SMC2801

dupilumab 300 mg solution for injection in pre-filled pen or pre-filled syringe (Dupixent®)

Sanofi

04 July 2025

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

dupilumab (Dupixent®) is not recommended for use within NHSScotland.

Indication under review: 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.

In two phase III studies, the addition of dupilumab compared with placebo to triple inhaler therapy significantly reduced the annualised rate of moderate or severe COPD exacerbations in patients with uncontrolled COPD with raised blood eosinophils.

The submitting company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

Co-Vice Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Dupilumab is a recombinant human immunoglobulin (Ig)-G4 monoclonal antibody that inhibits interleukin (IL)-4 and IL-13 signalling, both major drivers of type 2 inflammation in conditions including chronic obstructive pulmonary disease (COPD). Elevated IL-4 and IL-13 levels have also been observed in patients with COPD during acute exacerbations. Dupilumab is the first biologic medicine licensed for this indication.[1-3]

The recommended dose of dupilumab as an add-on maintenance treatment for COPD is 300 mg administered by subcutaneous (SC) injection every other week. Consideration should be given to discontinuing treatment in patients who have shown no response after 52 weeks of treatment. See the Summary of Product Characteristics (SPC) for details.[1, 2]

1.2. Disease background

COPD encompasses a group of lung conditions (including emphysema, bronchiolitis and chronic bronchitis), characterised by chronic respiratory symptoms (such as breathlessness, cough and sputum production) and persistent, often progressive, airflow obstruction. Tobacco smoking is the main cause of COPD, although air pollution and occupational exposure to dusts, fumes and chemical agents are also potential causes. COPD is a leading cause of morbidity and mortality worldwide and many people suffer for years from the burden of this disease. It is more common in smokers, ex-smokers and people aged 40 years and older. Periods of acute worsening of respiratory symptoms (called exacerbations) is a key contributor to further disease progression. Type 2 inflammation (as indicated by raised blood eosinophils) is present in up to 40% of patients and has been associated with increased exacerbations and risk of mortality.[3-6]

1.3. Treatment pathway and relevant comparators

The aim of treatment for COPD is to reduce symptoms and the risk of future exacerbations. The Global Initiative for COPD (GOLD) recommends that a combined assessment strategy, based on level of symptoms, risk of exacerbations, severity of airflow limitation, eosinophil count and co-morbidities, is used to determine disease severity and guide choice of treatment. Four disease grades are defined based on severity of airflow limitation: GOLD grade 1 (mild, forced expiratory volume in 1 second [FEV1] ≥80% predicted), GOLD grade 2 (moderate, FEV1 ≥50% and <80% predicted), GOLD grade 3 (severe, FEV1 ≥30% and <50% predicted) and GOLD grade 4 (very severe, FEV1 <30% predicted).[4]

In addition to smoking cessation, GOLD guidelines recommend a combination of a long-acting beta2-agonist (LABA) and a long-acting muscarinic antagonist (LAMA) for patients at high risk of exacerbation. Triple therapy (that is, the addition of ICS to LABA and LAMA) is recommended for patients with raised blood eosinophils (defined as ≥300 cells per microlitre).[4] Standard of care with triple inhaler therapy alone (or LABA plus LAMA when ICS is not suitable) was the most relevant comparator.

There are currently three triple inhaler therapies licensed for COPD and available within NHSScotland: Trelegy® Ellipta® (fluticasone/vilanterol/umeclidinium) (SMC1303/18), Trimbow® (beclometasone/formoterol/glycopyrronium) (SMC1274/17) and Trixeo® Aerosphere®

(budesonide/formoterol/glycopyrronium) (SMC2321). These are accepted for restricted use by SMC in patients with severe COPD (defined as FEV1 <50% predicted normal). Clinical experts consulted by SMC considered that dupilumab fills an unmet need as add-on therapy in patients with uncontrolled COPD and raised blood eosinophils.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence for dupilumab for this indication comes from the replicate studies, BOREAS and NOTUS. Details are provided in Table 2.1.

Table 2.1. Overview of relevant studies[3, 7, 8]

Criteria	BOREAS and NOTUS
Study design	Two replicate international, randomised, double-blind, phase III studies.
Eligible patients	• Adults aged 40 to 80 years (BOREAS); 40 to 85 years (NOTUS). • Physician-diagnosed COPD for ≥12 months. • Background triple inhaler therapy (ICS, LABA and LAMA), or double therapy (LABA and LAMA) if ICS was contraindicated, for ≥3 months and a stable dose for ≥1 month before screening. • Moderate to severe COPD (defined as post-BD FEV1/FVC ratio <0.70 and post-BD FEV1 >30% to ≤70% of predicted value) at screening. • Had at least two moderate or at least one severe exacerbation within the previous year (at least one of the moderate exacerbations had required treatment with systemic glucocorticoids and at least one exacerbation had occurred when receiving background triple therapy [or double therapy if ICS was contraindicated]). • MRC Dyspnoea Scale grade ≥2. • Patient-reported signs and symptoms of chronic bronchitis (chronic productive cough) for ≥3 months in the previous year, in the absence of other known causes of chronic cough. • Raised blood eosinophils (≥300 cells per microlitre) during screening. • Current or former smokers with a smoking history of ≥10 pack-years.
Treatments	Dupilumab 300 mg or placebo as a SC injection every 2 weeks for 52 weeks. All patients continued to receive maintenance triple therapy (ICS, LABA and LAMA), or double therapy (LABA and LAMA) if ICS was contraindicated.
Randomisation	Patients were randomised equally, stratified according to country and ICS dose at baseline (high dose: yes or no). Enrolment of current smokers was capped at 30%.
Primary outcome	Annualised rate of moderate or severe COPD exacerbations over the 52-week treatment period. Moderate exacerbations were defined as those that required systemic glucocorticoids, antibiotics, or both. Severe exacerbations were defined as those that led to hospitalisation or an emergency medical care visit (with observation for >24 hours) or resulted in death.
Key secondary outcomes	• Change in pre-BD FEV1 from baseline to week 12. • Change in pre-BD FEV1 from baseline to week 52. • Change in pre-BD FEV1 from baseline to week 12 in the subgroup of patients with baseline FeNO ≥20 ppb. • Change in pre-BD FEV1 from baseline to week 52 in the subgroup of patients with baseline FeNO ≥20 ppb. • Change from baseline to week 52 in SGRQ total score. • Proportion of patients with SGRQ improvement ≥4 points (MCID) at week 52. • Change in E-RS-COPD total score from baseline to week 52.

	• Annualised rate of moderate or severe COPD exacerbations over the 52-week treatment period in the subgroup of patients with baseline FeNO ≥20 ppb.
Statistical analysis	A hierarchical testing strategy was applied in both studies with no formal testing of outcomes after the first non-significant outcome in the hierarchy. Key secondary outcomes were tested in the hierarchical order above, at a two-sided significance level of 0.049 (an administrative penalty of 0.001 was taken from the significance level due to a planned interim analysis).

Abbreviations: BD = bronchodilator; COPD = chronic obstructive pulmonary disease; E-RS-COPD = Evaluating Respiratory Symptoms in COPD; FeNO = fractional exhaled nitric oxide; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; ICS = inhaled corticosteroid; LABA = long-acting beta2-agonist; LAMA = long-acting muscarinic antagonist; MCID = minimum clinically important difference; MRC = Medical Research Council; ppb = parts per billion; SC = subcutaneous; SGRQ = St George's Respiratory Questionnaire.

Available results come from the final analysis of the BOREAS study and a prespecified interim analysis of the NOTUS study, which became the primary and final analysis since the primary outcome had been met. As an add-on maintenance treatment, dupilumab significantly reduced the primary outcome (annualised rate of moderate or severe COPD exacerbations) compared with placebo in both studies. In BOREAS, there were also significant improvements in all key secondary outcomes with dupilumab compared with placebo. In NOTUS, dupilumab failed to reach statistical significance for the secondary outcome of change in pre-bronchodilator (pre-BD) FEV1 from baseline to week 52 among patients with a baseline fractional exhaled nitric oxide (FeNO) level ≥20 ppb and further statistical testing was stopped with results for subsequent outcomes considered descriptive only and not inferential (no p-values reported).[3, 7, 8] See Table 2.2 for details.

Table 2.2. Results of primary and key secondary outcomes from BOREAS and NOTUS (ITT populations).[1-3, 7, 8]

	BOREAS		**NOTUS**	
	Dupilumab (n=468)	**Placebo (n=471)**	**Dupilumab (n=470)**	**Placebo (n=465)**
Primary outcome: Annualised rate of moderate or severe COPD exacerbations during the 52-week treatment period				
Adjusted annualised rate, events per year	0.78	1.10	0.86	1.30
Rate ratio versus placebo (95% CI)	0.70 (0.58 to 0.86), p<0.001		0.66 (0.54 to 0.82), p<0.001	
Key secondary outcomes				
Change in pre-BD FEV1 from baseline to week 12				
LSM change (95% CI), L	0.16	0.08	0.14	0.06
Difference versus placebo (95% CI)	0.08 (0.04 to 0.12), p<0.001		0.08 (0.04 to 0.12), p<0.001	
Change in pre-BD FEV1 from baseline to week 52				
LSM change, L	0.15	0.07	(n=362) 0.12	(n=359) 0.05

Difference versus placebo (95% CI)	0.08 (0.04 to 0.13), p<0.001		0.06 (0.01 to 0.11), p=0.02	
Change in pre-BD FEV1 from baseline to week 12 among patients with baseline FeNO level ≥20 ppb				
LSM change, L	(n=195) 0.23	(n=188) 0.11	(n=172) 0.22	(n=183) 0.08
Difference versus placebo (95% CI)	0.12 (0.04 to 0.20), p=0.002		0.14 (0.06 to 0.22), p=0.001	
Change in pre-BD FEV1 from baseline to week 52 among patients with baseline FeNO level ≥20 ppb				
LSM change, L	(n=195) 0.25	(n=188) 0.12	(n=132) 0.18	(n=132) 0.10
Difference versus placebo (95% CI)	0.13 (0.04 to 0.21), p=0.003		0.08 (-0.02 to 0.18), p=0.11[a]	
Change in SGRQ score from baseline to week 52[b]				
LSM change	-9.7	-6.4	(n=362) -9.8	(n=359) -6.4
Difference versus placebo (95% CI)	-3.4 (-5.5 to -1.3), p=0.002		-3.4 (-5.8 to -0.9)	
Proportion with SGRQ improvement ≥4 points at week 52[b]				
% (n/N)	51% (241/468)	43% (203/471)	51% (186/362)	46% (167/359)
Odds ratio versus placebo (95% CI)	1.4 (1.1 to 1.9), p=0.009		1.2 (0.9 to 1.6)	
Change in E-RS COPD total score from baseline to week 52[c]				
LSM change	-2.7	-1.6	(n=362) -2.4	(n=359) -1.8
Difference versus placebo (95% CI)	-1.1 (-1.8 to -0.4), p=0.001		-0.6 (-1.4 to 0.2)	
Annualised rate of moderate or severe COPD exacerbations among patients with baseline FeNO level ≥20 ppb				
Adjusted annualised rate, events per year	(n=195) 0.70	(n=188) 1.12	(n=172) 0.74	(n=183) 1.57
Rate ratio versus placebo (95% CI)	0.62 (0.45 to 0.87), p=0.005		0.47 (0.33 to 0.68)	

Abbreviations: BD = bronchodilator = CI = confidence interval; COPD = chronic obstructive pulmonary disease; E-RS COPD = Evaluating Respiratory Symptoms in COPD; FeNO = fractional exhaled nitric oxide; FEV1 = forced expiratory volume in 1 second; ITT = intention-to-treat; l = litres; LSM = least squares mean; ppb = parts per billion; SGRQ = St George's Respiratory Questionnaire.

[a]This result was not statistically significant and subsequent outcomes were not formally tested. Therefore the results reported for these outcomes are descriptive only (no p-values reported).

[b]The St George's Respiratory Questionnaire (SGRQ) is a 50-item questionnaire used to assess health-related quality of life (HRQoL) in adult patients with chronic airflow limitation. Scores range from 0 to 100, with lower scores indicating better HRQoL, and a minimum clinically important difference of 4 points.

[c]The Evaluating Respiratory Symptoms in COPD (E-RS-COPD) is an 11-item instrument used to assess the effect of treatments on the severity of respiratory symptoms in patients with stable COPD. Scores range from 0 to 40, with lower scores indicating less severe respiratory symptoms.

In both studies, prespecified subgroup analyses were also conducted according to demographics, baseline disease characteristics and type 2 inflammation biomarkers (including blood eosinophils and FeNo levels). These were generally consistent with results in the overall study populations, although there appeared to be a greater treatment effect in patients with type 2 inflammation.[3, 7, 8]

The submitting company presented results of pooled analyses of the two studies based on the final analysis of BOREAS and the interim analysis of NOTUS reported above. These analyses were prespecified but were not controlled for multiplicity; results were used to inform the economic base case. Details are presented in Table 2.3.

Table 2.3: Primary and key secondary outcomes from pooled analyses of BOREAS and NOTUS (ITT population)[1-3, 9]

	Dupilumab (n=938)	**Placebo (n=936)**
Primary outcome: Annualised rate of moderate or severe COPD exacerbations during the 52-week treatment period		
Adjusted annualised rate, events per year	0.79	1.16
Rate ratio versus placebo (95% CI	0.69 (0.60 to 0.79)	
Change in pre-BD FEV1 from baseline to week 12		
LSM change, L	0.15	0.06
Difference versus placebo (95% CI)	0.08 (0.05 to 0.11)	
Change in pre-BD FEV1 from baseline to week 52		
LSM change, L	(n=830) 0.13	(n=830) 0.06
Difference versus placebo (95% CI)	0.07 (0.04 to 0.11)	
Change in pre-BD FEV1 from baseline to week 12 among patients with baseline FeNO level ≥20 ppb		
LSM change, L	(n=367) 0.22	(n=371) 0.09
Difference versus placebo (95% CI)	0.13 (0.07 to 0.19)	
Change in pre-BD FEV1 from baseline to week 52 among patients with baseline FeNO level ≥20 ppb		
LSM change, L	(n=327) 0.21	(n=320) 0.10
Difference versus placebo (95% CI)	0.11 (0.04 to 0.17)	
Change in SGRQ score from baseline to week 52		
LSM change	(n=830) -9.9	(n=830) -6.6
Difference versus placebo (95% CI)	-3.40 (-4.95 to -1.78)	
Proportion with SGRQ improvement ≥4 points at week 52		
% (n/N)	51% (427/830)	45% (370/830)
Odds ratio (95% CI)	1.31 (1.07 to 1.61)	
Change in E-RS-COPD total score from baseline to week 52		
LSM change	(n=830) -2.52	(n=830) -1.60
Difference versus placebo (95% CI)	-0.91 (-1.44 to -0.39)	
Annualised rate of moderate or severe COPD exacerbations among patients with a baseline FeNO level ≥20 ppb		
Adjusted annualised rate, events per year	(n=367) 0.73	(n=371) 1.32
Rate ratio versus placebo (95% CI)	0.55 (0.43 to 0.70)	

Abbreviations: BD = bronchodilator = CI = confidence interval; COPD = chronic obstructive pulmonary disease; E-RS COPD = Evaluating Respiratory Symptoms in COPD; FeNO = fractional exhaled nitric oxide; FEV1 = forced expiratory

volume in 1 second; ITT = intention-to-treat; l = litres; LSM = least squares mean; ppb = parts per billion; SGRQ = St George's Respiratory Questionnaire.

In addition, in the pooled analysis of BOREAS and NOTUS, the annualised rate of severe COPD exacerbations (defined as exacerbations requiring hospitalisation, or observation for >24 hours in an emergency department/urgent care facility or resulting in death) was 0.08 in the dupilumab group (n=938) compared with 0.12 in the placebo group (n=936); rate ratio 0.67 (95% CI 0.44 to 1.04).[1, 2]

2.2. Health-related quality of life outcomes

Health-related quality of life (HRQoL) was assessed as key secondary outcomes in both studies, including change in St George's Respiratory Questionnaire (SGRQ) score from baseline and the proportion with a minimally important difference of ≥4-point improvement in SGRQ score, both assessed at week 52. Details are presented in Table 2.2.[1-3, 7, 8]

3. Summary of Safety Evidence

Overall, dupilumab as an add-on maintenance treatment for COPD was well tolerated. The safety profile was generally consistent with its known safety profile in other indications and no new safety signals were identified.[3]

A pooled safety analysis of the BOREAS and NOTUS studies, including safety data up to week 52, was presented in the company submission. Placebo plus standard of care triple or double inhaler therapy is considered a relevant comparator in this submission. Any treatment-emergent adverse event (AE) was reported by 72% (676/938) of patients in the dupilumab group and 71% (663/934) of patients in the placebo group, and these were considered treatment-related in 5.3% and 3.9% respectively. In the dupilumab and placebo groups respectively, patients with a reported serious AE were 13% versus 16% and patients discontinuing treatment due to an AE was 3.4% versus 3.0%.[3, 10]

The most common treatment-emergent AEs in the dupilumab group versus the placebo group were: nasopharyngitis (7.8% versus 7.4%), headache (7.8% versus 6.6%), COVID-19 (6.9% versus 7.1%), accidental overdose (6.1% versus 6.6%), upper respiratory tract infection (5.3% versus 6.1%) and COPD (5.3% versus 6.9%).[3, 10]

Overall, 19 patients (2.0%) in the dupilumab group and 15 patients (1.6%) in the placebo group died due to a treatment-emergent AE but none of these deaths were considered treatment-related by the investigator.[3, 10]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- In two large, randomised, double-blind, phase III studies (BOREAS and NOTUS), dupilumab significantly reduced the annualised rate of moderate or severe COPD exacerbations compared with placebo over the 52-week treatment period (by 30% and 34% respectively; 31% reduction in the pooled analysis). This treatment effect was maintained through the

52-week treatment period. Overall, these results were considered clinically meaningful by the regulator.[3, 7, 8]

- Results for key secondary outcomes, including lung function, respiratory symptoms and HRQoL, which were controlled for multiplicity, were supportive in both studies.[3, 7, 8]
- Prespecified subgroup analyses were generally consistent and supported a treatment benefit with dupilumab for most subgroups. The European regulatory review noted that a similar treatment benefit was observed in patients with emphysema, current and former smokers and patients aged >65 years. Secondary outcomes in the subgroup of patients with FeNO levels ≥20 ppb were hierarchically tested and controlled for multiplicity.[3, 7, 8]
- Overall, dupilumab was well tolerated in patients with uncontrolled COPD, and the safety profile was generally consistent with its known safety profile in other indications.[3, 7, 8]
- The introduction of dupilumab would offer the first biologic medicine for add-on maintenance treatment in patients with uncontrolled COPD and raised blood eosinophils.[1, 2]

4.2. Key uncertainties

- Available evidence for this indication is limited to the 52-week treatment periods of both studies. Therefore, there is uncertainty about the long-term efficacy and safety of dupilumab for the treatment of COPD, which is a chronic and progressive condition. The BOREAS and NOTUS studies did not assess the treatment effect of dupilumab on mortality. The SPC notes that dupilumab is intended for long-term treatment in COPD but that dosing beyond 52 weeks has not been studied and that consideration should be given to discontinuing treatment in patients who have shown no response after 52 weeks of treatment for COPD. There is evidence of exposure to dupilumab for up to 5 years in other licensed indications, although elderly patients are less well represented.[1-3, 7, 8]
- The annualised rate of moderate or severe COPD exacerbations in the placebo groups of the BOREAS and NOTUS studies was lower (1.1 and 1.3 respectively) during the treatment period than the required inclusion criterion and the baseline number of exacerbations (2.3 and 2.1 respectively). Both studies were partially conducted during the COVID-19 pandemic and public health measures may have resulted in fewer COPD exacerbations and affected the size of the treatment effect. However, a subgroup analysis by year of enrolment indicated that meaningful reductions in exacerbations and improvements in lung function were seen across the years of enrolment.[3, 7, 8]
- The treatment effect of dupilumab on the primary outcomes was mainly driven by a reduction in moderate COPD exacerbations. In each study, the number of severe exacerbations was low and the confidence intervals around the rate ratios included 1. However, additional analyses in the pooled population provided to the regulator suggested a trend toward a similar reduction in the rate of severe exacerbations (33%).[3]
- Available results of the NOTUS study are derived from the planned interim analysis, which became the primary analysis after a statistical reduction was achieved in the primary

outcome with dupilumab compared with placebo; this analysis included data for 77% of the completed study population and reduced the power of some week 52 outcomes.[3, 7]

- Results of the pooled analysis of BOREAS and NOTUS have been used within the economic base case. However, although prespecified, these analyses were not controlled for multiplicity and should be considered descriptive only.[3]
- The submitting company considered that uncontrolled COPD was defined as at least two moderate or at least one severe exacerbation having occurred within 12 months and raised blood eosinophils as a count ≥300 cells/microlitre. These definitions align with the evidence from the clinical studies but may differ with how patients may be defined in clinical practice.[7, 8]
- There is limited evidence in patients with FEV1 <30% (GOLD grade 1) or >70% (GOLD grade 4). Patients with current or prior asthma were excluded from both studies therefore the generalisability of study results in those with concomitant COPD and asthma diagnosis is uncertain.[1, 2, 7, 8]

4.3. Clinical expert input

Clinical experts consulted by SMC considered that dupilumab fills an unmet need and is a therapeutic advancement due to limited treatment options.

4.4. Service implications

Dupilumab would require SC injection every 2 weeks, which may have implications for patients to self-administer and the service to initiate, possibly administer and monitor.

5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from Asthma + Lung UK, which is a registered charity.
- Asthma + Lung UK has received 5.3% pharmaceutical company funding in the past two years, including from the submitting company.
- Patients with COPD suffer from a range of symptoms, including breathlessness, cough and sputum production, poor sleep, depression, and skeletal muscle loss—such a symptom burden can significantly impact people living with COPD's quality of life. As a long-term chronic condition, the impact on family members of a loved one living with COPD can grow over time, as someone becomes more disabled by the breathlessness caused by their condition.
- The current therapeutic approach does not meet all the needs of patients with COPD. Some patients are trapped in a vicious cycle of exacerbations and lung function decline.
- By reducing exacerbations dupilumab has the potential to improve the quality of life for many people with COPD and type 2 inflammation and help them manage this progressive and debilitating condition. Patients living with COPD told the patient group that dupilumab makes them hopeful that they will have a "better life quality and will be able to manage this disease."

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

A summary of the economic analysis provided by the submitting company is outlined in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	Lifetime time horizon of 35 years.
Population	For adults as add-on maintenance treatment for uncontrolled COPD characterised by raised blood eosinophils on a combination of an ICS, a LABA, and a LAMA, or on a combination of a LABA and a LAMA, if ICS is not appropriate.
Comparators	Dupilumab, in combination with background therapy, was compared with background therapy alone, which was a weighting of various ICS plus LAMA plus LABA regimen (or LAMA plus LABA if ICS is not appropriate).
Model description	The model started with a one-year decision tree, during which patients were assigned to health states based on COPD severity (mild, moderate, severe and very severe) using the GOLD criteria and exacerbation (none, moderate and severe) history. Following this, a 13-state Markov model simulated disease progression using COPD severity stages and exacerbation status, with responders to dupilumab continuing treatment and non-responders reverting to background therapy. Patients could experience adverse events annually, and disease progression was modelled through changes in FEV1 and exacerbations, with only deterioration permitted over time. An absorbing death state was also included. The model had a cycle length of 1 year with a half-cycle correction applied.
Clinical data	The data underpinning the decision tree phase of the model came from two replicate international, randomised, double-blind, phase III studies (BOREAS and NOTUS).[3, 7, 8] Pooled analyses of the two studies were used in the base case utilising the final analysis of BOREAS and the interim analysis, which became the final analysis, of NOTUS. These analyses were prespecified but were not controlled for multiplicity.
Extrapolation	For the Markov model the submitting company had to model transition probabilities within a COPD stage (ie capturing the occurrence and severity of exacerbations), between COPD stages and to the death health state. The transition probabilities within a COPD stage were based on adjusted exacerbation incidence rate ratios from Whittaker et al. 2022.[11] The transition probabilities between COPD stages were based on real world evidence (RWE) on FEV1 decline from the TORCH study, with a Type 2 inflammation modifier based on the CanCOLD study.[12, 13] The submitting company also assumed a 2 year FEV1 treatment effect duration based on the TRAVERSE study.[14] An annual discontinuation rate of 15% was assumed based on Asthma data held by the submitting company along with an advisory board conducted by the submitting company.[15, 16] The mortality rate associated with the different COPD stages was based on UK RWE (Whittaker et al. 2024)[17], with a dupilumab treatment-specific multiplier, aligning with the mortality reduction observed in the IMPACT study associated with triple over double therapy.[18]
Quality of life	The submitting company developed their own mapping algorithm using data directly from the studies to derive utilities from SGRQ to EQ-5D-3L. The resulting values differed between COPD state as well as between the treatment arms. The base case values were classed as commercial in confidence, and so cannot be reported. Disutilities from exacerbations and cardiovascular events were included and utility values were age-adjusted.
Costs and resource use	Medicine costs included were acquisition costs and self-injection training costs. Other costs included were COPD management costs, exacerbation costs and cardiovascular event costs.

PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a discount was offered on the list price.

6.2. Results

The base case analysis suggested that dupilumab was associated with higher NHS costs, but also better health outcomes for patients. The main drivers of the higher costs were the acquisition cost for dupilumab. The main source of the health benefits was from dupilumab patients being less likely to enter the more severe COPD stages and being less likely to experience severe exacerbations.

The estimated incremental cost-effectiveness ratio, inclusive of the PAS discount on dupilumab, was £29,590.

*Other data were also assessed but remain confidential.**

6.3. Sensitivity analyses

The company used sensitivity and scenario analysis to explore areas of uncertainty. A selection of scenarios thought most relevant for decision making are presented in Table 6.3. The presented economic results are inclusive of the PAS discount on dupilumab.

Table 6.3 Sensitivity and Scenario Analysis Results (PAS prices)

	Parameter	Base case	Scenario	Incr. Costs (£)	Incr. QALYs	ICER (£/QALY)
	Base case			CiC	CiC	£29,590
1	Time horizon	35 years	20 years	CiC	CiC	£30,152
2	Continued FEV1 treatment effect duration beyond 52 weeks	2 years	1 year	CiC	CiC	£33,364
3			None	CiC	CiC	£40,489
4	Markov transition probabilities (transitions related to exacerbation)	Adjusted incidence rate ratios from Whittaker et al. 2022.	Background therapy - Pooled BOREAS and NOTUS; Dupilumab + background therapy - RR vs background therapy alone With pooled ITT baseline exacerbation taken during the trial	CiC	CiC	£38,817
5	Risk of severe exacerbations	Lower in dupilumab arm	Equal between treatment arms	CiC	CiC	£42,534
6	Excess mortality due to exacerbation	Whittaker et al 2024 SMRs with an adjustment based on the IMPACT trial	Hoogendoorn 2011 (with Whittaker 2024 mortality due to COPD GOLD stages and no treatment-specific mortality)	CiC	CiC	£23,862
7	Utility values	Treatment arm specific	Consistent across treatment arms	CiC	CiC	£32,897

8	Mortality adjustment for dupilumab patients	Applied	Not applied	CiC	CiC	£41,258
9	Combined scenario	1. Time horizon - 20 years 2. Continued FEV1 treatment effect duration beyond 52 weeks – None 3. Risk of a severe exacerbation - equal between the treatment arms 4. Utility values – consistent across treatment arm 5. Mortality adjustment for dupilumab patients – not applied		CiC	CiC	CiC

Abbreviations: COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; ICER = incremental cost-effectiveness ratio; ITT = intent-to-treat; NACAP = National Asthma and COPD Audit Program; PAS = patient access scheme; RR = risk ratio; RWE = real-world evidence; CiC = commercial in confidence

6.4. Key strengths

- The health states chosen and the progression of disease were appropriate for the disease profile of COPD.
- In BOREAS and NOTUS, dupilumab significantly reduced the annualised rate of moderate or severe COPD exacerbations compared with placebo over the 52-week treatment period.

6.5. Key uncertainties

- While the decision tree component of the model is supported by study data, the Markov model predominantly relies on assumptions not directly informed by evidence, introducing uncertainty. Furthermore, as the available clinical data from the BOREAS and NOTUS studies are limited to a 52-week treatment period, there remains considerable uncertainty regarding the long-term efficacy of dupilumab in the management of COPD, a chronic and progressive disease.
- There are several limitations with the submitting company's approach to modelling the transition between exacerbation states. The study informing transitions for patients without prior exacerbations (Wallace et al., 2019) included a high proportion of patients (42%) on monotherapy, whereas 98% of the ITT population in the central dupilumab studies received triple therapy, making the populations poorly aligned. Similarly, the study used to inform transitions for patients with prior exacerbations (Whittaker et al., 2022) included only around 25% of patients on triple therapy. Additionally, no statistically significant difference in severe exacerbations was observed between treatment arms during the 52-week dupilumab studies, but a difference in the rate of severe exacerbations was projected in the model. The model also assumed the relative reduction in exacerbation rates with dupilumab continues indefinitely, despite the absence of long-term data to support this. This may overestimate clinical and economic benefits. An alternative scenario, which projects the occurrence of exacerbations over time using the study data led to an increase in the ICER (see Scenario 4, Table 6.3). A scenario where the risk of severe exacerbation is equal between the treatment arms also increased the ICER (Scenario 5).

- There are several limitations regarding the approach taken to model transition probabilities between COPD severity stages in the Markov phase. A treatment effect period, in which all patients maintained their COPD severity status, was applied for two years in the dupilumab arm. This was partially justified based on the findings of the TRAVERSE asthma study, however, a key exclusion criterion in the BOREAS and NOTUS studies was the presence of asthma. In addition, asthma is not progressive like COPD and patients with COPD cannot be assumed to respond equally to treatment. The submitting company also claimed that the two-year treatment effect post-study period was supported by clinicians, however, the aggregated responses from the experts suggested a difference of less than a year. Scenarios exploring a shorter treatment duration increased the ICER (Scenarios 2 and 3). Further, the applied transitions were estimated using data from the TORCH study, which was old, dating from 2004, and so may be clinically out of date. Within the TORCH study, all patients were also on double therapy. These patients may have been at a medical disadvantage compared with patients in the BOREAS and NOTUS studies, who predominantly received triple therapy.
- The dupilumab SMR adjustment factor was the most sensitive parameter identified in the deterministic sensitivity analysis. Given that BOREAS and NOTUS were not powered for mortality outcomes, direct evidence was lacking, and this was a source of uncertainty in the economic evaluation. When the adjustment factor to the mortality of dupilumab patients was removed the resulting ICER increased (Scenario 8).
- It is likely that treatment arm specific utility values will be double counting the benefits of dupilumab as the submitting company has already modelled benefits in the transition to the more severe COPD stages and the more severe exacerbations compared with background therapy throughout the model time horizon.

7. Conclusion

After considering all the available evidence, the Committee was unable to accept dupilumab for use in NHSScotland.

8. Guidelines and Protocols

The National Institute for Health and Care Excellence (NICE) published the guideline: “Chronic obstructive pulmonary disease in over 16s: diagnosis and management” in December 2018, which was last updated in July 2019.[19]

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) published the “Global Strategy for the Diagnosis, Management and Prevention of COPD” report in 2001, which was last updated in 2025.[4]

9. Additional Information

9.1. Product availability date

09 September 2024

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
Dupilumab	**300 mg SC injection every 2 weeks**	**16,444**

Costs from BNF online on 30 April 2025. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 2,153 patients eligible for treatment with dupilumab in year 1 and 2,187 patients in year 3. SMC is unable to publish the with PAS budget impact due to commercial in confidence issues.

*Other data were also assessed but remain confidential.**

References

1. Sanofi. Dupilumab solution for injection in pre-filled pen (Dupixent®) Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk Last updated 24 January 2025.
2. Sanofi. Dupilumab solution for injection in pre-filled syringe (Dupixent®) Summary of product characteristics. Electronic Medicines Compendium www.medicines.org.uk Last updated 22 January 2025.
3. European Medicines Agency (EMA). European Public Assessment Report. Dupilumab (Dupixent®). 12/09/2024, EMA/291386/2024. www.ema.europa.eu 2024.
4. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2025. Available from: https://goldcopd.org/2025-gold-report/.
5. BMJ Best Practice. Chronic obstructive pulmonary disease (COPD). 2024 [cited 2025 Apr 3]; Available from: https://bestpractice-bmj-com.knowledge.idm.oclc.org/topics/en-gb/7.
6. George L, Brightling CE. Eosinophilic airway inflammation: role in asthma and chronic obstructive pulmonary disease. Therapeutic Advances in Chronic Disease. 2016;7(1):34-51.
7. Bhatt SP, Rabe KF, Hanania NA, Vogelmeier CF, Bafadhel M, Christenson SA*, et al.* Dupilumab for COPD with Blood Eosinophil Evidence of Type 2 Inflammation. New England Journal of Medicine. 2024;390(24):2274 EP - 83.
8. Bhatt SP, Rabe KF, Hanania NA, Vogelmeier CF, Cole J, Bafadhel M*, et al.* Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts. New England journal of medicine. 2023;389(3):205-14.
9. Sanofi. [Data on File] Summary of Clinical Efficacy (Chronic Obstructive Pulmonary Disease). 18 December 2023.
10. Sanofi. [Data on File] Summary of Clinical Safety (Chronic Obstructive Pulmonary Disease). 19 December 2023.
11. Whittaker H, Rubino A, Müllerová H, Morris T, Varghese P, Xu Y, et al. Frequency and Severity of Exacerbations of COPD Associated with Future Risk of Exacerbations and Mortality: A UK Routine Health Care Data Study. Int J Chron Obstruct Pulmon Dis. 2022;17:427-37.
12. Tan WC, Bourbeau J, Nadeau G, Wang W, Barnes N, Landis SH, et al. High eosinophil counts predict decline in FEV(1): results from the CanCOLD study. Eur Respir J. 2021;57(5).
13. Fenwick E, Martin A, Schroeder M, Mealing SJ, Solanke O, Risebrough N, Ismaila AS. Cost-effectiveness analysis of a single-inhaler triple therapy for COPD in the UK. ERJ Open Res. 2021;7(1).
14. Wechsler ME, Ford LB, Maspero JF, Pavord ID, Papi A, Bourdin A, et al. Long-term safety and efficacy of dupilumab in patients with moderate-to-severe asthma (TRAVERSE): an open-label extension study. Lancet Respir Med. 2022;10(1):11-25.
15. Sanofi. [Data on File] Homecare data for dupilumab in asthma. 2024.
16. Sanofi. [Data on File] Dupilumab COPD NICE HTA Advisory Board Meeting Report, Date: 12 – 19 July 2024. 2024.
17. Whittaker H, Rothnie KJ, Quint JK. Cause-specific mortality in COPD subpopulations: a cohort study of 339 647 people in England. Thorax. 2024;79(3):202-8.
18. Lipson DA, Crim C, Criner GJ, Day NC, Dransfield MT, Halpin DMG, et al. Reduction in All-Cause Mortality with Fluticasone Furoate/Umeclidinium/Vilanterol in Patients with Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2020;201(12):1508-16.
19. National Institute for Health and Care Excellence (NICE). Chronic obstructive pulmonary disease in over 16s: diagnosis and management. NICE guideline (NG115). 2019. Available from: https://www.nice.org.uk/guidance/NG115.

This assessment is based on data submitted by the applicant company up to and including 13 June 2025.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.