NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

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

1 Recommendations

Allergic rhinitis

1.1 12 standard quality house dust mite sublingual lyophilisate (SQ-HDM SLIT) is recommended, within its marketing authorisation, as an option for treating moderate to severe house dust mite allergic rhinitis in people 12 to 65 years that is:

- diagnosed by clinical history and a positive test of house dust mite sensitisation (skin prick test or specific immunoglobulin E [IgE]) and
- persistent despite use of symptom-relieving medicine.

Allergic asthma

1.2 12 SQ-HDM SLIT is not recommended, within its marketing authorisation, for treating house dust mite allergic asthma in adults that is:

- diagnosed by clinical history and a positive test of house dust mite sensitisation (skin prick test or specific immunoglobulin E [IgE]) and
- associated with mild to severe house dust mite allergic rhinitis and
- not well controlled by inhaled corticosteroids.

1.3 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.

Why the committee made these recommendations

Standard care for moderate to severe allergic rhinitis caused by house dust mites for people 12 to 65 years includes treatments to relieve symptoms such as intranasal corticosteroids and antihistamines. Standard care for allergic asthma caused by house dust mites 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, compared with placebo plus standard care, 12 SQ-HDM SLIT plus standard care may reduce:

- rhinitis symptoms and medicine use in people with house dust mite allergic rhinitis, and
- asthma exacerbations in people with house dust mite allergic asthma.

But these results are uncertain. It is unclear exactly how much the treatment would benefit people in clinical practice because the way the trials were done does not reflect NHS clinical practice. There is more uncertainty about the clinical effectiveness of 12 SQ-HDM SLIT for allergic asthma than for allergic rhinitis.

There are uncertainties in the economic modelling. This is because of uncertainties in the clinical evidence and because the model structures do not completely reflect how people would have treatment in NHS clinical practice. Taking into account the uncertainties, 12 SQ-HDM SLIT is cost effective for treating allergic rhinitis caused by house dust mites, but is not cost effective for treating allergic asthma caused by house dust mites. So, 12 SQ-HDM SLIT is recommended only for persistent moderate to severe house dust mite allergic rhinitis. Some of the eligible population may also have allergic asthma, which would not prevent them having 12 SQ-HDM SLIT to treat their allergic rhinitis.

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 (12 SQ-HDM SLIT). This treatment aims to target the 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. It also considered that 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 and before biological treatments. 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. Allergic respiratory disease 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. 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 initially be prescribed in secondary care. A clinical expert with experience of using 12 SQ-HDM SLIT in NHS practice stated that repeat prescriptions could be provided in primary care. A patient expert who was also a GP agreed with starting treatment in secondary care, but noted that some GPs would have enough experience to prescribe. The committee concluded that 12 SQ-HDM SLIT would initially be prescribed in secondary care, but repeat prescriptions could be provided in primary care.

Eligibility criteria for people with allergic asthma

3.5 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 allergic 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 allergic asthma was having fewer exacerbations. At the first meeting, the committee was 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. In response to the draft guidance, the company explained that 'asthma not well controlled by inhaled corticosteroids' could include people having treatment with inhaled corticosteroids alone, or in

combination with long-acting beta-agonists. It also noted that 12 SQ-HDM SLIT is contraindicated if people have a lung function of forced expiratory volume in 1 second of less than 70% predicted, or have experienced a severe asthma exacerbation within the last 3 months. Other stakeholders responded that asthma control questionnaire (ACQ; see section 3.7) scores could be used to indicate asthma control, but interpretations of the thresholds varied. The committee concluded that people with allergic asthma would be eligible for treatment if, overall, their asthma was not well controlled. But, treatment with 12 SQ-HDM SLIT would not be started if a person was experiencing severe asthma exacerbations. There is not a clear cut-off value for defining not-well-controlled asthma based on ACQ. But, the committee was satisfied that 12 SQ-HDM SLIT would not be started unless medicines used to treat symptoms were not providing asthma control.

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 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.

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.

- 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 company said excluding people from MT-04 with an ACQ score of more than 1.5 at randomisation was consistent with the anticipated use of 12 SQ-HDM SLIT in UK clinical practice. The EAG noted that ACQ restrictions were not included in the

marketing authorisation (section 2.1). The reduction in inhaled corticosteroids was to induce an exacerbation in a controlled way to assess the efficacy of 12 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 company explained that prohibiting some symptom-relieving medicine was to allow for more consistency in the concomitant treatments that people had in the trials and to reduce potential confounding. But it also said the prohibited treatments were not likely to meaningfully impact patient outcomes. The EAG considered this to be contradictory. 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 response to treatment was assessed when exposure to the allergen was at its peak and less likely to be caused by another allergen such as pollen. The company also noted post-hoc MT-06 results for total combined rhinitis score split by people both with and without sensitisation to grass or tree pollen showed consistent treatment benefit throughout the course of a whole year including the pollen season. But the EAG was concerned that the same subgroup analysis was not presented for MT-04. The company recognised the trial durations were shorter than the 3 years of allergy immunotherapy in the summary of product characteristics. 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 designed in line with regulatory objectives. But it concluded that this meant 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. Although for allergic asthma 12 SQ-HDM SLIT would be started when it was safe to do so and the trial reflected this, in the NHS inhaled corticosteroids would not be stopped. For people with allergic rhinitis and for people with allergic asthma with rhinitis it would be used throughout the year and alongside a broader potential range of

symptom-relieving medicines than allowed in the trials. The committee concluded that it would consider the uncertainty resulting from the clinical trial design in its decision making.

Clinical efficacy estimates

Allergic rhinitis

3.8 In MT-06 a statistically significant mean difference in total combined rhinitis score (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. 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 company said the placebo effect was because people had retraining on how to use symptom-relieving medicines and more frequent access to healthcare professionals than expected in routine practice. It said that the placebo effect in the trial reduced the relative treatment effect of 12 SQ-HDM SLIT in comparison with placebo. The company also stated that the US Food and Drugs administration says that in allergy immunotherapy trials for allergic rhinitis a 15% improvement compared with placebo is clinically relevant because of the placebo effect. The committee agreed with the EAG that the effect of retraining on use of symptom-relieving medicines would be expected to be the same in both treatment arms so should not impact the relative treatment effect. At the first meeting, 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. The committee noted the stakeholder comment that the World Allergy Organization's suggestion of a 20% cut-off was based on expert opinion rather than evidence. At the second meeting, a clinical expert stated that they expected that a 15% improvement in rhinitis symptoms could be meaningful to patients because it may allow some improvement in sleep and more manageable symptoms throughout the day. The committee took into account 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. Overall the committee concluded that, based on the trial evidence, 12 SQ-HDM SLIT would show a clinical benefit for allergic rhinitis compared with established clinical management in the NHS, but the size of this benefit remained uncertain.

Allergic asthma

3.9 The primary outcome in MT-04 was time to first moderate or severe asthma exacerbation during the efficacy assessment phase, which was

during the period of mandated inhaled corticosteroid withdrawal. 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. 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 considered the company's survey of 46 clinical experts. This reported that 76% of experts stated that the clinical trial data supported improved allergic asthma control and 24% of experts said it 'maybe supports improved allergic asthma control'. A clinical expert at the committee meeting stated that the relative effect size was smaller than seen other asthma trials, such as those investigating biological treatments. The committee concluded that there was uncertainty in whether 12 SQ-HDM SLIT had a clinically meaningful effect compared with placebo in MT-04. 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 (where inhaled corticosteroids would not be stopped). Based on the trial evidence, the committee could not conclude that 12 SQ-HDM SLIT would show a meaningful clinical benefit for allergic asthma 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 company had provided additional observational data from several studies on allergy immunotherapy as supporting evidence on using house dust mite allergy immunotherapy. These studies included:

- REACT (Fritzsching et al. 2021), a German retrospective analysis of data from people included in a health insurance database who had treatment with allergy immunotherapy for allergic rhinitis with and without allergic asthma. The allergy immunotherapies included both sublingual and subcutaneous treatments for house dust mite, grass and tree allergies. Both the company and EAG noted that there were limitations with the observational evidence provided. These limitations included a lack of comparator arm, inclusion of allergy immunotherapy for sensitisation to other allergens, and inclusion of immunotherapy which was administered either subcutaneously or sublingually. A clinical expert at the second committee meeting also noted that REACT may have included a broader population than the group of people who would be expected to have treatment with SQ-HDM SLIT in NHS clinical practice. Also, the house dust mite extract included in the treatments in REACT may have been of variable quality, which would affect outcomes.
- RE-LY (unpublished data provided by company in response to consultation). This was a Danish and Swedish registry study that compared reduction in allergic rhinitis medicine over 5 years in people with allergic rhinitis with or without allergic asthma. The company provided data from a subgroup of people in this study who had 12 SQ-

HDM SLIT with a propensity matched control cohort. In RE-LY allergic rhinitis medicine prescriptions decreased in both the 12 SQ-HDM SLIT and control group, but decreased more in the 12 SQ-HDM SLIT group, and the difference increased over time.

- The committee noted that 12 HQ-HDM SLIT is already listed on some integrated care systems' formularies. The company also presented data from the British Society of Allergy and Clinical Immunology BRIT registry, which the company suggested showed a greater improvement in quality of life at 1 year than seen in MT-04 and MT-06. The EAG noted that this analysis was based on small numbers of people.

The committee concluded that the real-world evidence had limitations. But, this evidence supported what it heard from clinical experts and stakeholders at consultation that there was a benefit of 12 SQ-HDM SLIT for treating allergic rhinitis, although the size of that benefit remains unclear.

Adherence to treatment

3.11 In response to consultation on the draft guidance, the EAG noted a real-world evidence study by Pfaar et al. (2023). This study reported low levels of adherence to HDM SLIT use at 1 year (23% to 27%), and very low levels of adherence at 3 years (6% to 8%) in comparison with the 80% to 90% adherence at 12 to 18 months in the MT-04 and MT-06 trials. So the EAG said that there was uncertainty in the discontinuation rates for 12 SQ-HDM SLIT and the size and duration of treatment effect in people who do stop treatment. At the second meeting the clinical experts noted that Pfaar et al. was a German study in which people with milder rhinitis or asthma symptoms may have access to HDM SLIT of variable quality. The clinical experts stated that in NHS clinical practice they would expect people for whom medicine had not relieved symptoms adequately to be highly motivated to continue taking 12 SQ-HDM SLIT compared with people with milder symptoms. The clinical experts noted that adherence to standard symptom-relieving medicines can also be problematic and it is

part of the clinical management to encourage the continued use of daily medicines during follow-up visits. The committee heard that side effects of allergy immunotherapies tended to be in the first month of treatment. People would be monitored after a month and followed up multiple times within the first year, either in person or by phone. Overall, the clinical experts confirmed that the encouragement and retraining on how to use treatments in the NHS would be similar to that in the trials. The committee concluded that it was reasonable to expect that levels of adherence to treatment in NHS clinical practice would be similar to that seen in MT-04 and MT-06.

Economic model

Company's modelling approach

3.12 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. Both models compared 12 SQ-HDM SLIT taken alongside established clinical management with established clinical management alone. At the first committee meeting, the committee did not consider either model suitable for decision making. It said that the allergic asthma with allergic rhinitis model had more issues than the allergic rhinitis model. After reviewing the consultation comments and further analysis provided by the company, the committee were able to make a decision using the models (section 3.13 and 3.14).

Allergic rhinitis model

3.13 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 established clinical management people had in each health state was a blend of the treatments people with each allergic rhinitis severity would have in clinical practice. The EAG had the following concerns with the company's modelling approach:

- The model had a 1-year cycle length. So the company assumed an average level of disease severity throughout the year rather than potential fluctuations throughout the year.
- The model was informed by the MT-06 trial, which the EAG had noted had methodological limitations. Also, to estimate the proportion of people in each health state in the model the company had used a post-hoc analysis from MT-06, which added to the uncertainty.
- The company used data from the adult population in MT-06 and generalised this to young people (aged 12 to 17 years) to model the cost effectiveness for people 12 and over with house dust mite allergic rhinitis. This implicitly assumed that there was no difference in clinical effectiveness between adults and young people (aged 12 to 17 years). 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. But the EAG was unable to explore the impact of the difference in its critique.

At the first committee meeting the committee wanted to see more evidence to support the company's modelling approach for the allergic rhinitis population at this position in the treatment pathway. It also said the allergic rhinitis model should consider the costs and benefits of 12 SQ-HDM SLIT for the whole population for whom it is licenced, including people 12 to 17 years. In response to consultation, the company provided a scenario analysis with a starting age of 12 years and different utility values for the subgroup of young people (aged 12 to 17 years) from the P001 trial. The EAG was concerned that evidence of treatment effectiveness (that is, the modelled transition probabilities between health states) for young people 12 to 17 years with house dust

mite allergic rhinitis was not included in the modelled scenario. This scenario showed a greater increase in QALYs with 12 SQ-HDM SLIT compared with standard care than the company base case. A patient expert noted that 12 SQ-HDM SLIT may be particularly welcomed by young people who may prefer a once daily medicine that may reduce the frequency of using symptom-relieving medicines in public. The committee noted that although the company had provided data on the treatment-specific utility values for a population of young people, it had not updated the model to include clinical data from this group. The committee noted that adherence to treatment may be greater in young people to reduce the need to take symptomatic medicines. The committee concluded that it could make a decision for people aged 12 to 65 using the allergic rhinitis model. But, it would consider in its decision making how well the modelled results reflected the whole age range with allergic rhinitis who would be eligible for 12 SQ-HDM SLIT covered by the marketing authorisation.

Allergic asthma with rhinitis model

3.14 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. The established clinical management people had in each health state was a blend of the treatments people with each asthma severity would have in clinical practice. The EAG had the following concerns with the company's modelling approach:

- The model had a 1-year cycle length. So the company assumed an average level of asthma control throughout the year rather than potential fluctuations throughout the year.
- The model was informed by the MT-04 trial, which the EAG had noted had methodological limitations. Also, to estimate the proportion of

people in each health state in the model the company had used a post-hoc analysis from MT-04, which added to the uncertainty.

- The model did not explicitly model rhinitis outcomes.
- Asthma exacerbations were assumed to be the same across asthma control health states, which was implausible.
- The allergic asthma model did not include people with an ACQ score reflecting uncontrolled asthma, that is, 1.5 or more.

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. In response to consultation, the company explained that the primary objective of treatment for allergic asthma is disease management, and that stepping down of treatment is only considered once control is achieved. So, it did not update the allergic asthma with rhinitis model structure to allow stepping up and stepping down, but updated its model assumptions so that allergic asthma treatment costs were informed by asthma control level. The EAG noted that treatment costs by asthma control level was uncertain and that the company's update approach was not supported by any additional empirical evidence. The company's updated model also based the incidence of exacerbations by asthma control level. The EAG remained concerned that the incidence of exacerbations was based on data collected in the mandated inhaled corticosteroid withdrawal phase in MT-04 and so is not representative of clinical practice (see

section 3.7). The company included additional allergic rhinitis management costs in the model, based on distributions of management from MT-06. But the EAG noted that the model already included allergic rhinitis management costs based on distributions from a Delphi panel by the company. So, it said the company's updated model double counted these costs and did not address the committee's concerns that the model for people with allergic asthma with allergic rhinitis did not model outcomes for allergic rhinitis. The committee stated that the company had not updated the model structure as requested. However, it took into account the company's arguments and concluded that it could reach a decision based on the model, but would take into account the considerable structural uncertainty in its decision making.

Long-term effectiveness

3.15 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 (see section 3.10) 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 company also presented preliminary results from the RE-LY study as supportive evidence that the findings over 9 years in REACT were generalisable to 12 SQ-HDM SLIT (see section 3.10). The company said that this

supported that long-term outcomes for subcutaneous immunotherapy are likely to be at least generalisable to SLIT. The company also noted that the reduction in allergic rhinitis prescriptions increased over a 5-year period in RE-LY. The committee noted that that this data was from a subgroup of people in RE-LY who had 12 SQ-HDM SLIT, so was more directly relevant to the appraisal than REACT, which included a variety of HDM and other allergy immunotherapies against other allergens (grass and tree). Based on the evidence presented at the first meeting the EAG preferred to assume that from 2 to 10 years people stayed in the same health states in the 12 SQ-HDM SLIT arm, because REACT showed that the treatment effect was maintained rather than increased over time. The EAG considered that there was no evidence beyond 10 years so assumed that after 10 years people in the 12 SQ-HDM SLIT arm of the model 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 committee concluded that it was plausible that an allergen immunotherapy could have a persistent effect. Also, the committee concluded that it was plausible the treatment effect could improve after stopping treatment, because 12 SQ-HDM SLIT would accelerate the desensitisation that would be expected over time as people were exposed to HDM in their daily lives. The committee also stated that this conclusion was supported by RE-LY, which had shown a greater reduction in allergic rhinitis medicine over time. Also, it noted that the data from RE-LY was specific for 12 SQ-HDM SLIT but the duration and size of the benefit was uncertain. The committee concluded that the company's assumptions about long-term effectiveness were acceptable, but there was considerable remaining uncertainty that it would consider in its decision making.

Costs

Secondary resource use

3.16 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 in secondary care resource use 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 of secondary care resource use. Assuming a smaller reduction in secondary care costs in the 12 SQ-HDM SLIT arm had a large effect on the cost-effectiveness results. In response to consultation, the company presented evidence of reductions in allergic rhinitis prescriptions, hospitalisations and primary and secondary care visits for people having 12 SQ-HDM SLIT treatment based on the RE-LY study and the opinions of UK clinicians. Both the company and the EAG acknowledged that the key uncertainty was how much the treatment affected secondary healthcare resource use. The committee was concerned that the modelling assumptions might overestimate savings in secondary care costs of 12 SQ-HDM SLIT. The committee recalled that the company and clinical experts had explained that a package of follow-up care was typically needed to support adherence to allergy treatment, including 12 SQ-HDM SLIT. The committee also thought it was unlikely that people with severe

house dust mite allergic rhinitis would be discharged, as was implied by the larger reductions of secondary care resource use values applied by the company. So the committee preferred the EAG's relative reduction in secondary care resource use with 12 SQ-HDM SLIT compared with standard care (7.35% for people with allergic asthma with allergic rhinitis and 4.9% for people with allergic rhinitis only).

Modelling health-related quality of life

3.17 In its base case for both models, the company applied a treatment-specific approach to model utilities. This assigned a specific utility value to treatments which was the same irrespective of health state. For the allergic asthma with 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 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 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 control only. The committee recognised that allergic rhinitis in addition to asthma can affect health-related quality of life. So it initially accepted that this could be a valid approach to modelling health-related quality of life in the absence of a model that included the costs and benefits associated with allergic rhinitis, but it requested an updated model. The committee had also concluded

that in the updated models the utility values should be representative of the whole population within the marketing authorisation. The committee understood that the company did not update its allergic asthma with rhinitis model structure in response to consultation on the draft guidance. The committee also reflected on the need for strong evidence to support the use of treatment-specific utilities. It noted the EAG's concern that the treatment-specific utilities were assumed constant across asthma control levels, which lacked face validity. The committee agreed with the EAG that this was not clinically plausible. So, taking into account the company's rationale for its approach, the structural uncertainties, and the face validity of the utility values, the committee preferred to use the EAG's health-state specific utilities in the models.

Cost-effectiveness estimates

Committee's preferred assumptions

3.18 The committee noted that in both the allergic rhinitis and allergic asthma with allergic rhinitis models its preferred assumptions were:

- the company's assumptions about long-term effectiveness, that after 2 years there is a continued improvement in benefit to 10 years, with treatment waning from 15 years (section 3.15)
- the EAG's assumptions about the extent to which 12 SQ-HDM SLIT reduces secondary care resource costs (section 3.16)
- the EAG's approach of using health-state specific utility values rather than treatment-specific utility values.

In the allergic asthma model, for other assumptions that differed between the company and EAG but had less of an impact on the ICER, the committee preferred the EAG's more conservative approach which included:

- using data from MT-04 period 2 that did not include the mandated inhaled corticosteroid withdrawal to inform the model

- not modelling asthma exacerbations because data informing this in the company's base case came from the mandated inhaled corticosteroid withdrawal phase.

The EAG also included the costs of the biological treatments (omalizumab and tezepelimab), which could be follow-on treatments in this population. In the allergic asthma model the committee agreed with the EAG's corrections of the company base case, which included removing the double counting of allergic rhinitis costs.

Acceptable ICER

3.19 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £20,000 per QALY gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. But it will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, specifically from:

- the extent of clinical benefit of 12 SQ-HDM SLIT compared with standard NHS treatments in both the allergic rhinitis and allergic asthma with rhinitis populations
- the extent the structure of the model would reflect the treatment pathway and outcomes for people having standard care, particularly in the allergic asthma with rhinitis model
- whether the transition probabilities in the allergic rhinitis model based on data from people 18 to 65 years would be the same as the full population in the marketing authorisation (people 12 to 65 years), noting that young people may have a greater quality-of-life benefit with 12 SQ-HDM SLIT compared with adults
- the long-term assumptions that were based on clinical opinion and limitations of the real-world data used to support these assumptions.

So, the committee concluded that an acceptable ICER would be around £20,000 per QALY gained. Applying the committee's preferred assumptions resulted in an ICER of £18,126 per QALY gained for people with allergic rhinitis and an ICER of over £20,000 per QALY gained for allergic asthma with allergic rhinitis. The exact ICER cannot be reported here because of subsequent treatments for allergic asthma that have confidential prices. The committee concluded that 12 SQ-HDM SLIT was cost effective for treating allergic rhinitis, but not for treating allergic asthma.

Other factors

Equality

3.20 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

3.21 The committee recommended 12 SQ-HDM SLIT for persistent moderate to severe house dust mite allergic rhinitis not well controlled by symptom-relieving medicine in people 12 to 65 years, because it is cost effective in this group. The committee did not recommend 12 SQ-HDM SLIT for house dust mite allergic asthma not well controlled by inhaled corticosteroids and associated with mild to severe house dust mite allergic rhinitis in adults, because it is not cost effective in this group. 12 SQ-HDM SLIT is recommended specifically for people needing treatment for their persistent moderate to severe allergic rhinitis. Some of the eligible

population may also have allergic asthma, which would not prevent them having 12 SQ-HDM SLIT to treat their allergic rhinitis.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 90 days of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has allergic rhinitis and the healthcare professional responsible for their care thinks that 12 SQ-HDM SLIT is the right treatment, it should be available for use, in line with NICE's recommendations.

5 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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