Cost-effectiveness of HDM extract (Acarizax®) indicated in adult patients (18 to 65 years) with house dust mite allergic asthma not well controlled by inhaled corticosteroids and associated with mild to severe house dust mite allergic rhinitis.

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of HDM extract (Acarizax®). Following assessment of the Applicant's submission, the NCPE recommends that HDM extract (Acarizax®) not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the NCPE to carry out an evaluation of the Applicant's, ALK-Abelló, dossier of evidence House Dust Mite extract (Acarizax®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified. Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **February 2023**

Summary

In April 2022, ALK-Abelló submitted a dossier which investigated the clinical effectiveness, cost effectiveness and potential budget impact of house dust mite (HDM) extract (Acarizax®). Acarizax® is indicated in adult patients (18 to 65 years) with HDM allergic asthma not well controlled by inhaled corticosteroids (ICS) and associated with mild to severe HDM allergic rhinitis. Diagnosis of HDM allergic asthma should be confirmed by clinical history and a positive test of HDM sensitisation (skin prick test and/or specific IgE). Reimbursement of HDM extract is sought on the Community Drug Schemes.

HDM extract is an allergy immunotherapy. Allergy immunotherapy with allergen products is the repeated administration of allergens to allergic individuals with the purpose of modifying the immunological response to the allergen. The immune system is the target for the pharmacodynamic effect of allergy immunotherapy, but the complete and exact mechanism of action regarding the clinical effect is not fully understood.

HDM extract is taken as one oral lyophilisate, containing a dose of 12 SQ-HDM, once daily. International treatment guidelines refer to a treatment period of three years for allergy immunotherapy to achieve disease modification. If no improvement is observed during the first year of treatment, with HDM extract, there is no indication for continuing treatment.

HDM extract is an add-on therapy to standard of care (SoC). The basket of treatments which make up SoC include inhaled short-acting $beta_2$ agonists, ICS, corticosteroid/long-acting $beta_2$ agonist combination inhalers and leukotriene receptor antagonists. The comparator for this Health Technology Assessment is SoC alone.

1. Comparative effectiveness of HDM extract

The clinical efficacy of HDM extract in combination with SoC (HDM extract + SoC) compared with SoC alone was examined in the phase III, randomised, placebo-controlled, parallel group, double-blinded, multinational study MT-04. This trial included 834 adults with HDM allergic asthma not well controlled by ICS or combination products, and with HDM allergic rhinitis.

The trial had three phases. Period 1 (screening) lasted five to seven weeks and included screening and switching of all participants from their regular daily ICS to the equivalent daily dose of the ICS budesonide. Inhaled, short-acting $beta_2$ agonists were employed as reliever therapy. During Period 2 (treatment maintenance) eligible patients (N=834) were randomised 1:1:1 to one year of once daily treatment with 6 SQ-HDM sublingual tablets (n = 275), 12 SQ-HDM sublingual tablets (n = 282) or placebo (n = 277) in addition to ICS and short-acting $beta_2$ agonists. Only the 12 SQ-HDM tablets were subsequently licensed for use in Ireland. During Period 3 (ICS reduction/withdrawal), daily ICS dose was first reduced to 50% for three months (90 days) in all participants (herein referred to as the '50% ICS reduction period'), and subsequently withdrawn completely for an additional three months in those participants who did not experience an asthma exacerbation (i.e. a total ICS reduction/withdrawal period of 180 days). It was pre-specified that efficacy would be assessed during the entire six-months of Period 3.

Patient characteristics were generally balanced between groups. Overall, 52% of participants were male and the mean age was 33.4 years. The overall mean duration of allergic asthma was 13 years (standard deviation 11 years). Approximately one-third of the population was monosensitised to HDM, whereas one-third had three or more additional allergen sensitisations. The mean daily ICS use at randomization was 588µg of budesonide (standard deviation 252µg). An evaluation of the Global Initiative for Asthma control level showed that overall 72% of participants had partly controlled asthma and 28% of participants had uncontrolled asthma at randomisation. The primary endpoint was the time to first moderate or severe asthma exacerbation during Period 3.

The mean duration of treatment was 407 days and 425 days in the 12 SQ-HDM arm and placebo arms, respectively. HDM extract met its primary endpoint. After ICS dose reduction/withdrawal, 12 SQ-HDM reduced the time to moderate or severe asthma exacerbation compared with placebo (Hazard Ratio 0.69; 95% Confidence Interval 0.50 to 0.96, $p < 0.03$).

The major limitation of the MT-04 trial is that the comparator arm was not representative of clinical practice, due to the reduction and withdrawal of ICS during the efficacy assessment

period. As such, the MT-04 trial does not provide direct clinical evidence of an incremental benefit for HDM extract over SoC. Furthermore, there is no evidence on the long-term effectiveness of HDM extract, with the treatment duration in the trial being shorter than the standard course of allergy immunotherapy (three years).

2. Safety of HDM extract

In MT-04, 599 participants reported adverse events (AEs). The majority of all AEs were mild (n=1,387; 67%), 31% of AEs (n=640) were moderate and 3% (n=57) were severe. This pattern was similar across all groups; however, the number of patients with mild and moderate AEs was higher in the groups on HDM extract than in the placebo group. Among 28 patients (3%), 32 serious adverse events (SAEs) were reported; 11 patients (4%) with 12 SAEs were from the placebo group, 10 patients (4%) with 10 SAEs were from the 6 SQ-HDM and seven patients (2%) with 10 SAEs were from the 12 SQ-HDM group. Of the 32 SAEs, five were assessed as possibly treatment related (two patients from the placebo group, two patients from the 6 SQ-HDM group and one patient from the 12 SQ-HDM group).

The three most frequently reported treatment related adverse events were oral pruritus, mouth oedema, and throat irritation. No deaths occurred during the trial and there were no anaphylactic reactions, severe systemic allergic reactions, AEs requiring epinephrine, or local allergic reactions compromising the airways.

3. Cost effectiveness of HDM extract

Methods

The cost effectiveness of HDM extract + SoC versus SoC alone was investigated in a de-novo cost-utility model. The model was a cohort-level Markov model. The population in the model was in line with the licenced indication and demographics were based upon the MT-04 trial. The assumed duration of treatment with HDM extract was up to three years. The model had a lifetime horizon.

The model structure consisted of four health states, three of which measured levels of asthma control defined by the Global Initiative for Asthma criteria: ‘well controlled,’ ‘partially controlled’ and ‘uncontrolled,’ and a fourth absorbing state of ‘death’. Individuals

could experience asthma exacerbations at any time in the model, which were classified as either 'moderate' or 'severe.' Exacerbations were associated with dis-utilities and costs, which varied according to severity.

The treatment benefit of HDM extract consisted of an improvement in health-related quality of life and a reduction in healthcare costs arising from fewer moderate and severe asthma exacerbations. In the base case, no effect on long-term asthma control levels was applied. In the Applicant's base case, exacerbation rates in each treatment arm were informed by the first 90-days (i.e. the 50% ICS reduction period) of Period 3 of the MT 04 trial. The treatment effect was assumed to be maintained over the full three-year treatment period and for an additional six years following completion of treatment. Treatment waning was implemented after Year 9, with the treatment effect of HDM extract reducing by 20% annually until reaching null (i.e. SoC exacerbation rates) at Year 14.

The Review Group were concerned with the use of exacerbation rates from the 90-day '50% ICS reduction period':

- The analysis of efficacy during the '50% ICS reduction period' only does not appear to have been pre-specified
- Exacerbation rates actually decreased in both arms following 100% ICS withdrawal, compared with 50% ICS reduction. Therefore, restricting the analysis to the '50% ICS reduction period' may overestimate baseline (i.e. SoC) exacerbation rates.
- The use of the '50% ICS reduction period' gives a shorter follow-up period and lower event numbers (than in the pre-specified six-months of Period 3) resulting in less precise estimates of exacerbation rates
- The observed treatment effect of HDM extract was considerably lower during the second half of Period 3 for which there is no obvious explanation

With these considerations in mind, the Review Group concluded that there was a high risk that the use of the 90-day '50% ICS reduction period' resulted in a chance overestimation of the treatment effect of HDM extract. In the NCPE adjusted base case, exacerbation rates were therefore estimated based on the full (pre-specified) 180-day Period 3. The Review

Group highlight that neither efficacy period is representative of clinical practice due to ICS reduction and/or withdrawal, therefore generalisability of these exacerbation rates, particularly for the SoC arm, is unknown. In the NCPE adjusted base case no changes were made to the Applicant's assumptions regarding the duration and magnitude of treatment effectiveness in the long-term. Although this was identified as the main area of uncertainty in the model, there is currently no robust evidence on the long-term efficacy of HDM allergy immunotherapy in the treatment of HDM allergic asthma. Other changes made in the NCPE adjusted base case addressed costs and treatment effectiveness following early discontinuation, and the application of an age-related utility adjustment.

Results

In the NCPE-adjusted base case, HDM extract + SoC was associated with an incremental cost of €1,634 and an incremental quality-adjusted life year (QALY) of 0.01 resulting in an incremental cost-effectiveness ratio (ICER) of €146,573 per QALY.

Table 1 Cost-effectiveness results (NCPE adjusted base case)

Technology	Total Costs (€)	Total QALYs	Inc. Costs (€)	Inc. QALYs	ICER (€/QALY)
Deterministic					
HDM extract + SoC	14,999	18.33			
SoC alone	13,365	18.32	1,634	0.01	146,573

Inc.: incremental; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; HDM: house dust mite; SOC: standard of care
Note: figures in the table are rounded and calculations may not be directly replicable. In line with national HTA guidelines, a discount rate of 4% per annum is applied to both costs and QALYs.

Under the Applicant's base case assumptions, HDM extract + SoC was associated with a gain in QALYs and a reduction in costs relative to SoC alone, i.e. HDM extract was dominant

Table 2 Cost-effectiveness results (Applicant base case)

Technology	Total Costs (€)	Total QALYs	Inc. Costs (€)	Inc. QALYs	ICER (€/QALY)
Deterministic					
HDM extract + SoC	18,176	16.77			
SoC alone	19,044	16.74	-868	0.03	Dominant

Inc.: incremental; QALY: quality-adjusted life year; ICER: incremental cost-effectiveness ratio; HDM: house dust mite; SOC: standard of care
Note: figures in the table are rounded and calculations may not be directly replicable. In line with national HTA guidelines, a discount rate of 4% per annum is applied to both costs and QALYs.

In both the Applicant and NCPE-adjusted analyses, the probabilistic results were aligned with the respective deterministic results.

Sensitivity analysis

Under the NCPE adjusted base case the probabilities of cost-effectiveness at a willingness-to-pay threshold of €20,000 per QALY and €45,000 per QALY were 4% and 10%, respectively. Under the Applicant's assumptions, the probabilities of cost-effectiveness were 98% at the €20,000 per QALY threshold and 100% at the €45,000 per QALY threshold. The Review Group notes that none of these probabilities capture the uncertainty surrounding the duration of treatment effectiveness and should be interpreted with caution.

Under the NCPE-adjusted base case assumptions the Review Group estimate that a price reduction of approximately 52% would be required to achieve cost-effectiveness at the €45,000 per QALY threshold although this figure is highly sensitive to the assumptions made regarding long-term effectiveness

As the duration of treatment effectiveness of HDM extract following end-of-treatment was identified as a major area of uncertainty, the Review Group carried out scenario analyses in which the long-term effectiveness of HDM extract was adjusted. All scenario analyses were conducted on NCPE adjusted base case assumptions. In the most conservative scenario, where a full loss of treatment effect was assumed to occur immediately following treatment discontinuation, the ICER increases to €785,872 per QALY (incremental cost: €2,519, incremental QALYs: 0.003). At the other extreme, if the full treatment effect is maintained over a lifetime, HDM extract is dominant (incremental costs: -€237, incremental QALYs: 0.027).

4. Budget impact of HDM extract

The price to wholesaler for one pack (30 oral lyophilisates) of HDM extract is €78.67. The annual drug treatment cost per patient including pharmacy fees is €1,026.92 (applying a Framework Agreement of 7.75%). No value-added tax (VAT) is payable on HDM extract**.** Based on a treatment duration of three years, the Applicant predicts the cumulative number of patients per year for five years to be 3,045. The five-year cumulative gross budget impact is an estimated €2.23 million. HDM extract is an add-on therapy to SoC and will not be displacing any other treatments. Therefore, the gross budget impact is equal to the net budget impact. The Review Group note that the budget impact estimates assume all

patients attend and are tested for HDM sensitisation by a specialist. The rate of testing for HDM sensitisation is uncertain and so budget impact estimates are also uncertain. Furthermore, as HDM extract has a number of other licensed indications (including allergic rhinitis), patient numbers and budget impact could be much higher if the prescribing per indication is not appropriately managed.

5. Patient submissions

A patient organisation submission was received from the Asthma Society of Ireland.

6. Conclusion

The NCPE recommends that HDM extract (Acarizax®) for the treatment of adult patients (18 to 65 years) with house dust mite allergic asthma not well controlled by inhaled corticosteroids and associated with mild to severe house dust mite allergic rhinitis not be considered for reimbursement unless cost-effectiveness can be improved relative to existing treatments*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.