house dust mite immunotherapy delivered subcutaneously or sublingually, or for sublingual therapies for house dust mite and other allergens used to treat allergic rhinitis and allergic asthma).

Economic model

Company's modelling approach

3.11 The company provided 2 Markov models to calculate lifetime costs and quality-adjusted life years (QALYs) for treatment with 12 SQ-HDM SLIT compared with established clinical management. One model was for the allergic rhinitis only population and 1 for the allergic asthma with allergic rhinitis population. Each model was comprised of 3 mutually exclusive health states to describe what could happen to the population of interest over time. The health states for the allergic rhinitis population were defined based on a modified version of the ARIA severity classification (Valero et al. 2007). The health states were mild, moderate and severe and populated using data from MT-06. The 3 health states for the allergic asthma with allergic rhinitis population were defined to reflect asthma control according to the GINA guidelines (Reddel et al. 2021). The states were uncontrolled asthma, partly controlled asthma and well controlled asthma. The company used ACQ data from MT-04 and mapped this to the GINA classification health states. Both models compared 12 SQ-HDM SLIT taken alongside established clinical management with established clinical management alone. The established clinical management people had in each health state was a blend of the treatments people with each allergic rhinitis severity, or asthma level of control, would have in clinical practice. The EAG had the following concerns with the company's modelling approach:

- Each model had a 1-year cycle length. So the company assumed an average level of disease control or severity throughout the year rather than potential fluctuations throughout the year.
- The models were informed by the MT-04 and MT-06 trials, which the EAG had noted had methodological limitations. Also, to estimate the proportion of people in each health state in the models the company had used a post-hoc analysis from the MT-04 and MT-06 trials, which added to the uncertainty.
- The allergic asthma with allergic rhinitis model did not explicitly model rhinitis outcomes and asthma exacerbations were assumed to be the same across asthma control health states, which was implausible.
- The allergic rhinitis model did not include data from young people aged 12 to 17 years. The company's approach for both models did not reflect a stepping up of treatment when symptoms persist and stepping down of treatment when symptoms are well controlled.
- The allergic asthma with allergic rhinitis model did not include people with an ACQ score reflecting uncontrolled asthma, that is, 1.5 or more.

The committee did not consider either model suitable for decision making, but the allergic asthma with allergic rhinitis model had more issues. The committee stated that both models should reflect the treatment pathway, allowing stepping up and stepping down of treatments. This was less of an issue for the allergic rhinitis model because 12 SQ-HDM SLIT is anticipated to be used last line. But, the committee would like to see more evidence to support the company's modelling approach for the allergic rhinitis only population at this position in the treatment pathway (see section 3.8). The rhinitis model should consider the costs and benefits of 12 SQ-HDM SLIT for the whole population for whom it is licenced, including people aged 12 to 17 years (see section 3.12). For the allergic asthma with allergic rhinitis model the committee preferred to see a model structure more reflective of the stepping up and stepping down of treatments and disease progression. The committee noted that NICE's technology appraisal guidance on tezepelumab for treating severe asthma

and benralizumab for treating severe eosinophilic asthma had structured their models around asthma control in line with the BTS and SIGN guideline, based on ACQ score, rather than the definition in the GINA guidelines (Reddel et al. 2021), which the company had used. The committee preferred a consistent approach. It also stated that the model for people with allergic asthma with allergic rhinitis should also include the costs and benefits on allergic rhinitis in both treatment arms. The committee's discussions on modelling assumptions in the current models, which may be of relevance to the requested updated models, are described in sections 3.12 to 3.15.

Assumptions

Modelling in young people with allergic rhinitis

3.12 The company used data from the adult population in MT-06 and generalised this to people aged 12 to 17 years to model the clinical effectiveness for people 12 and over with house dust mite allergic rhinitis. This implicitly assumed that there was no difference in effectiveness between the 2 subgroups. The EAG noted that subgroup evidence from P001 suggested there was a larger difference in the TCRS scores in people aged 12 to 17 compared with the adult subgroups (see section 3.8). But the EAG was unable to explore the impact of the difference in its critique. The committee considered this remained an area of uncertainty that would need to be resolved by additional evidence on health-related quality of life for this subpopulation.

Long-term effectiveness

3.13 There was no clinical trial data beyond 2 years. In both models the company assumed that having 12 SQ-HDM SLIT would improve health from 2 to 10 years, whereas on established clinical management people would remain stable (stay in the same health states over the whole of the modelled period). Treatment waning was modelled in the 12 SQ-HDM SLIT arm from 15 years onwards. By year 20, 80% of people

having 12 SQ-HDM SLIT would match the distribution of people having standard care. The company assumptions were informed by clinical opinion collected in a Delphi panel. The company had supplemented its long-term effectiveness assumptions with evidence from the REACT study (Fritzsching et al. 2021). This was a German retrospective cohort study of people with allergic rhinitis and asthma who had, and had not, had allergic immunotherapy (subcutaneous or sublingual against various antigens). This assessed group differences across 9 years of follow up and found that over this period people who had allergen immunotherapy had fewer rhinitis and asthma prescriptions than people who had not. The EAG considered that there was no evidence beyond 10 years and preferred to assume that from 2 to 10 years people stayed in the same health states in the 12 SQ-HDM SLIT arm and then after 10 years matched the distribution across health states of standard care. A clinical expert specialising in treating allergic rhinitis gave anecdotal evidence that for sublingual immunotherapy for pollen allergy, results were variable but they would expect 10 years of benefits. The effects of immunotherapies were likely transferable for different allergens. A patient expert reported that a person who had 3 courses of 12 SQ-HDM SLIT would have a treatment effect lasting 20 years. The committee concluded that it was plausible that an allergen immunotherapy could have a persistent effect, but further evidence was needed for assuming a class effect across immunotherapies for different allergens and routes of administration. The committee also noted that the current models assumed 1 course of treatment and if retreatment is expected in clinical practice the updated models should reflect that.

Costs

Primary and secondary resource use

3.14 Management costs in the company's base case included the costs for primary care and secondary care. In both models, 12 SQ-HDM SLIT reduced primary and secondary care costs compared with standard care.

In the allergic asthma with allergic rhinitis model, the company's base case assumed a 54.58% relative reduction of secondary care resource use with 12 SQ-HDM SLIT compared with standard care, based on the number of emergency visits in MT-04. The EAG noted that the number of emergency visits in MT-04 was generally low across treatment arms. So there was high uncertainty in the company's assumption. In the allergic rhinitis only model the company assumed a relative reduction of 73.53%, based on El Qutob et al. (2016). This was a before-and-after study of subcutaneous immunotherapy for house dust mite allergic rhinitis and allergic asthma. So it was unclear whether the treatment effects would be generalisable to sublingually administered 12 SQ-HDM SLIT. The EAG had noted that the before-and-after design of this study may have produced biased estimates. Assuming a smaller reduction in secondary care costs in the 12 SQ-HDM SLIT arm had a large effect on the cost-effectiveness results. The EAG had noted that the company's approach to modelling the reduction in primary care visits in the allergic asthma with allergic rhinitis model was complicated. And was poorly aligned with the economic model. The estimates relied on strong assumptions to translate data from MT-04 on primary care visits to the modelled health states, which had not been justified. The committee was concerned that the modelling assumptions might overestimate savings in primary and secondary care costs of 12 SQ-HDM SLIT. It recognised that it would need additional evidence to support the company's modelling assumptions for the extent of any reduction in primary or secondary care visits associated with 12 SQ-HDM SLIT. The committee also concluded that if data was used from people having subcutaneous house dust mite immunotherapy to estimate the relative reduction in secondary care for 12 SQ-HDM SLIT, it would need justification that reduced secondary care visits for subcutaneous immunotherapy could be generalised to sublingual immunotherapy.

Modelling health-related quality of life

3.15 In its base case for both models, the company applied a treatment-specific approach to model health-state specific utilities. This assigned a specific utility value to treatments. For the allergic asthma and allergic rhinitis population it used post-hoc data from MT-04 to transform SF-36 scores into preference-based utilities. For the allergic rhinitis only population, the company used a post-hoc analysis of EQ-5D data collected in MT-06. The EAG was concerned that a treatment-specific approach did not align with both model structures. It preferred to use health-state specific utilities that provide quantitative measures of how strongly a person values a certain health state. The EAG also noted that the EQ-5D measure the company used in the allergic rhinitis only model has only been validated for adults. So, results from this measure may not be applicable to people aged 12 to 17 years with allergic rhinitis. The company stated that it had used treatment-specific utilities because these could apply to people who were on or off treatment. It considered this was more appropriate than using health-state utility values, because it would capture other factors beyond allergic control. The company also noted that in the model for allergic asthma with allergic rhinitis, using treatment-specific utility values would allow 12 SQ-HDM SLIT's effect on quality of life associated with allergic rhinitis to be captured in the utility values, because the health states modelled asthma only. The committee recognised that allergic rhinitis in addition to asthma can affect health-related quality of life. So it accepted this was a valid approach to modelling health-related quality of life. The committee concluded that in the updated models the utility values should be representative of the whole population within the marketing authorisation.

Cost-effectiveness estimates

3.16 The committee was not able to determine whether 12 SQ-HDM SLIT had a clinical benefit in the population who would have it in NHS clinical practice (see section 3.7). Also, it could not determine a plausible incremental cost-effectiveness estimate for the comparison of 12 SQ-HDM SLIT with standard care for either the allergic rhinitis only

population or the allergic asthma with rhinitis population. This was because the models were not suitable for decision making (see section 3.11). The committee agreed it would need to see the following changes to inform its decision making:

- Further clinical evidence, if available, to allow the committee to determine if 12 SQ-HDM SLIT would provide additional benefits to established clinical management alone in NHS clinical practice (see section 3.7).
- Revised cost-effectiveness models for both the allergic rhinitis only and allergic asthma with allergic rhinitis populations. These should reflect the treatment pathway used in the NHS with and without 12 SQ-HDM SLIT which allows any stepping up and down of treatments to be modelled (see section 3.11).
  - For the allergic rhinitis model, the modelled cohort should include data relevant to people aged 12 to 17 years. Also, any differences in clinical or quality of life benefits with 12 SQ-HDM SLIT in the population aged 12 to 65 years should be explored.
  - For the allergic asthma with rhinitis model, a similar structure to asthma models used in previous NICE technology appraisals may be considered. The effects of 12 SQ-HDM SLIT on costs associated with, and benefits for, allergic rhinitis should be included.
- While the committee considered it plausible that a treatment effect could continue after stopping 12 SQ-HDM SLIT, clinical evidence on retreatment rates should be presented, and retreatment should be considered in the model (see section 3.13).
- Any assumptions relating to a relative decrease in primary care or secondary care costs with 12 SQ-HDM SLIT using indirect data sources should show an assessment of generalisability of the data informing these assumptions to 12 SQ-HDM SLIT (see section 3.14).
- Treatment-specific utility values may be appropriate, but the company should explore whether the quality-of-life measures used in the trial

fully capture utility with and without 12 SQ-HDM SLIT for the whole population covered by its marketing authorisation (see section 3.15).

Other factors

Equality

3.17 The committee considered that some people with allergic rhinitis and allergic asthma may have a disability, are an older age, or are pregnant. These are protected characteristics under the Equality Act 2010. But because its recommendation does not restrict access to treatment for some people over others, the committee agreed these were not potential equalities issues.

Conclusion

Recommendation

3.18 The committee's concerns about the clinical evidence and cost-effectiveness modelling meant that it was not confident that the results presented reflected the clinical and cost effectiveness of 12 SQ-HDM SLIT as it would be used in the NHS. It could not recommend 12 SQ-HDM SLIT. The committee suggested further data, analyses and necessary model revisions which may allow it to better understand the clinical and cost effectiveness of 12 SQ-HDM SLIT in NHS clinical practice. It welcomes the company to provide these in response to consultation on its draft recommendations.

4 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

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