NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Dupilumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease

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

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

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

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

Issue date: April 2025

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
At that meeting, the committee will also consider comments made by people who are not stakeholders.
After considering these comments, the committee will prepare the final draft guidance.

- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using dupilumab in the NHS in England.

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

The key dates for this evaluation are:

Closing date for comments: Thursday 15 May 2025

Second evaluation committee meeting: 03 June 2025

Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Dupilumab should not be used as an add-on maintenance treatment for uncontrolled chronic obstructive pulmonary disease (COPD) in adults with raised blood eosinophils, who are taking:

- an inhaled corticosteroid, a long-acting beta2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA; triple therapy), or
- a LABA and a LAMA (double therapy) if inhaled corticosteroids are not appropriate.

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 is not required to be funded in the NHS in England to treat uncontrolled COPD in adults with raised blood eosinophils who are taking triple therapy, or double therapy if inhaled corticosteroids are not appropriate. It should not be used routinely in the NHS in England.

This is because there is not enough evidence to determine whether dupilumab is value for money.

Why the committee made these recommendations

Usual treatment for uncontrolled COPD with raised blood eosinophils is triple therapy, or double therapy if inhaled corticosteroids are not appropriate.

For this evaluation the company defines uncontrolled COPD as 1 or more severe exacerbations, or 2 or more moderate exacerbations, in the previous 12 months. It defines a raised blood eosinophil count as 300 cells or more per microlitre.

Clinical trial evidence shows that dupilumab reduces the number of exacerbations and improves lung function compared with triple therapy or double therapy.

There are uncertainties in the economic model about:

- the impact of dupilumab on the rate of severe exacerbations and mortality
- how long any benefits of dupilumab last.

Because of the uncertainties in the economic model, it is not possible to determine the most likely cost-effectiveness estimates for dupilumab.

So, dupilumab should not be used.

2 Information about dupilumab

Marketing authorisation indication

2.1 Dupilumab (Dupixent, Sanofi) is indicated in 'adults as add-on maintenance treatment for uncontrolled chronic obstructive pulmonary disease (COPD) characterised by raised blood eosinophils on a combination of an inhaled corticosteroid (ICS), a long-acting beta2-agonist (LABA), and a long-acting muscarinic antagonist (LAMA), or on a combination of a LABA and a LAMA if ICS is not appropriate'.

Dosage in the marketing authorisation

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

Price

2.3 The list price of dupilumab is £1,264.89 for a 2-pack of 300 mg per 2 ml pre-filled pens or pre-filled syringes. (excluding VAT; BNF online accessed March 2025).

2.4 The company has a commercial arrangement. This makes dupilumab available to the NHS with a discount and it would have also applied to this indication if dupilumab had been recommended. The size of the discount is commercial in confidence.

Carbon Reduction Plan

2.5 Information on the Carbon Reduction Plan for UK carbon emissions for Sanofi will be included here when guidance is published.

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.

The condition

Details of condition

3.1 Chronic obstructive pulmonary disease (COPD) is a progressive condition characterised by obstruction of the airways and reduced lung function. Common symptoms include shortness of breath, chronic cough, sputum production, wheezing, chest tightness, exercise intolerance, and episodic flare-ups of respiratory symptoms known as exacerbations. COPD is diagnosed using spirometry to detect persistent airflow obstruction. The severity of airflow obstruction is classified into 4 grades, based on post-bronchodilator forced expiratory volume in the first second (FEV_1), with grade 4 being the most severe. A patient expert explained that COPD affects his life enormously, including his ability to carry out daily tasks. For example, he requires oxygen daily and this restricts where he can go because of the requirement to carry cannisters of oxygen. He also explained that he has to be cared for by his wife, who constantly worries about his condition. He stated that exacerbations can be particularly debilitating, usually lasting for between 1 to 2 weeks and often requiring hospitalisation. The exacerbations are usually treated with oral

corticosteroids, which can lead to serious side effects. He explained that he has been in trials for biologics, which significantly reduced the number of exacerbations and 'completely changed his life'. Another patient expert, from Asthma + Lung UK, advised that the symptoms of COPD are extremely distressing for patients and the people they live with. People with COPD often have to give up working entirely or reduce working hours because of their condition. She added that the most common comorbidities with COPD are anxiety and depression, which are often a result of the restricted ability to carry out daily activities. The committee concluded that the symptoms and exacerbations associated with moderate to severe COPD can substantially affect health-related quality of life.

Clinical management

Treatment options

3.2 Dupilumab is licensed as an add-on maintenance treatment for uncontrolled COPD with triple therapy (combination of an inhaled corticosteroid, a long-acting beta2-agonist [LABA], and a long-acting muscarinic antagonist [LAMA]) or double therapy (combination of a LABA and a LAMA) if an inhaled corticosteroid is not appropriate. In UK clinical practice, off-label azithromycin or roflumilast may also be used as add-on treatments. NICE's guideline on chronic obstructive pulmonary disease in over 16s recommends considering azithromycin for people who do not smoke and continue to have frequent (typically 4 or more per year) exacerbations with sputum production, prolonged exacerbations or exacerbations resulting in hospitalisation. NICE technology appraisal guidance 461 recommends roflumilast for people with severe COPD (defined as an FEV_1 of 50% or less) and chronic bronchitis, who have had 2 or more exacerbations in the previous year. The clinical experts explained that roflumilast is not widely used in UK clinical practice because of adverse effects and tolerability issues, and that azithromycin is used in a different population to the anticipated target population for

dupilumab (see section 3.3). The clinical and patient experts explained that there is an unmet need in terms of add-on treatments that reduce exacerbations, improve lung function and improve quality of life for people with uncontrolled moderate to severe COPD. The clinical experts also explained that dupilumab is the first treatment to target the eosinophilic phenotype and could substantially improve long-term outcomes. The committee concluded that dupilumab would offer a new treatment for people with the eosinophilic phenotype who currently have limited options.

Target population and comparators

3.3 The company stated that it expects dupilumab to be used line with its full licensed indication as add-on maintenance treatment for adults with uncontrolled COPD, characterised by a raised blood eosinophil count, who are taking triple therapy (or double therapy if inhaled corticosteroids are not appropriate). It defined uncontrolled COPD as 1 or more severe exacerbations or 2 or more moderate exacerbations in the previous 12 months and a raised blood eosinophil as 300 cells per microlitre or more, in line with the clinical trials (see section 3.4). The company stated that the only relevant comparator was standard care without dupilumab, and the EAG agreed: that is, triple therapy or double therapy if inhaled corticosteroids are not appropriate. The company did not consider azithromycin to be a relevant comparator because there is limited overlap between the population for whom azithromycin can be considered, according to the NICE guideline (see section 3.2) and the target population for dupilumab. The EAG's clinical experts also noted that azithromycin is only used as an add-on therapy for a small subgroup of people with severe COPD, who would be eligible for dupilumab. They added that azithromycin targets different symptoms than dupilumab, so it would be unlikely to be considered as an alternative option. The company also noted there is limited overlap between the population for whom roflumilast is recommended (section 3.2) and the target population for dupilumab. It added that roflumilast is associated with a range of side effects and that only about 5% of people who were eligible for roflumilast

in 2022 and 2023 actually had it. The EAG's clinical experts supported this view. The clinical experts at the committee meeting agreed with the company and EAG's rationale for the exclusion of roflumilast and azithromycin as comparators. One of the clinical experts added that roflumilast is currently only prescribed for about 37 people in England, and that azithromycin is used in a different biological phenotype to dupilumab (section 3.2). The committee concluded that the only relevant comparator was standard care without dupilumab.

Clinical effectiveness

BOREAS and NOTUS

3.4 The clinical evidence for dupilumab plus background therapy came from the BOREAS and NOTUS trials. These were phase 3, placebo-controlled, double-blind, randomised multicentre trials, with participants randomised to either 300-mg dupilumab given subcutaneously once every 2 weeks or placebo. The trials recruited people with moderate to severe COPD with a blood eosinophil count of 300 cells per microlitre or more, with a documented history of high exacerbation risk. Moderate to severe COPD was defined as a post-bronchodilator ratio of FEV_1 to forced vital capacity of 0.7 or less, and a post-bronchodilator percentage predicted FEV_1 ($ppFEV_1$) of more than 30% but less than or equal to 70%. A high exacerbation risk was defined as 2 or more moderate exacerbations or 1 or more severe exacerbations within the previous 12 months. Both trials included a 52-week treatment phase, but NOTUS was stopped early at the planned interim analysis because the primary efficacy endpoint was met. As a result, 21.3% of participants in the trial did not reach the 52-week endpoint before the database lock. The company presented pooled results from BOREAS and NOTUS as part of a pre-specified protocol to increase the statistical power of the analyses. The pooled analysis comprised 938 people in the dupilumab arm and 936 people in the placebo arm. The company stated that this approach was appropriate because the studies had almost identical designs and there were no

significant differences in the outcomes. The primary outcome for both trials was adjusted annualised rate of moderate or severe exacerbations. The adjusted annualised rate of moderate or severe exacerbations per year was 0.79 (95% confidence interval [CI] 0.69 to 0.92) for dupilumab compared with 1.16 (95% CI 1.01 to 1.33) for placebo (rate ratio 0.69, 95% CI 0.60 to 0.79). A key secondary endpoint was change in pre-bronchodilator FEV_1 from baseline to week 12 and week 52. At week 12, the least squares (LS) mean change from baseline in pre-bronchodilator FEV_1 was 147 ml for dupilumab compared with 64 ml for placebo (LS mean difference +83 ml; 95% CI 53 to 112). At week 52, the LS mean change from baseline in pre-bronchodilator FEV_1 was 133 ml for dupilumab compared with 59 ml for placebo (LS mean difference +73 ml; 95% CI 40 to 107). Another key secondary endpoint was the change in the Saint George's Respiratory Questionnaire (SGRQ) score. At week 52, dupilumab resulted in a greater reduction (improvement) in SGRQ total score compared with placebo (LS mean difference -3.4; 95% CI -5.0 to -1.8). The committee concluded that dupilumab reduced moderate to severe exacerbations, improved pre-bronchodilator FEV_1 and improved SGRQ score compared with placebo.

Impact of COVID-19

3.5 BOREAS and NOTUS took place during the COVID-19 pandemic. The company noted that measures were put in place to ensure study continuity and protect the safety of participants. These included the implementation of temporary or alternative mechanisms for study visits and assessments, such as on-site visits being replaced with remote monitoring or phone calls. The company clarified that the total number of affected visits in the pooled population was low (2.5% of visits in the placebo arm and 2.1% of visits in the dupilumab arm). The EAG stated that given the relatively small proportion of visits affected, it did not consider the effects of the pandemic likely to have had a major impact on outcome assessment. But it noted that research suggests people with COPD had fewer exacerbations during the pandemic, which may be a

result of shielding. It stated that the impact of this on trial outcomes was unclear because this would depend on the extent to which people in both arms were affected. It added that the potential impact on the trial results of people in the trial having a COVID-19 infection should also be considered. The company provided subgroup analyses for people who reported treatment-emergent adverse events (TEAEs) caused by COVID-19. This was provided for the annualised rate of moderate or severe COPD exacerbations, pre-bronchodilator FEV_1 and SGRQ score. The EAG noted that differences between the outcomes in the dupilumab and placebo arms were smaller for people who reported a TEAE caused by COVID-19 than those who did not. This could indicate that the inclusion of people who had a COVID-19 infection in the analyses resulted in an underestimation of the effects of dupilumab. But results were similar for the subgroup who did not report a TEAE caused by COVID-19 and the overall analysis, indicating that the pandemic may not have had a substantial impact on the results. Overall, the EAG concluded that the effect of COVID-19 on the trial results are unclear. The clinical experts agreed that exacerbations were considerably reduced during COVID-19. A clinical expert stated that this was partly because of the impact of isolation and shielding but also because people were more reluctant to go to a hospital during this time. They clarified that severe exacerbations involve admission to hospital. So, the pandemic impacted the number of severe exacerbations in particular. They added that the ratio of moderate to severe exacerbations in the dupilumab trials was about 10 to 1, but in clinical practice the ratio is usually about 3 to 1. They estimated that the number of overall exacerbations decreased by 80% in this time. The committee noted that COVID-19 impacted the results of BOREAS and NOTUS, particularly the number of exacerbations. But it had not seen any evidence to suggest whether the impact of COVID-19 was different in the dupilumab arm compared with the placebo arm.

Minimal clinically important differences

3.6 The EAG considered whether the results from BOREAS and NOTUS represented clinically meaningful improvements. The company provided minimal clinically important difference (MCID) thresholds for exacerbation rate, change in FEV_1 and SGRQ. It also provided a MCID threshold for the Evaluating Respiratory Symptoms in COPD (ERS-COPD) score but this was not used to inform any parameters in the model. The company stated that a MCID threshold for SGRQ of 4 points or more is widely accepted and validated. It acknowledged that the mean improvement in SGRQ score between dupilumab and placebo in the pooled analysis was less than 4 points (see section 3.4). But it noted that 51.4% of people in the dupilumab arm had an improvement of 4 or more points from baseline, compared with 44.6% of people in the placebo arm. For the exacerbation rate, the company stated that any statistically significant reduction in exacerbations might be considered clinically meaningful given the serious clinical consequences associated with exacerbations. It also stated that clinical experts noted that a decrease in the exacerbation rate of between 20 to 25% is often considered clinically significant. It added that a 22% exacerbation reduction can be anchored to an SGRQ MCID of 4 points. Based on this, it believed that the pooled analysis results (section 3.4) for exacerbation rate were clinically meaningful. For FEV_1, the company stated that any statistically significant improvement in FEV_1 might be considered clinically meaningful in the context of a condition characterised by progressive lung function decline. It noted that in Crim at el. 2021, clinical experts believed that an improvement of 100 ml or more would generally be considered clinically meaningful depending on the individual person's starting point. But a lower FEV_1 improvement might still be clinically meaningful for someone with an initially low FEV_1. It acknowledged that the mean improvement in pre-bronchodilator FEV_1 between dupilumab and placebo in the pooled analysis was less than 100 ml (section 3.4). But it noted that 42.2% of people in the dupilumab arm had an FEV_1 improvement of 100 ml or more at week 12 from baseline, compared with 31.1% of people in the placebo arm. The EAG

stated that there was no evidence of validation for the thresholds used to represent MCIDs for change in exacerbation rate or FEV_1. So, the EAG stated it was uncertain whether dupilumab resulted in clinically meaningful improvements in clinical practice. One of the clinical experts at the committee meeting noted that for SGRQ, despite the incremental benefit for dupilumab being less than 4 points compared with placebo, the improvement from baseline was 9.9 points in the dupilumab arm. They stated that the SGRQ is a comprehensive assessment of respiratory symptoms and they believed this to be a clinically meaningful difference. For exacerbation rate, they stated that generally, a change of 20% in exacerbation rate is thought to be clinically significant. This is because each exacerbation reduces lung function and requires a course of oral corticosteroids. The clinical expert stated that a clinically meaningful difference in terms of FEV_1 is more difficult to quantify. This is because people with COPD are more concerned about the impact of lung function on quality of life rather than lung function as a standalone measure. The committee noted that except for the SGRQ, the thresholds for MCIDs proposed by the company for change in exacerbation rate and FEV_1 have not been widely accepted or validated. But it noted that reductions in exacerbations and improvements in SGRQ are important to people because of the limiting nature of COPD symptoms and the consequences of exacerbations. It recalled that dupilumab resulted in a reduction of 31% in moderate or severe exacerbations compared with placebo, and an improvement of 9.9 points in the SGRQ score from baseline. It concluded that the results from BOREAS and NOTUS represent clinically meaningful improvements.

Economic model

Model structure

3.7 The economic analysis compared dupilumab plus background therapy (from here, referred to only as dupilumab) with standard care without dupilumab (from here, referred to only as background therapy). The

company provided a cohort-level short-term decision tree leading to a Markov state transition model with an annual cycle length. The short-term decision tree reflected the trial period of 52 weeks. People whose condition did not respond to treatment during the 52-week trial period were classed as 'non-responders' at the end of the decision-tree period and from then on had outcomes comparable to background therapy. Health states were classified in line with the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria based on $ppFEV_1$:

- GOLD stage 1: mild COPD, $ppFEV_1$ 80 or more
- GOLD stage 2: moderate COPD, $ppFEV_1$ more than or equal to 50 and less than 80
- GOLD stage 3: severe COPD, $ppFEV_1$ more than or equal to 30 and less than 50
- GOLD stage 4: very severe COPD, $ppFEV_1$ less than 30.

In addition to COPD severity, health states were split based on exacerbation status (no exacerbation, moderate exacerbation or severe exacerbation). Moderate and severe exacerbation states were further stratified to capture the number of exacerbations experienced (1, 2, or 3 or more). People entered the Markov state transition model based on the distribution at the end of the 52-week trial period. As per the decision tree, health states were split by both COPD severity and exacerbation status. This resulted in 12 health states plus an absorbing state for death. Exacerbations could be experienced within each COPD severity health state. Overall, the EAG thought the model structure was appropriate. The committee concluded that the model structure was suitable for decision making but had concerns about some of the assumptions (see sections 3.8 to 3.12.)

Long-term annual decline in FEV_1

3.8 To estimate transition probabilities between COPD severity health states, the company used estimates of long-term decline in FEV_1 from Fenwick et

al. 2021. This provided estimates separately for people with and without a recent exacerbation. Fenwick et al. estimated an annual decline in FEV_1 of 40.9 ml for people without a recent exacerbation and 71.5 ml for people with a recent exacerbation. The company's target population included the criteria for a raised blood eosinophil count (300 cells per microlitre or more). But the Fenwick et al. study was not specifically based on people with an eosinophil count of 300 cells per microlitre or more. So, the company applied a multiplier of 1.52 to the Fenwick et al. FEV_1 decline estimates to represent increased rates of annual decline for people with an eosinophil count of 300 cells per microlitre or more. The multiplier was estimated based on COPD subgroup data from the CanCOLD study, comparing the annual rate of decline in people with COPD based on their eosinophil count. The application of the multiplier resulted in an annual decline in FEV_1 of 62.17 ml for people with no recent exacerbations and 108.68 ml for people with a recent exacerbation. The EAG noted that the Fenwick et al. FEV_1 decline estimates were based on the TORCH study, in which people were having dual therapy. So, the annual rate of decline may be overestimated compared with people who would have triple therapy. The EAG also had concerns about the applicability of the multiplier estimated from CanCOLD. It noted that because of the population in CanCOLD, the rate of FEV_1 decline may be overestimated compared with the population of interest for the current evaluation. For example, most people in the study had mild COPD, which is associated with a faster FEV_1 decline than people with more advanced COPD. The EAG also noted that the authors of the CanCOLD study controlled for exacerbations in their regression analysis for FEV_1 decline. So, applying the multiplier to people with recent exacerbations may not be appropriate. One of the EAG's clinical advisers thought that the 62 ml per year decline for people without a recent exacerbation seemed reasonable but was unable to comment on the plausibility of the estimate of 109 ml per year for people with recent exacerbations in the previous year. Another of the EAG's clinical advisers stated that the annual rates of decline estimated

by the company are higher than would be expected in clinical practice. The EAG preferred to inform transition probabilities between COPD severity states based on Fenwick et al., without the multiplier. One of the clinical experts at the committee meeting highlighted that the eosinophil count is an important factor when considering the rate of disease progression and lung function. They stated that this has been demonstrated in COPD studies, which consistently demonstrate that higher levels of eosinophils predict a higher rate of lung function decline. For example, a large prospective cohort study in the US with 12 years of follow-up data found an increase of about 50% in the rate of decline in FEV_1 for people with a raised eosinophil count. The committee noted that this was aligned with the multiplier applied in the company's base case, as predicted by the CanCOLD study. It noted that the resulting rate of FEV_1 decline may be overestimated because the unadjusted rate of FEV_1 decline in Fenwick et al. was based on a population not having triple therapy. But it thought that the application of a multiplier seemed reasonable based on the target population having an eosinophil count of 300 cells per microlitre or more. It concluded that it preferred to inform transition probabilities between COPD severity states based on Fenwick et al., with the multiplier of 1.52.

Rates of severe exacerbations

3.9 The company applied a rate ratio to the background therapy arm to obtain the annualised rate of exacerbations for the dupilumab arm. The rate ratios were applied separately for moderate exacerbations and severe exacerbations, and were calculated from the pooled trial data. The exact rate ratios are considered confidential by the company and cannot be reported here. The EAG noted that the pooled trial data showed a statistically significant decrease in the combined rate of moderate and severe exacerbations for people in the dupilumab arm. But there was no statistically significant difference in severe exacerbations between the 2 treatment arms in the 52-week trial period, and 90% of exacerbations were moderate. The company acknowledged this but still believed it was

appropriate to model different rates of severe exacerbations between treatment arms. It stated that BOREAS and NOTUS were not powered to measure a difference in the rate of severe exacerbations. It added that the number of severe exacerbations observed during the trials may be lower than would be expected in clinical practice, similar to other phase 3 COPD studies. This would have impacted the statistical power to detect significant differences. It also stated that there were statistically significant differences between treatment arms in the time to first severe exacerbation and the adjusted annualised severe exacerbation rate. Clinical experts consulted by the company indicated that the mechanism for moderate and severe exacerbations is broadly similar. They added that although the absolute number of exacerbations may differ, the rate reduction would be expected to be similar. This view was supported by the clinical experts at the committee meeting. The EAG noted that the company stated that the trials were not powered to detect a significant difference in severe exacerbations. So, the EAG assumed that the analyses for the time to first severe exacerbation and the adjusted annualised severe exacerbation rate were post-hoc assessments. It acknowledged the limitations associated with the small number of severe exacerbations observed in the trial setting. The EAG agreed with the company that it would not be appropriate to assume no difference in severe exacerbations between treatment arms. But it still considered the magnitude of the reduction in severe exacerbations to be uncertain. It noted that differences in the rate of severe exacerbations are a key driver of cost effectiveness because of the impact on costs, quality of life and mortality. Overall, the committee thought it was reasonable to assume that dupilumab would result in a reduction in the number of severe exacerbations compared with background therapy only. But it noted that the rate ratio estimates used to calculate the annualised rate of exacerbations for the dupilumab arm were based on a low number of severe exacerbations. It was concerned that this resulted in a high level of uncertainty about the calculated rate ratios and the magnitude of the

reduction in severe exacerbations. The committee requires further evidence from the company to show whether the magnitude of reduction in severe exacerbations in BOREAS and NOTUS was applicable to clinical practice.

Long-term treatment effect maintenance period of dupilumab

3.10 People in the dupilumab arms of BOREAS and NOTUS stopped treatment at the end of the 52-week trial period. So, there is no long-term trial data available to observe the long-term changes in FEV_1. In the absence of this, the company used long-term data from people with moderate or severe asthma having dupilumab in the TRAVERSE study. This showed improvements in pre-bronchodilator FEV_1 were maintained from the 52-week trial period and during the 96-week follow up. Based on this, the company assumed that for dupilumab, the treatment effect on FEV_1 is maintained for 2 years beyond the end of the trial period (3 years in total). After this, the same transition probabilities between COPD health states as for background therapy are applied. The company stated that the mechanism of action of dupilumab is expected to be the same in asthma as in COPD, supporting the use of the TRAVERSE data to inform the treatment effect maintenance period. The EAG's clinical experts stated that using data from TRAVERSE may be reasonable. But people with COPD would be older with more comorbidities, so may be expected to decline more quickly. The company did a reweighting analysis of a subgroup of people in TRAVERSE matched to people in the pooled BOREAS and NOTUS populations based on age and pre-bronchodilator FEV_1. The company suggested that this analysis demonstrated that there is no increased rate of lung function decline for people in TRAVERSE matched to the pooled BOREAS and NOTUS populations. The EAG noted that the company only weighted the baseline age and pre-bronchodilator FEV_1. It stated that because other baseline characteristics such as comorbidities have not been adjusted for, uncertainty remains about the similarity between the populations. Overall, because of a lack of alternative data to inform the treatment effect maintenance period for

dupilumab, the EAG agreed with the use of TRAVERSE data. So, it included a 3-year treatment effect maintenance period for dupilumab in its base case. But it advised this is optimistic and highly uncertain. The clinical experts at the committee meeting stated that the long-term treatment effect of dupilumab was uncertain. But they agreed it was reasonable to assume a 3-year treatment effect maintenance period for dupilumab based on the TRAVERSE data. The committee acknowledged the lack of long-term data for dupilumab in people with COPD on which to estimate the long-term treatment effect. So, it thought it was reasonable to base this on TRAVERSE. It recalled that after the 3-year treatment effect maintenance period, the same transition probabilities between COPD health states as for background therapy are applied. And because of the higher FEV_1 for people in the dupilumab arm at 3 years, a treatment effect is maintained throughout the lifetime of the model (while people remain on dupilumab). Specifically, on average, people in the dupilumab arm continue to stay in less severe COPD severity health states compared with people in the background therapy arm. The committee noted that the company had not provided evidence to support this assumption and decided it was highly uncertain. It considered whether to assume a 3-year treatment effect maintenance period for dupilumab. But it requires evidence from the company to support its assumption of a maintained treatment benefit for dupilumab compared with background therapy for the lifetime of the model.

Excess mortality for severe exacerbations

3.11 The company captured the increased risk of death from COPD by applying a standardised mortality ratio (SMR) to general population mortality. The company sourced the SMRs from the Whittaker et al. 2024 study, which estimated all-cause mortality hazard ratios associated with COPD severity based on a UK dataset. The company noted that excess mortality from COPD has been linked to both COPD severity stage and to exacerbations. So, to account for the increased risk of mortality because of exacerbations, it applied a separate case fatality rate (CFR) of 15.6%

derived from Hoogendoorn et al. 2011, per severe exacerbation. The EAG removed this from its preferred analysis because of serious concerns about this approach, including:

- the impact of exacerbations on mortality may already have been accounted for within the COPD severity mortality, so including a separate CFR may lead to double counting. It noted that Whittaker et al. 2024 controlled for recent exacerbation history in the regression models used to estimate the hazard ratio associated with COPD severity
- the Hoogendoorn et al. study was based on a meta-analysis of 6 non-UK studies, with the latest study using data collected between 2000 to 2005. So, the studies may not reflect current clinical practice.

The company acknowledged that the SMRs from Whittaker et al. 2024 may include baseline exacerbation risk but that does not mean it has fully adjusted for the effects of exacerbations on mortality. It thought that removing the CFR for severe exacerbations was not appropriate. It stated that the SMRs calculated by Whittaker et al. 2024 are based on treatment consisting of dual and triple therapy only, not on biologics such as dupilumab. So, the SMRs are not fully applicable to the dupilumab treatment arm, which would be expected to reduce mortality through reduced exacerbation rates. The company also stated that two-thirds of people in Whittaker et al. 2024 had no previous exacerbations so the risk of mortality may be lower in that population. In response to the EAG's concerns, the company suggested that a plausible alternative to including the CFR would be to apply separate SMRs for each COPD severity health state by treatment arm. It provided this as a scenario analysis. The company assumed that improvement in mortality from dupilumab would be equal to the reduction in mortality observed between dual compared with triple therapies from the IMPACT trial. It obtained a hazard ratio of 0.72 from IMPACT and multiplied this by the SMRs in the dupilumab arm. The EAG advised

there was no robust evidence to justify the company's alternative approach, advising that:

- the extent to which dupilumab may reduce mortality is uncertain because the dupilumab studies were not powered to detect this
- IMPACT was not powered to examine the influence of triple therapy on mortality.

The EAG acknowledged there may be an additional impact of severe exacerbations on mortality. It noted that the company had provided another scenario analysis using mortality incidence rate ratios from Whittaker et al. 2022 to estimate the excess mortality for exacerbations. The EAG also used this in a scenario analysis, noting that it was used in the model to derive transition probabilities for exacerbation rates and it preferred to use a consistent data source. The committee considered the link between exacerbations and mortality and the various assumptions and data sources used in the model. One of the clinical experts explained that the link between exacerbations and mortality is well established. They added that national audit data showed that the mortality rate at 90 days after a severe exacerbation is 12%. Additionally, data from approximately 60,000 people with COPD in Canada showed a median survival of about 4 years after a severe exacerbation. So, the clinical experts thought that the projected median survival of about 13 years in the background therapy arm in the EAG's base case (without a separate CFR) and about 7 years in the company's base case (with the CFR) both overestimated survival. But of the 2 options, they advised that the projected survival in the company's base case was more plausible. Another clinical expert noted that because of the similar number of deaths between the dupilumab and placebo arms in the pooled analysis of BOREAS and NOTUS, it was difficult to predict whether the company's base case was accurate. This is because the company's base case resulted in a survival benefit for dupilumab. They added that the true survival benefit for dupilumab

may fall between the company's and EAG's base cases. The committee decided it was highly uncertain whether the survival predictions in any of the base cases or scenarios presented reflected clinical practice. It noted that this was the largest driver of the cost-effectiveness results, and that this driver was based on mortality and severe exacerbation benefits that were not directly observed in the trial. It decided that modelling a survival benefit for dupilumab was highly uncertain because the trials were not powered to show a statistically significant mortality benefit. It also agreed with the EAG that applying the SMRs may already account for the impact of severe exacerbations. But the extent of this was unclear. The committee concluded that it would like to see more evidence to support the assumptions used in the model, including:

- data on real-world survival for the population covered by the evaluation to inform the model and validate survival outputs from the model
- data estimating how much of the mortality in the population covered by the evaluation is attributable to exacerbations
- further evidence to support applying a CFR to account for the increased risk of mortality from exacerbations in addition to the SMRs to estimate mortality associated with COPD severity
- alternative sources of evidence for the CFR (if a separate CFR is supported by the evidence)
- a scenario applying a CFR from exacerbations, but without the application of SMRs or any other adjustment for mortality. It acknowledged this scenario may be conservative but noted it would be useful for assessing the impact of this assumption on cost-effectiveness estimates.

Utility values

3.12 Health-related quality of life date were collected in NOTUS and BOREAS using both the SGRQ and EQ-5D-5L. But because of the low collection timepoints of the EQ-5D-5L, the company was not able to directly use the

EQ-5D data to inform utility values for the model. So, the company developed a mapping algorithm using data from visits when both SGRQ and EQ-5D-5L were collected, to obtain EQ-5D-5L utilities. These were then converted to EQ-5D-3L values using the UK crosswalk tariffs for use in the economic model. The company's base-case analysis used treatment specific utility values for each COPD severity health state. The company stated it did this because BOREAS and NOTUS showed sustained improvements in key outcomes (see section 3.4). The EAG noted that the regression analysis for utilities (mapping algorithm) showed that only the coefficients for SGRQ at baseline, severity of airflow obstruction and exacerbation risk were statistically significant. The coefficient for treatment group and the interaction terms between treatment and severity of airflow obstruction groups were not statistically significant. The company stated that although the coefficients for these terms were not statistically significant, there was a directional impact suggesting higher utility when included in the regression analysis. But the EAG advised there was not robust evidence of a separate treatment-related benefit to justify using treatment-arm specific utilities. The company provided a scenario analysis including only statistically significant covariates in the utility regression analysis. In this analysis, treatment group was not included as a covariate, and the resulting utilities were independent of treatment arm. In its base case, the EAG preferred using utilities derived from the utility regression model including only statistically significant covariates. The clinical experts stated that real-world evidence supports data from BOREAS and NOTUS and indicates that dupilumab treatment results in improved quality of life. The committee accepted that treatment with dupilumab improves lung function and reduces exacerbations, which improve quality of life. But it noted that this had already been captured in the economic model. This was because of the slower rate of transitions into worse COPD severity states (associated with lower utility values) for dupilumab compared with background therapy. The committee also noted that the impact of exacerbations on

quality of life had been captured through the application of a disutility applied for each exacerbation event. The committee decided that it had not seen sufficient evidence to support an additional utility benefit for dupilumab over and above these benefits which were already accounted for. The committee concluded that it preferred using utilities derived from the utility regression model including only statistically significant covariates (that is, non-treatment arm specific utility values).

Other issues identified by the EAG

3.13 The committee noted that the EAG's base case included alternative assumptions (compared with the company's base case) relating to several other issues that the EAG had identified. These were not considered as key issues by the EAG because they had less impact on the cost-effectiveness results. The committee noted that the alternative assumptions when applied to the company's base case had a small impact on the cost-effectiveness results and so did not discuss these further.

Cost-effectiveness estimates

Company and EAG cost-effectiveness estimates

3.14 In the company's base-case analysis, the deterministic and probabilistic incremental cost-effectiveness ratios (ICERs) for dupilumab are £25,515 per quality-adjusted life year (QALY) and £23,624 per QALY, respectively. In the EAG's base-case analysis, the deterministic and probabilistic ICERs for dupilumab are £68,832 per QALY and £73,154 per QALY, respectively. The committee concluded that further analyses were needed to determine the most plausible estimates for decision making (see section 3.17).

Acceptable ICER

3.15 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 about:

- the calculated rate ratios for severe exacerbations for dupilumab compared with background therapy (that is, the magnitude of the reduction in severe exacerbations; see section 3.9)
- the long-term treatment effect for dupilumab compared with background therapy (see section 3.10)
- the plausibility of the modelled survival predictions in both arms of the model (see section 3.11)
- the extent to which the SMRs from Whittaker et al. 2024 account for the impact of severe exacerbations (see section 3.11)
- the modelled survival benefit for dupilumab relative to background therapy (see section 3.11).

So, the committee concluded that an acceptable ICER would be around £20,000 per QALY.

The committee's preferences

3.16 For the cost-effectiveness analysis, the committee preferred:

- informing transition probabilities between COPD severity states based on Fenwick et al., with the multiplier of 1.52 to represent increased rates of annual decline for people with an eosinophil count of 300 cells per microlitre or more (see section 3.8)
- using utility values derived from the utility regression model including only statistically significant covariates (that is, non-treatment arm specific utility values; see section 3.12).

The committee's requests for additional analyses

3.17 The committee could not determine the most plausible ICER without further analyses. The committee requested the following:

- evidence to determine whether the magnitude of reduction in severe exacerbations in BOREAS and NOTUS was applicable to clinical practice (see section 3.9)
- evidence to support the company's assumption of a maintained treatment benefit for dupilumab compared with background therapy for the lifetime of the model (see section 3.10)
- data on real-world survival for the population covered by the evaluation to inform the model and validate survival outputs from the model (see section 3.11)
- data estimating how much of the mortality in the population covered by the evaluation is attributable to exacerbations (see section 3.11)
- further evidence to support applying a CFR to account for the increased risk of mortality from exacerbations in addition to the SMRs to estimate mortality associated with COPD severity (see section 3.11)
- alternative sources of evidence for the CFR (if a separate CFR is supported by the evidence, see section 3.11)
- a scenario analysis applying a CFR due to exacerbations without the application of SMRs, or any other adjustment for mortality (see section 3.11).

Other factors

Equality

3.18 The committee considered whether NICE's duties under the equality legislation required it to alter or add to its recommendations. It noted that the following points had been raised by stakeholders:

- COPD disproportionately affects people of certain demographics. For example, it is more common in men, people over 40 and people from lower socioeconomic backgrounds

- age-standardised mortality rates from COPD differ depending on geographic region and are higher for some ethnic groups
- there are disparities in the quality of care such as differential prescribing of pharmacological treatments and differential referral rates for COPD rehabilitation for people of different ethnicities, socioeconomic backgrounds and depending on geographical location
- people from more deprived areas find accessing healthcare difficult because of practicality and cost.

Stakeholders noted that the provision of dupilumab has the potential to alleviate inequalities because people would have access to it in all geographic regions, if dupilumab were recommended. The committee noted that age, race and sex are protected characteristics under the Equality Act 2010. But issues related to differences in prevalence or incidence of a disease cannot be addressed in a technology appraisal. So, the committee agreed these were not potential equalities issues. The committee noted the disparities in care and unequal access to care based on specific demographics. It concluded that access to care is an issue that cannot be addressed by a NICE technology appraisal recommendation.

Uncaptured benefits

3.19 The company stated that there are benefits of dupilumab that may not be captured in the QALY calculation. It noted that people with COPD can be significantly affected by cold weather and experience more breathlessness and coughing in winter. This is reflected by the increase in GP visits and hospitalisations during the winter months. It stated that dupilumab has the potential to relieve some of this healthcare system pressure through a reduction in symptoms and inpatient admissions for exacerbations. It also stated that another potential uncaptured benefit was the greater reduction (improvement) in the ERS-COPD scores in the dupilumab arm compared with the placebo arm in BOREAS and NOTUS. The ERS-COPD is a patient-reported outcome, as is the SGRQ. The

company said that because there is no mapping algorithm to convert ERS-COPD scores to EQ-5D, this benefit may have not been captured in the model. The company stated that a further potential uncaptured benefit relates to environmental impact. This is because the implementation of dupilumab for the treatment of COPD may be carbon neutral or carbon saving through reductions in healthcare resource use from improved outcomes. The committee concluded that the potential uncaptured benefits stated by the company did not outweigh the committee's concerns about the cost-effectiveness estimates and the uncertainty about the ICER.

Conclusion

3.20 The committee agreed that further information was needed before it could decide on all its preferred modelling assumptions and understand the full impact of the uncertainties. So, it was unable to establish that dupilumab was a cost-effective use of NHS resources. It concluded that dupilumab should not be used to treat uncontrolled COPD in adults with raised blood eosinophils who are taking triple therapy or double therapy if inhaled corticosteroids are not appropriate.

4 Evaluation committee members and NICE project team

Evaluation committee members

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

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.

Chair

Radha Todd

Chair, technology appraisal committee A

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.

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