NICE National Institute for Health and Care Excellence

NICE guidance

Dupilumab for treating severe chronic rhinosinusitis with nasal polyps

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces TA648.

1 Recommendations

1.1 Dupilumab, as an add-on to intranasal corticosteroids, can be used as an option to treat severe chronic rhinosinusitis with nasal polyps in adults if:

- the condition is not controlled well enough by systemic corticosteroids or sinus surgery, and
- they have had at least 1 sinus surgery, and
- the 22-item sinonasal outcomes test (SNOT-22) score is at least 50, and
- the company provides it according to the commercial arrangement.

1.2 This recommendation is not intended to affect treatment with dupilumab 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.

What this means in practice

Dupilumab must be funded in the NHS in England for the condition and population in the recommendations, if it is considered the most suitable treatment option. Dupilumab must be funded in England within 90 days of final publication of this guidance.

There is enough evidence to show that dupilumab provides benefits and value for money, so it can be used routinely across the NHS in this population.

NICE has produced tools and resources to support the implementation of this guidance.

Why the committee made these recommendations

Usual treatment for severe chronic rhinosinusitis with nasal polyps that is not controlled well enough by systemic corticosteroids or sinus surgery, or both, includes further corticosteroids (intranasal and systemic) and further sinus surgery.

For this evaluation, the company asked for dupilumab to be considered only for a subgroup of people who have had at least 1 sinus surgery and who have a SNOT-22 score of at least 50. This does not include everyone who it is licensed for.

Clinical trial evidence suggests that dupilumab plus usual treatment reduces symptoms and nasal polyp size compared with placebo plus usual treatment in this subgroup. But there are uncertainties because the trials were not designed to specifically collect evidence for a subgroup with a SNOT-22 score of at least 50.

But, even with the uncertainties, the most likely cost-effectiveness estimates are within the range that NICE considers a cost-effective use of NHS resources. So, dupilumab can be used.

2 Information about dupilumab

Marketing authorisation indication

2.1 Dupilumab (Dupixent, Sanofi) is indicated 'as an add-on therapy with intranasal corticosteroids for the treatment of adults with severe CRSwNP (chronic rhinosinusitis with nasal polyposis) for whom therapy with systemic corticosteroids and/or surgery do not provide adequate disease control'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for dupilumab.

Price

2.3 Dupilumab costs £1,264.89 per pack of 2 prefilled pens or prefilled syringes (excluding VAT, BNF online accessed July 2025).

2.4 The company has a commercial arrangement. This makes dupilumab available to the NHS with a discount. The size of the discount is commercial in confidence.

Sustainability

2.5 For information, the Carbon Reduction Plan for UK carbon emissions is published on Sanofi's webpage on sustainability.

3 Committee discussion

The evaluation committee considered evidence submitted by Sanofi, 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.

Severe chronic rhinosinusitis with nasal polyps

3.1 Rhinosinusitis is inflammation of the nasal cavity and the sinuses. Chronic rhinosinusitis is when it lasts for longer than 12 weeks. Up to 30% of people with chronic rhinosinusitis also have nasal polyps, which are non-cancerous growths in the sinonasal passages. Symptoms can be chronic and debilitating, and include loss of smell and taste, a blocked and runny nose, facial pain, headache, snoring, obstructive sleep apnoea and fatigue. Symptoms may last many years. Severe chronic rhinosinusitis (CRS) with nasal polyps is defined as uncontrolled symptoms rated 8 to 10 on a visual analogue scale, and evidence of disease on endoscopy. The patient experts said the most important symptom was loss of smell, especially because it also affects taste. They said it reduces the pleasure in life and can also be dangerous because people cannot smell smoke or a gas leak. They described how the condition affected them physically and mentally. It worsens ability to sleep and socialise, and affects family and work life. They also described their frustration with how long it takes to get a diagnosis, and the delays in access to each step of the treatment pathway. In particular, they said people can remain symptomatic for several years before being able to have sinus surgery. The committee concluded that severe CRS with nasal polyps is a distressing condition with a substantial impact on people's lives.

Clinical management

Treatment options

3.2 There are no approved medicines specifically for severe CRS with nasal polyps in the UK and treatment aims to control symptoms only. The main treatment is

intranasal corticosteroids, which are used throughout the treatment pathway. Short-term oral (systemic) corticosteroids can be offered to treat acute exacerbations to reduce polyp size and relieve symptoms. If people still have symptoms, endoscopic sinus surgery to remove the polyps is an option. But the clinical experts noted this does not treat the underlying inflammation. They estimated that surgery will not resolve symptoms at all for about 10% of people, who continue to have severe disease immediately after surgery. Published literature also suggests that nearly half of people have symptoms again within a year of sinus surgery (Lourijsen et al. 2022). The polyps can also regrow. The clinical experts said that people who got no benefit from surgery have the greatest need for another treatment option. People can have surgery again (revision surgery), and some have it repeatedly. The clinical experts said about 5% of people have multiple operations; published literature suggests around 8% have at least 2. The patient experts described their frustration with the available treatments because, after surgery and corticosteroids, there are no more options. Their only option is to try the same failed treatments again. The patient experts explained that it can take about 3 months to recover from sinus surgery, that it might be effective for only a short time, and that some people need corticosteroids again soon after. They noted the serious side effects associated with oral corticosteroids, and how hard it is knowing that they are risking their overall health to relieve their symptoms. The clinical experts said that repeated courses of oral corticosteroids are associated with obesity, hypertension, cataracts and osteoporosis. The committee acknowledged the lack of effective treatment options for severe CRS with nasal polyps and concluded that there was a need for an effective, targeted treatment.

Population

3.3 After draft guidance consultation, the company changed its positioning of dupilumab for people with severe CRS with nasal polyps. This was changed from the original population defined as 'uncontrolled CRS with nasal polyps and at least 1 sinus surgery' to an updated population defined as 'uncontrolled CRS with nasal polyps and at least 1 sinus surgery and a 22-item sinonasal outcomes test (SNOT-22) score of at least 50'. The original definition of severe disease came from the 2020 European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) criteria, based on the level of disease control. The updated definition after

consultation was based on advice the company received from healthcare professionals that disease severity can also be graded by SNOT-22 score. It cited a publication by Toma and Hopkins (2016), which proposed a definition of severe CRS with nasal polyps based on a SNOT-22 score of over 50. The company also noted that, in Europe, severe CRS with nasal polyps is generally classified as a SNOT-22 score of at least 50. It highlighted a phase 4 real-world study, DUPIREAL (De Corso et al. 2023), in people with severe disease, which used a SNOT-22 score of at least 50 as an inclusion criterion. Using the new definition of severe disease removed around half of the population from the key clinical trials (SINUS-24 and SINUS-52, see section 3.5) in the new analyses submitted by the company after consultation. The EAG said its clinical experts agreed that a SNOT-22 score of at least 50 can be used to indicate severe disease but they added that it should be used alongside EPOS criteria. The EAG noted that treatment groups in the SINUS trials were not stratified by SNOT-22 score. So updating the definition of the population breaks trial randomisation. This risks introducing bias into the results, that is, unknown imbalances in the groups that could affect comparative effectiveness. The EAG said that, while population demographics were similar between the original and updated populations, measures of disease severity were higher (as would be expected) in the updated population. In the baseline characteristics of the updated population, there was more systemic corticosteroid use in the previous 2 years, higher SNOT-22 scores, and a higher proportion of people who also had asthma. The clinical expert, who co-authored Toma and Hopkins (2016), explained that SNOT-22 is widely used in NHS Ear, Nose and Throat (ENT) services. They noted that scores are generally stable over time in people whose condition is unchanged, with only small variations of 1 or 2 points between assessments. They agreed with restricting the population by adding the criterion of a SNOT-22 score of at least 50, explaining that ENT healthcare professionals want to ensure treatment is available for the most severely affected people. The patient experts also agreed that dupilumab should be aimed at people with a clear unmet need who have the most severe symptoms. The committee accepted that it was reasonable to update the population to include only people with more severe disease, defined as uncontrolled CRS with nasal polyps and at least 1 sinus surgery and a SNOT-22 score of at least 50. It took into account the clinical and patient experts' advice that these were most in need of a new treatment option. But, it concluded that breaking randomisation in this way increased uncertainty in the trial results for the updated population. This is because it could introduce bias through

unidentified differences in the populations.

Comparators

3.4 The company's comparator was established clinical management, defined as a daily intranasal corticosteroid (the company used mometasone furoate in the key clinical trials), and oral corticosteroids and revision surgery as needed. The clinical experts agreed the comparator was appropriate. The committee concluded that, for this evaluation, it was appropriate to compare dupilumab plus established clinical management (corticosteroids and sinus surgery) with established clinical management alone, for people with severe CRS with nasal polyps who have had at least 1 surgery and have a SNOT-22 score of at least 50.

Clinical effectiveness

Key clinical trials: SINUS-24 and SINUS-52

3.5 Dupilumab 300 mg once every 2 weeks plus established clinical management was compared with placebo plus established clinical management in 2 trials: SINUS-24 (n=276; 24 weeks) and SINUS-52 (n=448; 52 weeks). Both were international, phase 3, placebo-controlled, double-blind, randomised trials in adults with previously treated severe CRS with nasal polyps. The primary outcome was change from baseline in bilateral nasal polyp score (NPS) and nasal congestion score at 24 weeks. Secondary outcomes included changes in health-related quality of life measured on the SNOT-22 scale. Both trials included people who had previous sinus surgery and people who had not. The company's submission focused on the prior surgery subgroup. As noted in section 3.3, after draft guidance consultation, the company updated the population so that the prior surgery subgroup only included people with a SNOT-22 score of at least 50. Pooled results at 24 weeks from SINUS-24 and SINUS-52 showed that, in this subgroup, dupilumab plus established clinical management significantly reduced polyps and improved SNOT-22 scores compared with placebo plus established clinical management. The company defined minimum clinically important differences as 1 point for NPS (based on a post-hoc pooled analysis of the SINUS

data) and 8.9 points for SNOT-22 (clinically validated). The bilateral NPS for people on dupilumab plus established clinical management was 2.42 points lower than for people on placebo plus established clinical management (least squares mean; 95% confidence interval -2.82 to -2.02, p<0.0001). SNOT-22 results at 24 weeks were significantly better for dupilumab plus established clinical management than for placebo plus established clinical management, with a reduction of 27.11 points (least squares mean; 95% CI -32.31 to -21.90, p<0.0001). The committee concluded that dupilumab is an effective treatment for severe CRS with nasal polyps in people who have had at least 1 previous surgery and who have a SNOT-22 score of at least 50. But it recalled the potential for bias introduced by breaking trial randomisation (see section 3.3), and concluded that there was uncertainty in the results.

Longer-term data: AROMA

3.6 Longer-term data for dupilumab was available from AROMA, an ongoing 36-month observational, open-label, single-arm registry study (n=639 at 2 years). People in the study were prescribed dupilumab in line with local clinical practice. Primary outcomes included nasal congestion score and SNOT-22 score. The lack of comparator treatment meant that this data could not be incorporated into the pooled analysis with the SINUS trials. Only about a fifth of people (19.1%) had previous surgery for nasal polyps in the year before baseline, which did not align with the company's base-case population (uncontrolled CRS with nasal polyps and at least 1 sinus surgery and a SNOT-22 score of at least 50). For the registry analysis set (RAS) population (that is, people who had and had not had surgery), the mean change from baseline in SNOT-22 score was -27.3 points (standard deviation 22.61) at 12 months and -18.0 points (standard deviation 16.63) at 24 months. After draft guidance consultation, the company updated its definition of severe CRS with nasal polyps (see section 3.3) but did not provide results for the updated population in AROMA. The EAG said that the results for the RAS population suggested a sustained benefit of dupilumab for health-related quality of life throughout the first year of treatment. It noted the smaller mean change from baseline at 24 months compared with 12 months suggested the treatment effect may start to wane after a year. But, because there was no comparator arm, it was not clear if benefits with established clinical management also decline. The company clarified that because AROMA is an ongoing registry

study, only 29 people had completed 24 months of follow up and some would also have missing data. The committee concluded that the data for dupilumab's relative treatment effectiveness beyond 1 year in people with severe CRS with nasal polyps who have had at least 1 sinus surgery and a SNOT-22 score of at least 50 was uncertain. A potential waning of treatment effect could not be excluded. This is because of the lack of a comparator arm in AROMA and because the population does not align with the company's base case.

Economic model

Company's modelling approach

3.7 The company's model had 2 parts, a cohort-level decision tree for the first year and a longer-term Markov model after year 1. In the decision tree, response was assessed at 24 weeks and 52 weeks. The need for oral corticosteroids or revision surgery (rescue therapy) was classified as non-response. After draft guidance consultation, the company changed its definition of response (see section 3.8). Responders continued dupilumab but non-responders stopped treatment. Response and need for surgery determined the health state in which people entered the Markov model. The Markov model had a 1-year cycle length and 4 health states based on disease control: controlled, inadequately controlled (a temporary state for 1 cycle to capture decline in health-related quality of life before the condition becomes uncontrolled), post-op controlled and uncontrolled. People could move from the uncontrolled or inadequately controlled health states to the post-op controlled health state after revision surgery. The committee noted that using a single health state for all uncontrolled disease made it hard to estimate revision surgery rates. It also complicated transition probabilities between the post-op controlled and uncontrolled states (see section 3.11). The EAG was mainly satisfied with the model structure. But it noted that the 1-year cycle length was not in line with dupilumab administration (every 2 weeks), so may not capture the timings of important clinical events. The committee noted that the model cycle length was long but concluded that the model structure was adequate for decision making.

Updated response criteria

3.8 In its original submission, the company model used the following definition of response: a reduction from baseline of at least 1 point in NPS and at least 8.9 points in SNOT-22. To align with the updated population after draft guidance consultation (see section 3.3), the company also updated its definition of response to: a reduction from baseline of at least 1 point in NPS and either a SNOT-22 score under 50 or a reduction of at least 8.9 points. The EAG had concerns about the updated response criteria. Firstly, the impact in the economic model was not clear. This was because the company's response to draft guidance consultation compared results using the original response criteria in the original population and results using the updated response criteria in the updated population. The EAG said it would have been more appropriate to compare the original and updated response criteria in the updated population so that it would be clear how many more responders were identified. Secondly, its clinical experts pointed out that using a SNOT-22 score of under 50 as a response criterion meant that someone with a baseline score of 51 would only need a 2-point reduction to be classified as a responder. They said that the reduction of 8.9 points was more important, aligning with the minimum clinically important difference identified in the original company submission. The clinical expert said they had some concerns around a response being defined as a small improvement that brings the SNOT-22 score to just under 50, and that this would not be a meaningful change. They said they agreed with the updated population (see section 3.3) but preferred the original response criteria. They said the aim of treatment was to achieve a very low SNOT-22 score – as near to normal as possible. The patient experts agreed, emphasising that the change needed to be meaningful from a patient perspective. The company noted that a 1-point improvement in NPS was needed as well as a change in SNOT-22 score. It suggested it was clinically implausible for someone to have a meaningful improvement in NPS without a corresponding improvement in SNOT-22 score. The company also noted that only 1 patient in the full analysis set of the SINUS trials was affected by the change in response criteria (that is, was now classified as a responder despite having an improvement in SNOT-22 score of less than 8.9). In this case, their SNOT-22 score reduced by 8 points, that is, 1 point short of the 8.9-point minimally clinically important difference. The committee noted that, in individuals, the change in SNOT-22 score would need to be at least 9 points, because the scale scores are whole numbers. It concluded that it

preferred the original response criteria, defined as a reduction from baseline of at least 1 point in NPS and at least 8.9 points in SNOT-22 score. This was because of concerns someone could be classified as having a response with only a small change in SNOT-22 score, which would not be a meaningful change in symptoms.

Treatment effect in year 1 of the model

3.9 Treatment effect in the first year of the model (the decision tree) used pooled response data, based on NPS and SNOT-22 scores from the SINUS trials. But, in the company's submission, clinical effectiveness was assessed using NPS and nasal congestion scores. The EAG said that using different outcomes to indicate treatment response could result in the clinical and economic analyses having different estimates of the relative effectiveness of dupilumab plus established clinical management. The EAG used the company's analysis in its base case but explored using only SNOT-22 results for response in a scenario. The clinical experts said that both measures were important because SNOT-22 measured symptoms that were important to people with the condition, while the NPS provided an objective measure. The committee noted the EAG's concerns but took into account the clinical experts' views on the most appropriate response measures. The committee recalled that the company updated its response criteria after draft guidance consultation, but the committee preferred the original response criteria (see section 3.8), which defined response as a reduction of at least 1 point in NPS and at least 8.9 points in SNOT-22 score. The EAG explained that the original response criteria could not be applied to the updated population (defined by the additional criterion of a SNOT-22 score of at least 50) because the necessary data was not available. To explore the impact of using the original response criteria, the EAG provided a scenario analysis using responder rates derived from the original criteria and the original population. These rates were then applied in the model for the updated population. The committee agreed that capturing both quality of life using SNOT-22 and an objective measure from the NPS were important to robustly assess response. It would have preferred to see the original response criteria applied directly to the updated population, but acknowledged that this was not possible. So it concluded that the most appropriate assumption for the treatment effect in the first year was to use responder rates derived from the original response criteria and the original population, applied in the updated model.

Treatment effect from year 2 onwards in the model

3.10 From year 2 onwards (the Markov part of the economic model) the company's model used AROMA discontinuation rates to estimate transitions from the controlled to inadequately controlled health states for dupilumab. Transitions for the established clinical management alone arm were based on extrapolated SINUS data. The EAG said this introduced uncertainty because the trials differed in design and eligible population (uncontrolled CRS with nasal polyps and at least 1 sinus surgery and a SNOT-22 score of at least 50; see section 3.6), and AROMA only reported SNOT-22 (whereas the first-year decision tree model used both NPS and SNOT-22). The EAG said it was inconsistent to use 2 different approaches for the 2 model arms. It said that if AROMA data was used to inform treatment effect beyond 1 year, it should be formally matched to the SINUS trials. After draft guidance consultation, the company reweighted the AROMA population using propensity scores to match the SINUS intention to treat (ITT) population, based on prior systemic corticosteroid use, NSAID-exacerbated respiratory disease, nasal congestion score and SNOT-22 score. The EAG noted that, after adjustment, baseline characteristics were broadly similar to the SINUS trials, although some differences remained, for example, ethnicity. It had some concerns about the methodology used for the matching exercise. Lack of NPS data in AROMA meant disease severity may not have been fully comparable. The EAG's clinical experts said that nasal congestion score, which was used instead, is more variable and less commonly used in clinical practice. Another concern of the EAG's was that matching was done to the SINUS ITT population, not the company's updated 'severe' population used in the base case, which may create inconsistencies. The company did not provide reweighted SNOT-22 results, limiting checks on comparability. In the dupilumab arm, the company used the matched AROMA dataset to classify responders up to 36 months based only on SNOT-22 score (because NPS was not available). Few people remained at later time points (only 6 people at 24 months, all responders), so the company fitted a linear trendline to estimate loss of response, combined with an annual discontinuation rate based on AROMA discontinuations. These assumptions informed long-term transition probabilities in the model. The EAG highlighted several concerns:

- response was defined using the company's updated response criteria (see section 3.8), which the EAG did not agree with

- use of SNOT-22 score alone (without NPS) differed from the first year of the model
- the linear trendline from year 2 onwards included baseline to 12-month data from AROMA; in the draft guidance the committee said this should not be used because SINUS data was used for year 1 of the model
- possible errors in converting discontinuation rates to probabilities.

After draft guidance consultation, the company also changed the transition rate for established clinical management from the controlled to inadequately controlled health state to 42.8%. This was to match the rate of loss of response after surgery (see section 3.11), which it said was a more conservative approach than used previously. The EAG noted the company did not provide an updated matched AROMA analysis using the original response criteria. The EAG considered both the AROMA-based dupilumab estimates and established clinical management assumptions to be highly uncertain. But, it accepted the company's approach for the updated base case, although it preferred an adjusted trendline to estimate dupilumab loss of response, excluding the baseline to 12-month data from AROMA. The EAG noted that alternative assumptions modestly increased the incremental cost-effectiveness ratio (ICER). The clinical expert said the updated response rates were plausible, although conservative. The committee thought that the company's approach seemed overly simplistic and queried why alternative approaches had not been taken. The company explained that it had explored alternatives, such as an exponential model, but the high level of response meant it could not be fitted appropriately. The committee noted additional analysis to account for competing risks could have been done. It thought that both the company's and EAG's approaches were simplistic and uncertain. The committee recalled the matched AROMA analysis did not use the original response criteria which increased the uncertainty. But it concluded the overall approach was suitable for decision making and that it preferred the EAG's approach of excluding the first 12 months of AROMA data from the trendline.

Transition probabilities between the post-op controlled and uncontrolled health states

3.11 The company's model assumed that people could either remain in the post-op controlled health state, or move to the uncontrolled state if their symptoms returned, at a rate of 42.8% per year. This estimate was derived from Benson et al. (2023), which found that 17% of people needed a third surgery within 2.4 years. The company's clinical experts advised that people typically wait around 2 years for revision surgery, and that symptoms return quickly in 40% to 50% of people. Adjusting for the waiting time and working backward from the study data produced the 42.8% figure. The company's model also assumed people in the uncontrolled health state could move back to the post-op controlled health state. At the first committee meeting, the rate was 15.1% per year (calculated from Benson et al.), which the EAG corrected to 14.8% after identifying a calculation error. This probability reflects the annual chance of revision surgery for everyone in the uncontrolled health state. This includes those on medical treatment, those whose symptoms had returned after surgery, and those ineligible or unwilling to have surgery. The EAG's clinical experts noted that rates of loss of control and revision surgery varied. In a scenario analysis, the EAG reduced the waiting time for surgery from 2 years to 1 year, which reduced the transition probability for moving from the post-op controlled to the uncontrolled health state to 12.1%. This increased the ICER considerably. The clinical experts confirmed that a 2-year waiting time was likely, given the referral time to an ENT specialist (about 12 months), surgery waiting list (at least 12 months) and potential wait for a CT scan. They also said that a rate of 42.8% per year for symptoms to return after surgery was reasonable. SINUS UK provided evidence from a survey of 51 people that showed that about half had their symptoms return within 6 months of surgery. The clinical experts also noted that the polyps regrow within 6 months in about a third of people. The EAG said it had concerns about how the transition probabilities had been calculated for the full loop of this part of the model; that is, from the post-op controlled to uncontrolled health state, and from the uncontrolled to post-op controlled health state after revision surgery. It said it was not clear how or why the data had been chosen to calculate it.

After draft guidance consultation, the company provided further detail on its calculations. It maintained its transition rate of 42.8% for the post-op controlled

to uncontrolled health state. But, it updated the annual rate of revision surgery to 7.1% from 14.8% using an updated extrapolation of the mean rate of surgery from Benson et al. The EAG corrected the company's transition rate from the post-op controlled to uncontrolled health state to 37.2% (from 42.8%) because it said the company had incorrectly converted the probability in its calculation to an annual probability. It was unable to verify the company's calculation for the transition probabilities. But it provided an alternative analysis of the Kaplan–Meier data from Benson et al., based on 14.5% having a third surgery 3 years after the second and assuming a 2-year waiting time. The EAG's transition rates were 15% from the post-op controlled to uncontrolled health state and 39.4% from the uncontrolled to post-op controlled health state. The clinical expert said that the company's transition rate of 42.8% for loss of control was in line with evidence from the Netherlands that, in clinical practice, symptoms return within 12 months of surgery in around 40% of people. They said that 14.5% of people having a third surgery 3 years after the second was plausible and reflects clinical practice. The company said that its 7.1% transition rate was for the whole uncontrolled health state, including people not waiting for surgery. It said that the EAG's transition rate was implausible because it assumed that everyone with uncontrolled severe CRS with nasal polyps was on the waiting list for surgery, whereas many would not be. The clinical expert explained that the annual rate of revision surgery is low, but they would not expect it to be as low as 7%. Patient experts said that it was reasonable to assume that not everyone in the uncontrolled health state would go on to have surgery. They explained that some people who had already had 2 surgeries would choose not to have another, and said the company's figures were more realistic. They added that the EAG's estimates did not look plausible because they suggested the probability of having surgery was higher than the probability of symptoms returning.

The committee discussed the calculations used to derive the transition rates from the post-op controlled to uncontrolled health state and from the uncontrolled to post-op controlled health state. It took into account the face validity of the figures, as discussed by clinical and patient experts. The committee considered that both the company's and EAG's estimates for the transition probabilities were extremely uncertain and did not align with clinical expectations, so were not appropriate for decision making. It thought that the company's transition probabilities were more in line with the views of the clinical and patient experts but were not mathematically correct. This was because the company did not use

valid methods to estimate event rates. It did not account for the time at risk for people who did not have the event in the denominators of the event rate calculations. In addition, the committee noted that applying the company's assumptions did not result in a figure of 14.5% having a third surgery at 3 years, from Benson et al. The committee thought that the EAG's approach was mathematically correct, and resulted in 14.5% having a third surgery at 3 years. But the transition probabilities it derived were less closely aligned with clinical and patient experts' opinions. The committee thought that the most reliable data presented was the estimate of 14.5% of people having a third surgery 3 years after the second, from Benson et al. This was because it was based on real-world evidence from UK patients. It considered that any calculation of the transition probabilities needed to be based on this figure. The committee was aware of a randomised controlled trial that compared endoscopic sinus surgery plus medical treatment with medical treatment alone in people with CRS with nasal polyps (Lourijsen et al. 2022). This paper reported that 12 months after surgery, 46.0% of people had uncontrolled CRS despite surgery. It also used a minimal clinically important difference of 9 points on the SNOT-22 scale, in line with the committee-accepted response criteria (see section 3.8). The committee considered that it was more appropriate to use the figure of 46.0% from Lourijsen et al. for the transition probability from the post-op controlled to uncontrolled health state. This was because it was evidence based. It also removed the need to assume a 2-year waiting list for surgery, which had previously been required in the EAG and company approaches, and which increased uncertainty because it substantially changed the result depending upon how it was applied. The committee noted that the rate of loss of control in the study was not constant and the rate of 46.0% was likely to be an overestimate, and may favour dupilumab. The committee noted it was possible to calculate a transition probability from the uncontrolled to post-op controlled health state by using both the:

- 14.5% figure from Benson et al. for the proportion of people having surgery at 3 years
- 46.0% figure from Lourijsen et al. for the proportion of people who transition from the post-op controlled to uncontrolled health state in the year after surgery.

This resulted in an estimate of 13.1% for the proportion of people transitioning

from the uncontrolled to post-op controlled health state. The committee noted the resulting transition probabilities aligned with the 14.5% figure from Benson et al., and with clinical and patient expert feedback that the probability of having surgery was lower than the probability of symptoms returning after surgery.

The committee noted the high level of uncertainty associated with the transition probabilities used in the model. It noted that the rate of loss of control from Lourijsen et al. was not constant and it would have preferred to account for the time varying nature of the probability. Based on the transition probabilities presented, it concluded that the following transitions were most appropriate for decision making:

- 46.0% from the post-op controlled to uncontrolled health state
- 13.1% from the uncontrolled to post-op controlled health state.

The committee chose these because they were based on evidence from a randomised controlled trial in people with CRS with nasal polyps, aligned with data from Benson et al., and reflected the experience of the clinical and patient experts. However, the committee emphasised that these transition probabilities were still associated with considerable uncertainty and limitations in the available evidence. It noted that the estimates were based on the best available data and expert opinion, but that more robust, prospective data would have been preferred to inform these parameters. The committee concluded that the approach taken in this case was not optimal, and that future evaluations should seek to use more clearly validated and transparently derived transition probabilities wherever possible.

Utility values

Source of utility values

3.12 Although the company collected health-related quality of life in the SINUS trials using the EQ-5D (NICE's reference case), it did not use this data to inform health state utility values in its original base case model. Instead, it used SNOT-22 data

from the SINUS trials mapped to EQ-5D. The company said that this was because the EQ-5D values collected in the trial were not plausible because, for example, responders at week 52 had a higher score than the UK general population. It also said the EQ-5D was not good at capturing quality of life for people with severe CRS with nasal polyps, particularly around loss of smell and poor sleep. The company said the EQ-5D had a 'ceiling effect' in this population. It noted that a quarter of people in the trial with severe uncontrolled CRS with nasal polyps reported a 'perfect' health state with the EQ-5D, so it was not possible to capture any benefit for them. It added that its clinical experts agreed that the SNOT-22 values looked more plausible than the EQ-5D values. The EAG noted that it was common for utility values to be higher in clinical trials than in real life. It noted that it was standard practice to adjust for this by capping the data at general population values and maintaining the relative difference between health states. The EAG said that using SNOT-22 had not been justified adequately. It noted that NICE's technology appraisal and highly specialised technologies guidance manual says that varying from EQ-5D must be supported by peer-reviewed evidence, and if the EQ-5D does not capture health-related quality of life in CRS with nasal polyps well enough, using an alternative generic preference-based measure is preferred. Mapping SNOT-22 to EQ-5D does not resolve this issue if EQ-5D itself is unsuitable. The EAG noted issues with the model used to map SNOT-22 to EQ-5D (Crump et al. 2017). Crump et al. used 3 regression models to estimate EQ-5D-3L utility values as a function of SNOT-22 items. Models 2 and 3 implausibly suggested that loss of smell and poor sleep improved quality of life. The EAG said that model 1, which the company chose, has the same issue, but the relationship is not as obvious because these symptoms are combined with others, like facial pain and pressure. It also questioned its generalisability, because the original data came from people waiting for surgery, not representing other health states. The EAG chose to use EQ-5D data from the SINUS trial in its base case, with utility values capped at general population age- and sex-matched utility values, and with proportional differences between health states retained. After draft guidance consultation, the company provided updated utilities based on the EQ-5D from the SINUS trials in the updated population (see section 3.3). It did not cap the values because it said they were now more plausible because they were from people with more severe symptoms. The utilities were 0.88 (population norm, 0.87) for controlled disease and 0.70 for uncontrolled disease. Patient experts agreed that the updated values more appropriately reflected their experience. The EAG agreed the company's updated

utility values were more appropriate, but capped them in its base case. The committee concluded that the updated utility values based on the EQ-5D from the SINUS trials in the updated population were more plausible. It also concluded that the utility values should be capped because it was not plausible for the utility for people with controlled CRS with nasal polyps to be higher than the population norm.

Utility gain from revision surgery

3.13 The company's original base case applied a utility gain from revision surgery of 0.051. This was sourced from Soler et al. (2011). The EAG noted that the paper derived utility values using the Short-Form 6D (SF-6D), and used data which was relatively out of date, from 2004 to 2009. The EAG preferred to use a value of 0.08 from Remenschneider et al. (2015) in its base case because it derived values from the EQ-5D, in line with NICE's reference case, and used more recent data from 2011 to 2012. After draft guidance consultation, the company used a utility gain of 0.064 from Tashman et al. (2024). It said this was a better source because it was a larger study with a longer follow up and used the EQ-5D. The EAG agreed. The committee concluded that Tashman et al. was the most appropriate source for the revision surgery utility gain.

Adherence

3.14 In its original submission, the company model used the adherence rate (that is, the extent to which people keep taking dupilumab in the way it was prescribed) from the pooled SINUS trials of 99.3%. After draft guidance consultation, it changed to using UK Sanofi homecare data and using a lower adherence rate. This was based on the average adherence rate for dupilumab in atopic dermatitis and asthma. It used this to estimate adherence over the entire model period (the exact number is considered confidential by the company so cannot be reported here). The company presented evidence from SINUS-52 suggesting that reducing the dose of dupilumab (to every 4 weeks after week 24) does not affect its effectiveness. Based on this, it applied a lower adherence rate after week 24. The EAG preferred to use the SINUS adherence rate in the first year, because SINUS data was also informing efficacy in that time period, and the asthma-alone

adherence rate from year 2 onwards (which was higher than the average for atopic dermatitis and asthma). The patient experts explained that adherence was likely to be high for people with severe CRS with nasal polyps who had already had 1 surgery and a SNOT-22 score of over 50. This is because if dupilumab worked for them they would continue taking it. The company argued that dupilumab in asthma had a very high adherence rate because of the condition's mortality risk, which was not the case for severe CRS with nasal polyps. The committee took into account the patient experts' advice that people with severe CRS with nasal polyps were likely to want to keep taking dupilumab if it worked for them. It agreed that it was logical to use adherence data from the SINUS trials for the first year of the model because that was also the source of the efficacy data. So it concluded it preferred the EAG's approach to adherence.

Other factors

Equality

3.15 The committee noted issues raised during scoping around variable access to services because of geographic location. It was also noted during scoping that people with comorbidities may not be able to take corticosteroids or have surgery, so would be excluded from the licensed population. Some stakeholders suggested that recommending dupilumab was likely to reduce inequalities by providing access to a targeted biological treatment for people with severe CRS with nasal polyps, which has already been recommended by NICE for other chronic type 2 inflammatory conditions such as severe asthma and atopic dermatitis. Because its recommendations do not have a different impact on people protected by the equality legislation than on the wider population, the committee agreed that these were not potential equality issues.

Uncaptured benefits

3.16 The committee considered whether there were any uncaptured benefits of dupilumab. It noted the company's and clinical and patient experts' concerns about the EQ-5D's lack of sensitivity in measuring health-related quality of life in

people with severe CRS with nasal polyps. It also noted the potential for dupilumab to reduce the need for oral corticosteroids and NHS surgery waiting lists. It concluded that some benefits of dupilumab may not have been captured in the quality-adjusted life-year (QALY) calculation.

Cost-effectiveness estimates

Acceptable ICER

3.17 NICE's technology appraisal and highly specialised technologies guidance manual 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 recalled the potential uncaptured benefits related to the lack of sensitivity of the EQ-5D in severe CRS with nasal polyps, and the potential for dupilumab to reduce the need for oral corticosteroids (see section 3.16). But the committee also noted the high level of uncertainty, specifically around the:

- potential for bias introduced into the SINUS results from changing the definition of 'severe' in the population and breaking trial randomisation (see section 3.3)
- updated definition of treatment response (see section 3.8)
- data used to estimate treatment effectiveness from year 2 in the model, including the methods used to match the AROMA trials to the pooled SINUS trials (see section 3.10)
- transition probabilities in the model for people moving from the post-op controlled to the uncontrolled health state and from the uncontrolled to post-op controlled health state (see section 3.11).

So, the committee concluded that an acceptable ICER would be around the middle of the range NICE considers a cost-effective use of NHS resources

(£20,000 to £30,000 per QALY gained).

The committee's preferred assumptions and cost-effectiveness estimate

3.18 The committee's preferred model assumptions were:

- the population of severe CRS with nasal polyps defined as uncontrolled disease, at least 1 sinus surgery, and a SNOT-22 score of at least 50 (see section 3.3)
- response defined as a reduction from baseline of at least 1 point in NPS and at least 8.9 points (9 points per individual) in SNOT-22 score (see section 3.8)
- treatment effect beyond 1 year based on AROMA data formally matched to the SINUS trials using a linear trendline to estimate loss of response that excludes the first year of AROMA data (see section 3.10)
- transition probabilities of 46.0% from the post-op controlled to uncontrolled health state and 13.1% from the uncontrolled to post-op controlled health state (see section 3.11)
- capped utility values based on EQ-5D data from the SINUS trials (see section 3.12)
- a utility gain from revision surgery (based on Tashman et al. 2024; see section 3.13)
- adherence rates for dupilumab from the SINUS trials in the first year and from Sanofi homecare data for asthma from year 2 onwards (see section 3.14).

  Based on these assumptions, the committee's preferred probabilistic ICER was £24,846 per QALY gained.

Conclusion

3.19 Using the committee's preferred assumptions, the ICER was within the range that

NICE considers a cost-effective use of NHS resources. So, dupilumab can be used in the NHS.

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 Section 4f of The Innovative Medicines Fund Principles states that a discretionary source of early funding (from the overall Innovative Medicines Fund budget) is available for certain medicines recommended by NICE. In this instance, interim funding has been agreed for dupilumab. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets.

4.3 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 60 days of the first publication of the final draft guidance.

4.4 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 severe chronic rhinosinusitis with nasal polyps and the healthcare professional responsible for their care thinks that dupilumab 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 B.

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chairs

Baljit Singh (first committee meeting)
Vice-chair, technology appraisal committee B

Charles Crawley (second committee meeting)
Chair, technology appraisal committee B

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser, a project manager and an associate director.

Emilene Coventry
Technical lead

Nigel Gumbleton

Technical adviser

Vonda Murray, Thomas Feist and Jeremy Powell
Project managers

Richard Diaz and Emily Crowe
Associate directors

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