# NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

## Final draft guidance

# Dupilumab for maintenance treatment of uncontrolled chronic obstructive pulmonary disease with raised blood eosinophils

## 1 Recommendations

1.1 Dupilumab can be used as an add-on maintenance treatment option for uncontrolled chronic obstructive pulmonary disease (COPD) with raised blood eosinophils in adults if:

- they are having:
  - triple therapy including an inhaled corticosteroid, a long-acting beta2-agonist (LABA) and a long-acting muscarinic antagonist (LAMA), or
  - double therapy including a LABA and a LAMA if inhaled corticosteroids are not appropriate, and
- the company provides dupilumab according to the commercial arrangement (see section 2).

Uncontrolled COPD is defined as 1 or more severe exacerbations or 2 or more moderate exacerbations in the previous 12 months. Raised blood eosinophils is defined as a blood eosinophil count of 0.3 x 10^9 cells per litre or more (300 cells per microlitre or more).

1.2 Assess response to dupilumab at 12 months. Stop dupilumab if, compared with the 12 months before starting it, the number of severe exacerbations:

- is higher, or
- is the same, and the number of moderate exacerbations is higher.

1.3 These recommendations are 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.

## 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.

The clinical trials for this evaluation used the following definitions:

- Uncontrolled COPD is 1 or more severe exacerbations or 2 or more moderate exacerbations in the previous 12 months.
- Raised blood eosinophils is an eosinophil count of 0.3 x 10^9 cells per litre or more (300 cells per microlitre or more).

The company also included a rule that dupilumab is stopped at 12 months if the COPD has not responded well enough. Applying the definitions and the stopping rule does not reflect everyone dupilumab is licensed for.

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

The cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, dupilumab can 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 December 2025).

2.4 The company has a commercial arrangement (commercial access agreement). This makes dupilumab available to the NHS with a discount. 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, reduced lung function and episodic flare-ups of respiratory symptoms, known as exacerbations. Common symptoms include shortness of breath, chronic cough, sputum production, wheezing, chest tightness and exercise intolerance. COPD is diagnosed using spirometry to detect persistent airflow obstruction. The severity of airflow obstruction is determined based on post-bronchodilator forced expiratory volume in the first second ($FEV_1$). A patient expert at the first committee meeting explained that COPD affects his life enormously, including his ability to carry out daily tasks. For example, he needs daily oxygen therapy and this restricts where he can go because of the need to carry oxygen cannisters. 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 1 to 2 weeks and often needing hospitalisation. The exacerbations are usually treated with oral corticosteroids, which can lead to serious side effects. He explained that he has been in trials of biological treatments, which significantly reduced the number of exacerbations and 'completely changed his life'. Another patient expert explained 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 COPD 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's technology appraisal guidance on roflumilast for treating COPD 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 they explained 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 there is an unmet need for 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 it 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

3.3 The company stated that it expects dupilumab to be used 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. It defined a raised blood eosinophil count as 0.3 x 10^9 cells per litre or more (300 cells per microlitre or more), in line with the clinical trials (see section 3.5). The company also proposed a stopping rule. This specified that response to dupilumab should be assessed at 12 months and treatment should be stopped if the number of severe exacerbations on treatment is higher than the 12 months before starting treatment. It added that if there is an equal number of severe exacerbations, treatment should be stopped if the number of moderate exacerbations on treatment is higher than the 12 months before starting treatment. At the second meeting, the clinical expert explained that people with a blood eosinophil count of 0.3 x 10^9 cells per litre or more (300 cells per microlitre or more) are at high risk of exacerbations and hospitalisation. They added that this group would benefit most from treatment with dupilumab. The clinical expert agreed that the company's stopping rule was reasonable and response to treatment would be seen within 12 months. They added that the company's stopping rule would allow treatment to be continued by people who are benefitting from it. The committee noted that the company's criteria for starting and stopping treatment were not specified in the marketing authorisation but were modelled by the company. The committee agreed that the company's criteria for starting treatment were aligned with the BOREAS and NOTUS trials and were appropriate for the

recommendations. The committee discussed the definition of benefit and how easy the stopping rule would be to implement in clinical practice. It considered whether 'change in eosinophil count' could be used to inform treatment continuation. But the clinical experts advised that a change in eosinophil count may not be a good enough indicator of benefit because it does not predict disease progression. So, the committee agreed with the company's stopping rule based on exacerbations only. It also agreed with the clinical experts' view that the 12-month timeframe would be long enough to assess benefit. The committee said that the company's stopping rule reflects what is likely to happen in clinical practice and ensures that dupilumab would only be continued by people who are benefitting from it. So it concluded that the stopping rule was appropriate for the recommendations.

## Comparators

3.4 The company stated that the only relevant comparator was standard care without dupilumab: that is, triple therapy, or double therapy if inhaled corticosteroids are not appropriate. The EAG agreed. The company did not consider azithromycin to be a relevant comparator because there is limited overlap between the population who would be offered azithromycin, 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 treatment 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 (see 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 (see section 3.2). The committee concluded that the only relevant comparator was standard care without dupilumab.

## Clinical effectiveness

### BOREAS and NOTUS

3.5 The clinical evidence for dupilumab came from BOREAS and NOTUS. These were phase 3, double-blind, randomised multicentre trials, with people randomised to either 300-mg dupilumab given subcutaneously once every 2 weeks or placebo. Both arms included background therapy, which comprised triple therapy or double therapy if inhaled corticosteroids were not appropriate. The trials recruited people with moderate to severe COPD with a blood eosinophil count of 0.3 x 10^9 cells per litre or more (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 people 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

3.6 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 people in the trial. These included implementing temporary or alternative mechanisms for study visits and assessments, such as replacing on-site visits 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 for people who did not. This could indicate that including people who had a COVID-19 infection in the analyses resulted in underestimating 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. This indicated 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 was unclear. The clinical experts agreed that exacerbations were considerably reduced during the COVID-19 pandemic. 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 about 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

3.7 The EAG considered whether the results from BOREAS and NOTUS represented clinically meaningful improvements. The company provided minimal clinically important difference (MCID) thresholds for SGRQ

exacerbation rate and change in $FEV_1$. The company stated that an 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 3.5). 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% and 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 (see section 3.5) 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 smaller $FEV_1$ 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 (see section 3.5). 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 a change of 20% is generally 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 about lung function as a standalone measure. In response to the draft guidance consultation, a professional group explained that any improvement in $FEV_1$ for a condition with non-reversible lung function decline is a clinical improvement. They added that a reduction in exacerbations of less than 20% is also clinically meaningful, and that preventing 1 exacerbation is likely to prevent multiple exacerbations. 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 acknowledged 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 represented clinically meaningful improvements.

# Economic model

## Model structure

3.8 The economic analysis compared dupilumab plus background therapy (from here, referred to as dupilumab) with background therapy without dupilumab (from here, referred to as background therapy). The company

provided a cohort-level short-term decision tree leading to a Markov state transition model with a cycle length of 12 months. 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.

### Long-term annual decline in $FEV_1$

3.9 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 (0.3 x 10^9 cells per litre or more [300 cells per microlitre or more]). But the Fenwick et al. study was not specifically based on people with an eosinophil count of 0.3 x 10^9 cells per litre or more (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 0.3 x 10^9 cells per litre or more (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. In the company's base case, applying 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 had dual therapy rather than triple therapy. The EAG also noted that most people in the CanCOLD study had mild COPD and had dual therapy without an inhaled corticosteroid. It noted that mild COPD has a faster $FEV_1$ decline than more advanced COPD. So, the rate of $FEV_1$ decline may be overestimated compared with the population of interest for the current evaluation, which considers a more severe population. 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 for people with recent exacerbations may not be appropriate. One of the EAG's clinical advisers thought that the decline of 62 ml per year for people without a recent exacerbation seemed reasonable but was unable to comment on the plausibility of the company's 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 company's estimated annual rates of decline 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 first committee meeting noted that the baseline 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 decided that applying a multiplier seemed reasonable based on the target population having an eosinophil count of 0.3 x 10^9 cells per litre or more (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 moderate and severe exacerbations

3.10 The company applied rate ratios to the background therapy arm to obtain the annualised rates of exacerbations for the dupilumab arm. The rate ratios were calculated from the pooled trial data and applied separately for moderate exacerbations and severe exacerbations. They were further split by COPD severity group based on GOLD categories, for everyone in the trial and for people classified as responders. The exact rate ratios applied in the model 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 maintained it was appropriate to model different rates of moderate and 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 seen 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 post-hoc analysis of 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 first committee meeting. The EAG acknowledged the limitations associated with the small number of severe exacerbations observed in the trials. It 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. The committee agreed that dupilumab would be expected to reduce the number of severe exacerbations compared with background therapy but 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.

In response to the draft guidance consultation, the company explained that the BOREAS and NOTUS data showed a 32.6% reduction in severe

exacerbations with dupilumab. It added that this was close to the threshold for statistical significance (p=0.0725). The company also presented a post-hoc tipping point analysis and 2 other post-hoc analyses in people who had had 52 weeks of treatment. In its critique of the company's draft guidance response the EAG stated that there was still considerable uncertainty about the magnitude of the reduction in severe exacerbations with dupilumab compared with background therapy. The EAG noted the wide 95% confidence intervals around the 32.6% reduction (95% CI -56.2% to +3.7%). It also noted that the company's additional post-hoc analyses did not address the uncertainty about the precise estimate for the reduction in severe exacerbations. The EAG recalled that in the economic model, individual rate ratios were split according to COPD severity group for everyone and for people classified as responders. It noted that splitting people into these smaller groups further increases uncertainty. The EAG also recalled that clinical experts at the first committee meeting expected the rate ratios to be similar for moderate and severe exacerbations. So, the EAG updated its base case to apply the moderate rate ratios for both moderate and severe exacerbations for each COPD severity group. The EAG stated that its preference would have been to apply rate ratios for each COPD severity group derived from moderate and severe exacerbations combined. But the EAG said that it did not have access to this data. At the second committee meeting, the company stated that the EAG's approach was methodologically incorrect because of how a responder is defined in the model. The company explained that a severe exacerbation is the key event that determines whether a person is classified as a responder and that responders would be expected to have lower rates of severe exacerbations. So, the company maintained that separate rate ratios are needed for moderate and severe exacerbations for the responder population based on the observed data. But the committee shared the EAG's concerns that there was still considerable uncertainty in the calculated rate ratios for severe exacerbations using the observed data from the trial. It recalled that the

primary outcome of BOREAS and NOTUS was the reduction in moderate and severe exacerbations combined. It also recalled that the trials were not powered to detect a difference in severe exacerbations because of the small number of events. The clinical expert at the second committee meeting stated that, while the mechanism of initiation for moderate and severe exacerbations is broadly the same, the impact on mortality from severe exacerbations is much greater. The committee noted that the model already takes into account the different consequences of moderate and severe exacerbations, and that this is reflected in the modelled outcomes. The committee concluded that its preferred approach for modelling the reduction in both moderate and severe exacerbations would be to apply rate ratios for each COPD severity group derived from the combined data on moderate and severe exacerbations. This would align with the primary outcome of the trials and would make use of all the available trial data. The company provided this analysis after the second meeting. The EAG was satisfied with the company's approach to deriving the updated rate ratios. The committee concluded that the company's updated analysis was appropriate for modelling the reduction in moderate and severe exacerbations.

## Long-term treatment-effect maintenance period of dupilumab

3.11 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 this population. 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 that improvements in pre-bronchodilator $FEV_1$ were maintained during the 96-week follow-up period after the trial. So, the company assumed that the treatment effect of dupilumab 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 had not been adjusted for, uncertainty remained 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 to use TRAVERSE data. So, it included a 3-year treatment-effect maintenance period for dupilumab in its base case. But it advised that this was 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 for dupilumab. 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 concluded that the company's assumption of a maintained treatment benefit for dupilumab for the lifetime of the model was highly uncertain.

In response to the draft guidance consultation, the company presented another reweighting analysis in which the population in TRAVERSE was weighted to match the pooled population of BOREAS and NOTUS. The company stated that results of this analysis further supported its assumption of a 3-year treatment-effect maintenance period for dupilumab. The company added that dupilumab has shown a maintained treatment effect for up to 5 years in other indications such as atopic dermatitis. It added that lifestyle interventions for COPD, such as smoking cessation, have long-term benefits on lung function. The EAG was reassured that the adjusted datasets indicated a sustained benefit with dupilumab. But it noted several limitations of the company's reweighting analysis and advised that the long-term benefits of dupilumab for people with COPD were still uncertain. At the second meeting, the committee accepted the company's and EAG's base-case assumption that the treatment effect of dupilumab would be maintained for 3 years, with the benefit compared with background therapy maintained for the lifetime of the model. But it concluded there was still considerable uncertainty about the long-term benefits of dupilumab.

## Approach to modelling mortality

3.12 The company captured the increased risk of death from COPD by applying standardised mortality ratios (SMRs) to general population mortality. The company sourced the SMRs from the Whittaker et al. (2024) study, which reported all-cause mortality hazard ratios by COPD severity, based on a UK dataset. The company noted that excess mortality from COPD has been linked to both COPD severity 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) for severe exacerbations. The

EAG initially had concerns about applying a separate CFR. It thought that the impact of exacerbations on mortality may have already been accounted for within the COPD severity mortality. So, including a separate CFR may lead to double counting. The EAG noted that Whittaker et al. controlled for recent exacerbation history in the regression models used to estimate the hazard ratio associated with COPD severity. At the first meeting, the committee agreed with the EAG that applying the SMRs may already account for the impact of severe exacerbations. But the extent of this was unclear. At the first meeting, 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. The committee concluded that it would like to see more evidence to support the mortality assumptions used in the model.

In response to draft guidance consultation, the company provided further evidence for applying a separate CFR to account for the increased risk of mortality from exacerbations. The company also noted 4 recently published cost-effectiveness analyses in COPD in which both a CFR and SMR were applied. The company added that only 4.3% of the study population in Whittaker et al. (the source the company used for the SMRs) had 1 or more severe exacerbations in the previous year. On considering the new evidence the EAG revised its base case to include a separate CFR. The EAG was reassured that the proportion of people having severe exacerbations in the Whittaker et al. population was small and that the proportion of patients who would die because of a severe exacerbation was even smaller. So, the EAG considered that the risk of double counting should be low. The committee considered that applying a separate CFR may still capture some background mortality. But it was reassured that the risk of double counting was low. It concluded that

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 was appropriate.

### Source of data for the case fatality rate

3.13 The company's assumed CFR of 15.6% was based on Hoogendoorn et al. (2011). But the EAG was concerned that this study was based on a meta-analysis of 6 non-UK studies, with the latest study using data collected from 2000 to 2005. So, the studies may not reflect current clinical practice. At draft guidance consultation the company provided alternative sources of evidence for the CFR but maintained that the Hoogendoorn et al. study was the most appropriate and robust evidence source. The company explained that Hoogendoorn et al. avoided arbitrary time cut-offs for the period in which exacerbation mortality is captured. It added that the study only captured excess mortality for severe exacerbations and excluded background mortality. In its critique of the company's response, the EAG remained concerned about the applicability of Hoogendoorn et al. given the age of the included studies. In its base case, the EAG preferred to use a CFR of 11.9% based on 90-day mortality data from the National Asthma and COPD Audit Programme (NACAP) for 2018 to 2020. The EAG noted that this was the largest and most relevant dataset available to provide an estimate of the CFR in England and Wales. The EAG added that it was not overly concerned by the 90-day cut-off in the NACAP data because people in the model were still at a higher risk of severe exacerbation in the following model cycle. At the second committee meeting, the clinical expert explained that key data had become available from the National Respiratory Audit Programme (NRAP) for 2021 to 2023. This reported a 90-day mortality of 14.2%. The clinical expert clarified that this is an update of the NACAP 2018 to 2020 data used by the EAG. One of the patient experts said that they supported using the latest data for mortality to reflect current clinical practice. The EAG noted that COVID-19-related events may have affected mortality in the latest NRAP dataset and it was unclear whether these had been

controlled for in the analysis. The clinical expert explained that the impact of the pandemic was unknown but that it was plausible that it could have affected mortality in either direction. The company also stated that NRAP data is collected for policy purposes and is less informative as a source of data for the CFR. This is because it reports mortality data for an exacerbation for 90 days following the exacerbation only, but people are at risk for up to 1 year. The company added that the Hoogendoorn et al. data is more appropriate because it provides an estimate of mortality from an exacerbation that is irrespective of time. The company added that the Echevaria et al. (2017) and Echevaria et al. (2022) studies reported a 90-day mortality estimate of 17.5%, which is higher than the CFR of 15.9% used in the company's base case. The committee agreed with the EAG's concerns about the applicability of the Hoogendoorn et al. data. It preferred the national audit data used by the EAG because it considered this the most comprehensive and relevant data on exacerbations in the NHS. It also recognised the benefits of using the latest NRAP data presented by the clinical expert at the meeting but noted remaining uncertainty about whether the analysis had been affected by the COVID-19 pandemic. The committee acknowledged there was uncertainty in all the estimates presented but concluded that its preference was to use the latest data from NRAP for the CFR.

## Utility values

3.14 Health-related quality of life data was collected in NOTUS and BOREAS using both the SGRQ and EQ-5D-5L. But because of the infrequent collection timepoints of the EQ-5D-5L, the company could not 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 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 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 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 applying a disutility 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).

## Cost-effectiveness estimates

### The committee's preferences

3.15 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 0.3 x 10^9 cells per litre or more (300 cells per microlitre or more) (see section 3.9)
- modelling the reduction in both moderate and severe exacerbations by applying rate ratios for each COPD severity group derived from the combined data on moderate and severe exacerbations (see section 3.10)
- assuming the treatment effect of dupilumab would be maintained for 3 years, with the benefit compared with background therapy maintained for the lifetime of model (see section 3.11)
- 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 3.12)
- applying a CFR based on NRAP 2021 to 2023 data (see section 3.13), which reported a 90-day mortality of 14.2%
- using utility values derived from the utility regression model including only statistically significant covariates (that is, non-treatment-arm-specific utility values; see section 3.14).

Based on these assumptions, the committee's preferred probabilistic incremental cost-effectiveness ratio (ICER) was £23,113 per quality-adjusted life year (QALY) gained.

### Acceptable ICER

3.16 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 that some of the uncertainties at the first committee meeting had now been addressed. But it noted there was still a high level of uncertainty about the:

- difference in the rate of severe exacerbations between treatment arms (see section 3.10)
- long-term treatment effect for dupilumab compared with background therapy (see section 3.11)
- true value of the CFR associated with severe exacerbations (see section 3.13).

The committee noted that the large population of people expected to be eligible for dupilumab treatment meant that the decision risk was high. But it acknowledged that more people from lower socioeconomic groups would benefit from dupilumab. It agreed that this was an uncaptured benefit that could help reduce health inequalities. 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).

## Equality and health inequality issues

3.17 The committee considered whether NICE's duties under the equality legislation required it to alter or add to its recommendations. It noted the following points 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 medicines and differential referral rates for COPD rehabilitation, for people of different ethnicities and socioeconomic backgrounds and depending on geographical location.
- People from more deprived areas find accessing healthcare difficult because of practicality and cost.
- Dupilumab has the potential to alleviate health inequalities because people would have access to it in all geographic regions.

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 equality issues. A patient expert at the second committee meeting explained that mortality from COPD is 5 times higher in the most deprived areas compared with the least deprived. But mortality from cardiovascular diseases is only 1.8 times higher. The committee acknowledged stakeholders' concerns about health inequalities. But it noted that a positive recommendation for dupilumab could not be expected to resolve all the social inequalities within COPD. The committee concluded that the broader social inequalities within COPD are outside the remit of NICE's technology appraisal programme. But it acknowledged that access to dupilumab would have greater impact for people from lower socioeconomic groups. It accepted that this could play a role in reducing health inequalities and took this into account when determining its preferred ICER threshold.

## Conclusion

### Recommendation

3.18 Clinical trial evidence shows that dupilumab plus triple therapy, or double therapy if an inhaled corticosteroid is not appropriate, reduces the number of exacerbations and improves lung function compared with double or triple therapy alone for uncontrolled COPD. The cost-effectiveness estimates are within the range that NICE considers an acceptable use of NHS resources. So, dupilumab can be used.

# 4 Implementation

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

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 60 days of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment ‘as an option’, the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has uncontrolled chronic obstructive pulmonary disease 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 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.

**Dilan Savani and Anna Willis**

Technical leads

**Zoe Charles**

Technical adviser

**Jennifer Upton**

Project manager

**Janet Robertson and Ian Watson**

Associate directors

ISBN: [to be added at publication]