Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2317

dupilumab 200mg and 300mg solution for injection in pre-filled syringe and pen (Dupixent®)

Sanofi

05 March 2021

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 accepted for restricted use within NHSScotland.

Indication under review: in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO), who are inadequately controlled with high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.

SMC restriction: for the treatment of patients with blood eosinophils ≥150 cells/microlitre and FeNO ≥25 parts per billion, and ≥4 exacerbations in the preceding year, who have previously received biologic treatment with anti-IgE or anti-IL-5 therapies.

In a phase III study dupilumab, compared with placebo, reduced asthma exacerbation rates and was associated with greater improvements in lung function, in patients with asthma uncontrolled with medium to high dose ICS plus one or two controller medicines.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

Chairman
Scottish Medicines Consortium

Indication

In adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO), who are inadequately controlled with high dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment.[1, 2]

Dosing Information

The recommended dose of dupilumab administered as subcutaneous (SC) injection for adults and adolescents (≥12 years) is:

- An initial dose of 400mg (two 200mg injections), followed by 200mg given every other week.
- For patients with severe asthma and who are on oral corticosteroids or for patients with severe asthma and co-morbid moderate-to-severe atopic dermatitis or adults with co-morbid severe chronic rhinosinusitis with nasal polyposis, an initial dose of 600mg (two 300mg injections), followed by 300mg every other week.

Patients receiving concomitant oral corticosteroids may gradually reduce their steroid dose once clinical improvement with dupilumab has occurred.

Dupilumab is intended for long-term treatment. The need for continued therapy should be considered at least on an annual basis as determined by physician assessment of the patient's level of asthma control.

Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of conditions for which dupilumab is indicated. Please see Summary of product characteristics (SPC) for further information.[1, 2]

Product availability date

7 May 2019

Summary of evidence on comparative efficacy

Dupilumab is a recombinant human immunoglobulin (Ig)-G4 monoclonal antibody that, by binding to the interleukin (IL)-4 receptor alpha subunit (IL-4Rα), inhibits IL-4 and IL-13 signalling, both major drivers of type 2 inflammatory disease. By blocking the IL-4/IL-13 pathway, dupilumab decreases many of the mediators of type 2 inflammation.[1]

The submitting company has requested that SMC considers dupilumab when positioned for use for the treatment of patients with blood eosinophils (EOS) ≥150 cells/microlitre and fractional exhaled nitric oxide (FeNO) ≥25 parts per billion (ppb), and ≥4 exacerbations in the preceding year, who have previously received biologic treatment with anti-IgE or anti-IL-5 therapies.

The key evidence supporting the efficacy and safety of dupilumab for the indication under review comes from QUEST, an international, randomised, double-blind, placebo-controlled, phase III study. The study recruited patients aged 12 years and older with a diagnosis of uncontrolled asthma for ≥12 months (according to the Global Initiative for Asthma [GINA] 2014 Guidelines). Patients could participate if their existing treatment consisted of medium to high dose inhaled corticosteroid (ICS) in combination with one or two additional controller medicines (such as long acting beta-2 agonist [LABA], leukotriene receptor antagonist [LTRA], long-lasting muscarinic antagonist [LAMA], or methylxanthines) for at least 3 months with a stable dose ≥1 month prior to screening. Patients had to have experienced within 1 year prior to screening either treatment with a systemic corticosteroid (oral or parenteral) for worsening asthma at least once or hospitalisation or emergency medical care visit for worsening asthma; a pre-bronchodilator forced expiratory volume in 1 second (FEV1) ≤80% (adults) or 90% (adolescents) of predicted normal prior to randomisation; a FEV1 reversibility of at least 12% and 200mL after short-acting beta-2-adrenergic receptor agonists (SABA) administration; and scored ≥1.5 at screening and baseline in the 5-Item Asthma Control Questionnaire (ACQ-5).[3]

Patients were randomised in a 2:2:1:1 ratio to receive, every other week for 52 weeks, add-on therapy with subcutaneous (SC) dupilumab at a dose of 200mg (with 400mg loading dose [n=631]) or 300mg (with 600mg loading dose [n=633]) or a matched-volume placebo for each active dose (1.14mL [n=317] or 2mL [n=321], respectively). Existing treatment was to be continued at a stable dose throughout the study. Patients were permitted to use a SABA as reliever medication as needed. Concomitant medication with systemic corticosteroids was prohibited. Randomisation was stratified according to age (<18 years, ≥18 years), central laboratory EOS count (<300 cells/microlitre, ≥300 cells/microlitre), ICS dose (medium, high), and country.[3]

The study co-primary efficacy outcomes were: annualised rate of severe exacerbations (defined as a deterioration of asthma leading to treatment for 3 days or more with systemic corticosteroids or hospitalisation or an emergency department visit leading to treatment with systemic corticosteroids) during the 52-week treatment period and absolute change from baseline in the FEV1 before bronchodilator use at week 12. A hierarchical statistical testing strategy was applied to the co-primary outcomes (and two doses) and secondary outcomes with no formal testing of outcomes after the first non-significant outcome in the hierarchy. The following hierarchical order was used for the co-primary outcomes and two doses: 1) annualised severe exacerbation rate for 300mg every 2 weeks versus placebo; 2) absolute change from baseline in pre-bronchodilator FEV1 at week 12 for 300mg every 2 weeks versus placebo; 3) annualised severe exacerbation rate for 200mg every 2 weeks versus placebo; 4) absolute change from baseline in pre-bronchodilator FEV1 at week 12 for 200mg every 2 weeks versus placebo. Efficacy analyses were performed in the intention-to-treat (ITT) population, which included all patients who underwent randomisation.[3,4]

Dupilumab was associated with a statistically significant reduction of severe asthma exacerbations during the 52-week treatment period and a statistically significant increase in pre-bronchodilator FEV1 at week 12 compared with placebo. The EMA noted that, although the minimally clinically

important difference in FEV1 has not been rigorously established, it was "likely that change of 100-200mL in FEV1 can be perceived by patients as clinically important".

Table 1: Co-primary outcomes of QUEST (ITT population) [3, 4]

	Dupilumab 200mg (n=631)	Placebo 1.14mL (n=317)	Dupilumab 300mg (n=633)	Placebo 2mL (n=321)
Adjusted annualised rate of severe exacerbation events during the 52-week treatment period				
Estimate	0.46	0.87	0.52	0.97
Relative risk versus matching placebo (95% CI)	0.52 (0.41 to 0.66)		0.54 (0.43 to 0.68)	
p-value	<0.001		<0.001	
Absolute change from baseline in the FEV1 before bronchodilator use at week 12				
LS Mean, L	0.32	0.18	0.34	0.21
Difference, LS Mean square (95% CI)	0.14 (0.08 to 0.19)		0.13 (0.08 to 0.18)	
p-value	<0.001		<0.001	

CI, confidence interval; FEV1, forced expiratory volume in 1 second; ITT, intent to treat; LS, least squares; L, litre.

Secondary outcomes and sensitivity analyses were consistent with the co-primary outcomes, although, there was a break in the hierarchic testing procedure after which the results of the remaining secondary outcomes were descriptive only and not inferential (no p-values reported).[1, 3]

Subgroup analyses demonstrated that the greatest effects of dupilumab on the exacerbations rate and on the change in pre-bronchodilator FEV1 were seen in patients with raised levels of both type 2 inflammation biomarkers, EOS and FeNO (≥150 cells/microlitre and ≥25 ppb). Patients with raised level in either one of these biomarkers also showed clinically meaningful effects. In patients with low baseline EOS and FeNO levels (<150 cells/microlitre and <25 ppb), no reduction on the rate of exacerbations and only small changes in pre-bronchodilator FEV1 were seen.[4] To support the proposed positioning, small post-hoc subgroup analyses of severe exacerbations were presented by the submitting company but SMC is unable to present these due to commercial confidentiality issues.

Patient reported outcomes (PRO) measured in this study included: the Asthma Quality Of Life Questionnaire (AQLQ; global scores range from 1 to 7, with higher scores indicating better quality of life), the 5- and 7-item Asthma Control Questionnaires (ACQ-5 and ACQ-7, scores range from 0 to 6, with higher scores indicating less control) and the European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L). These were descriptively analysed. At week 24, AQLQ and ACQ-5 scores improvements, from baseline, exceeded the minimal clinically important difference of 0.5 in all groups. Greater improvements were seen in both dupilumab groups compared with the matching placebo groups. For ACQ-5, the European Medicines Agency (EMA) noted that although observed mean difference between groups "was nominally significant, the clinical relevance of the observed differences is not clear".[1, 3]

Supportive evidence comes from the dupilumab asthma studies: DRI12544, a 24-week randomised, double blind, placebo-controlled, phase IIb dose ranging study, VENTURE which assessed the corticosteroid sparing effect of dupilumab, and TRAVERSE, an open label extension study.[4]

VENTURE was a 24-week randomised, double blind, placebo-controlled, phase III study in 210 adult and adolescent patients with severe corticosteroid-dependent asthma. Patients were randomised equally to receive SC dupilumab 300mg every other week (n=103) or placebo (n=107). After an OCS dose-adjustment before randomisation, OCS doses were adjusted in a downward trend from week 4 to week 20 and then maintained at a stable dose for 4 weeks. The primary outcome was the percentage reduction in OCS dose at week 24 compared with baseline. Statistically significant improvement was demonstrated with dupilumab in mean percent reduction in OCS dose at week 24. The secondary outcomes results supported the primary outcome results. This study supported approval of dupilumab highest dose (300mg every other week) in patients with maintenance OCS.[4, 5]

TRAVERSE was a multinational, multicentre, single-arm, open-label extension study. Patients who completed treatment in dupilumab asthma studies (including QUEST, DRI12544 and VENTURE) were eligible for enrolment in this study. All patients were to receive SC dupilumab 300mg every other week for up to 96 weeks (reduced to 48 weeks by amendment), as an add-on to ICS in combination with other controller medications maintained from the parent asthma study. Overall, 2,284 patients were enrolled. Efficacy was measured as a secondary outcome. Results were similar to those observed in the parent asthma studies and dupilumab effects on severe asthma exacerbation rate were sustained over the treatment period.[1, 6, 7]

The submitting company presented three pairwise Bucher indirect treatments comparisons (ITCs) comparing dupilumab with mepolizumab, benralizumab and omalizumab. The ITCs target population was defined as adult (≥18 years) and adolescent (≥12 to <18 years) patients with persistent/uncontrolled asthma on medium-to-high or high-dose of ICS plus LABA or any other controller for the outcome of annualised severe asthma exacerbations. The submitting company concluded that the results suggest that, dupilumab 200mg was more efficacious than benralizumab and mepolizumab in reducing the annual rate of severe exacerbations, and that it had a numerical advantage over omalizumab, although this advantage was not statistically significant.

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

Summary of evidence on comparative safety

Overall, dupilumab appeared to be well tolerated, as supported by a sufficient safety database size in adolescent and adult patients.[4]

In QUEST, at data cut-off 29 July 2017, in the combined dupilumab and combined placebo groups respectively, any treatment-emergent adverse event (AE) was reported by 81% (1023/1263) and 83% (527/634) of patients; serious AEs were reported by 8.2% versus 8.4% of patients; and, 5.0% versus 4.6% of patients discontinued treatment permanently due to treatment emergent AEs.[3]

The most frequently reported treatment-emergent AEs of any grade, with an incidence >5% in any group, for the combined dupilumab versus the combined placebo group were: viral upper respiratory tract infection (18% versus 20%), upper respiratory tract infection (12% versus 14%), bronchitis (11% versus 14%), influenza (5.9% versus 8.0%), sinusitis (4.9% versus 8.8%), headache (6.8% versus 8.0%), accidental overdose (5.2% versus 5.0%). In addition, injection-site reactions (such as erythema, oedema, pruritus) were seen in 17% versus 7.9%.[3]

Two deaths, assessed as related to dupilumab, occurred during the open-label extension study TRAVERSE: a case of metastatic lung cancer and a case of gastric adenocarcinoma. Malignancy is therefore listed as an Important Potential Risk in the Risk Management Plan of dupilumab and subject of further investigation.[4]

Summary of clinical effectiveness issues

Asthma is a common and heterogeneous chronic inflammatory disorder of the airways characterised by symptoms such as wheeze, shortness of breath, chest tightness and/or cough and by variable expiratory airflow limitation. Approximately 5 to 10% of all patients with asthma have a severe form, which has a significant impact on quality of life, and almost 25% of these have had a near fatal asthma attack. Type 2 inflammation, characterised by the release of IL-4/IL-5/IL-13 and associated with elevated levels in related biomarkers such as eosinophils and/or FeNO, affects approximately half of severe asthma patients.[4, 8] Standard of care in this setting for adolescents and adults consists of a combination of high-dose ICS, with controller therapies (such as LABA or LTRA, LAMA [tiotropium, for adults only], or theophylline). Patients may also require frequent or continuous OCS and become steroid dependent, which is associated with increased morbidity. For eligible patients, with uncontrolled severe asthma despite maximally optimised therapy and a high OCS burden, biological therapy may be used (anti-IgE [omalizumab] or anti-IL-5 [mepolizumab and benralizumab]).[8-10]

Clinical experts consulted by SMC considered that there is an unmet need in this therapeutic area, namely for therapies targeting different inflammatory circuit, for patients with severe asthma who remain inadequately controlled despite treatment with the available biologic therapies. They have

also indicated that patients on maintenance OCS are often the most difficult to manage, and potentially those that could benefit the most from add-on treatment with dupilumab. Dupilumab is the first in this class of therapy to be approved for asthma.

The submitting company has requested that SMC considers dupilumab when positioned for the treatment of patients with EOS≥150 cells/microlitre and FeNO≥25ppb, and ≥4 exacerbations in the preceding year, who have previously received biologic treatment with anti-IgE or anti-IL-5 therapies.

In QUEST, treatment with dupilumab 200mg every other week as add-on maintenance therapy was associated with a reduction of 48% in the relative risk of developing severe exacerbations over the 52-week treatment period and an improvement of 140mL in pre-bronchodilator FEV1 at week 12 when compared with placebo in adults and adolescents (≥12 years old) with uncontrolled asthma despite treatment with medium to high dose ICS in combination with one or two additional controllers, and without OCS. A dose of 300mg every other week was also tested and approved for patients with severe asthma on OCS. The higher dose was not approved for patients without OCS due to the lack of additional benefits and a slightly better safety profile with the lowest dose. Secondary outcomes, such as asthma control and quality of life, and sensitivity analyses were generally consistent with the co-primary outcomes results. [4]

While statistically significant, the treatment effects observed on severe exacerbations were considered "moderate" from a clinical perspective by the EMA (in both relative and absolute terms [reduction from 0.87 exacerbation/year observed in the matching-placebo group to 0.46 in the dupilumab 200mg group]). The observed difference in FEV1 over placebo is likely to be clinically significant. [4] Subgroup analyses demonstrated that the greatest effects of dupilumab on the co-primary outcomes were seen in patients with raised levels of both type 2 inflammation biomarkers, EOS and FeNO (specifically EOS≥150 cells/microlitre and FeNO ≥25 ppb). Patients with a raised level in either one of these biomarkers also showed clinically meaningful effects. Small paediatric subgroup analyses (n=107) showed consistent improvements in FEV1, however for severe exacerbations only the results with the 200mg dose were consistent with results of the overall study population.[4] The EMA noted that after stopping treatment the duration of dupilumab effects was unclear, as was the possibility of rebound. [4]

To support the proposed positioning, the submitting company presented severe exacerbations results from post-hoc subgroup analyses. These subgroups were very small thus the results are uncertain, although they are consistent with the primary analyses.

VENTURE demonstrated that in OCS-dependent patients, treatment with dupilumab (300mg every other week) was associated with a statistically significant improvement in OCS dose reduction; and this effect was considered clinically meaningful and important by the EMA, due to the possible side effects of higher dose chronic systemic corticosteroid use.

QUEST excluded patients with severe asthma exacerbation at any time from 1 month prior to the screening up to and including the baseline visit, or who received bronchial thermoplasty within 3 years prior to screening, or who are current smoker or stopped smoking within 6 months prior to screening visit or previous smoker with a smoking history >10 pack-years. This may limit the generalisability of the study results to the Scottish population. In addition, data in elderly patients (>65 years) are limited.

None of the patients in the dupilumab asthma studies had previously received a biological therapy, therefore the effectiveness in patients with prior lines of biological therapies with anti-IgE (omalizumab) or anti-IL5 is uncertain.

In QUEST, the comparator was placebo as add-on to treatment consisting of medium to high dose ICS in combination with one or two additional controllers and no OCS. However, in practice, the maximally optimised treatment for severe uncontrolled asthma, as highlighted by the EMA and according to guidelines, is principally with high dose ICS and additional controllers. [4] In addition, biologics (omalizumab, mepolizumab and benralizumab) are also used as add-on therapy for some patients. There are no direct comparative data versus all the relevant biologic comparators. The submitting company conducted ITCs comparing dupilumab with mepolizumab, benralizumab and omalizumab. There are a number of limitations that affect the validity of the ITCs results, including the methods used (pairwise method and matching process with data generated from subgroups of dupilumab patients based on US/global labels), the absence of any direct evidence and heterogeneity across studies. Therefore, the conclusions are uncertain.

The introduction of dupilumab would offer an additional therapeutic option with a new mechanism of action for adults and adolescents (12 years and older) with severe type 2 inflammation asthma, uncontrolled despite optimised therapy, and who have responded inadequately to available biological therapies or where these are not suitable.

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

Summary of comparative health economic evidence

The submitting company presented a cost-utility analysis evaluating the cost-effectiveness of dupilumab within a restricted population of patients who experienced ≥ 4 exacerbations in the previous year who have previously received biologic treatment with anti-IgE or anti-IL5 therapies. The analysis compared dupilumab with ICS plus LABA at a high or medium dose (defined as 'standard of care' [SOC]) in patients not receiving maintenance OCS. Scenarios evaluating dupilumab in a population receiving maintenance OCS, and comparisons with mepolizumab and benralizumab, were also provided.

A three-state Markov model structure was used, representing treatment with dupilumab plus SOC, SOC alone, and non-asthma related mortality. Five severity-related sub states were used within

each treatment-related state, 'controlled asthma' (ACQ<1.5 at last visit and no exacerbation), 'uncontrolled asthma' (ACQ ≥1.5 at last visit and no exacerbation), 'moderate exacerbation' (multiple criteria for rescue medication use or a decrease in AM/PM peak flow) and 'severe exacerbation' (use of systemic corticosteroids for ≥ 3 days or hospitalisation/emergency department visit requiring systemic corticosteroids). Patients could transition between each severity level at each cycle, as well as dying from 'severe exacerbation' only and moving to 'asthma-related death'. A cycle length of 4 weeks was used and a lifetime time horizon (100 years) applied.

Transition probabilities were derived from a subgroup of the QUEST clinical study, representing patients on high dose ICS with EOS≥150 and FeNO≥25 and a history of ≥2 severe exacerbations.[3] Transition probabilities for rate of response and moderate and severe exacerbations were adjusted with a ratio derived using a binomial regression model to represent the increased exacerbation risk in the restricted population (≥4 severe exacerbations). Patient age at model entry was set to 48 years, based on the mean age of this subpopulation (versus 44 years in the population with ≥4 severe exacerbations). Study data were separated into three distinct time periods (0 – 12 weeks, 12 – 52 weeks and >52 weeks), given the observation of a higher rate of change in the first 12 weeks and the 52 week duration of the clinical study. Following 52 weeks, a multiplier (derived from a previous NICE appraisal [TA431]) was applied to the 12 – 52 week probabilities for both arms. The submitting company stated this is necessary to adjust for aspects of the QUEST study design that may have excluded patients with more frequent exacerbations and/or experienced multiple exacerbations within a 28 day cycle. Asthma-related mortality was modelled following an approach used by the NICE evidence review group (ERG) in a previous NICE submission (TA431) and other-cause mortality used adjusted population life tables for Scotland (2016-2018).

Health state utility values were derived using EQ-5D-5L data collected in the QUEST study and valued using the van Hout cross-walk algorithm (controlled asthma = 0.91; uncontrolled asthma = 0.79; severe exacerbation disutility: GP visit = -0.08; A&E visit = -0.09; hospitalisation = -0.15).[11]

Costs of medicines acquisition, administration and monitoring (for the first three dupilumab administrations) were included. Costs of managing adverse events were not included, although the costs of OCS were included as part of the cost of managing exacerbations. Patients not achieving a response to dupilumab by 52 weeks were assumed to discontinue and receive SOC only; a separate annual discontinuation rate observed in the QUEST study was applied across the time horizon. Resource use estimates for the controlled and uncontrolled states were derived from a previous published economic evaluation[12] and a separate published study from the British Thoracic Society was used to estimate the costs of managing severe exacerbations in the UK.[13]

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 simple discount was offered on the list price of dupilumab. A PAS discount is in place for

mepolizumab and benralizumab and this was included in the relevant results for decision-making by using estimates of the comparator PAS price.

The base case results for the comparison with SOC are shown in Table 2, with scenario analyses in Table 3. The supplementary analyses in a population treated with maintenance OCS, and comparisons with biologic therapies, are shown in Table 4.

In the base case analysis, the main driver of additional quality-adjusted life-years (QALYs) comes from an increase in the proportion of time spent in the 'controlled' asthma state, whilst reducing the proportion of time spent with uncontrolled asthma and/or exacerbations (and associated mortality risk). The large proportion of severe exacerbations are modelled to be treated within clinics, and time spent in this clinic is reduced for dupilumab-treated patients. Additional costs are driven by the acquisition of dupilumab, with a small cost-offset from the reduced exacerbation rate.

Table 2: Base case results with PAS (dupilumab versus SOC)

Technology	Total LYG	Incremental LYG	ICER vs baseline (£/QALY)
SOC	13.27		
Dupilumab	14.87	1.60	£ 22,637

ICER, incremental cost-effectiveness ratio; LYG, life years gained; PAS, patient access scheme; QALY, quality-adjusted life year; SOC, standard of care.

Table 3: Key scenario analyses with PAS (dupilumab versus SOC)

	Scenario	Base case approach	Scenario approach	Impact on base-case ICER
	Provided in company's initial submission			
1.	Base-case			£ 22,967
2.	Severe exacerbation-related hospitalisation unit cost	Unit cost of severe exacerbation based upon BTS Difficult Asthma Registry[13]	NHS Reference Costs (DZ15M – DZ15R)	£ 24,560
3.	Distribution of settings for exacerbation treatments	Setting of treatment of exacerbation (office visit, A&E, hospital) based upon BTS Difficult Asthma Registry[13]	Setting of treatment of exacerbation taken from previous NICE submission (TA431)	£ 26,417
4.			Setting of exacerbation treatment is derived from the dupilumab clinical study (QUEST)	£ 31,825
5.	Severe exacerbations after trial period	Adjusted by multiplier	Extrapolated based on observed study data	£ 29,563

	Scenario	Base case approach	Scenario approach	Impact on base-case ICER
6.	Time horizon	100 years	Time horizon is 20 years	£ 26,186
7.			Time horizon is 10 years	£ 35,837
8.			Time horizon is 5 years	£ 49,152
	Additional scenarios requested by SMC			
9.	Age	Mean age = 48 years (based on QUEST sub-population)	Mean age = 42.1 years (based on Scottish data)[14]	£ 26,092
10.	Asthma-related mortality	Mortality based on ERG approach in NICE TA431	Mortality applied for all settings of treatment based on Roberts et al 2013[15]	£ 30,562
11.	Pooled population unrestricted by mOCS use	Patients receiving mOCS excluded from the analysis	Population weighted by proportions reported in Heaney et al 2010 (proportion on mOCS: 41.7%)	£30,586
12.	Combination of alternative estimates	As base case	Combination of scenarios 4, 9, 10, 11	£57,974

ICER, Incremental cost-effectiveness ratio; NPAF, New Product Assessment Form; BTS, British Thoracic Society; ERG, Evidence Review Group; SOC, standard of care.

The additional analyses in a population receiving maintenance OCS and comparisons with alternative biologics are presented below. The results presented for comparison with the alternative biologics do not take account of the PAS for mepolizumab, benralizumab or omalizumab or the PAS for dupilumab, but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company, which used an estimate of the PAS price for mepolizumab, benralizumab and omalizumab due to commercial confidentiality and competition law issues.

Table 4: Additional analyses

	Comparator	ICER
Population of patients receiving maintenance oral corticosteroids (with dupilumab PAS)		
1.	SOC	£ 40,907
Population of patients not receiving maintenance oral corticosteroids (shown at list price for all medicines)		
2.	Mepolizumab	Dominated
3.	Benralizumab	£ 66,234
4.	Omalizumab	£ 296,996

ICER, Incremental cost-effectiveness ratio; SOC, standard of care; dominated, dupilumab is less effective but more costly.

There are a number of important limitations to the submitted economic case:

- Following feedback from NDC, the company revised their positioning to include patients who will receive treatment with dupilumab in combination with maintenance OCS as expert responses received by SMC suggest that patients requiring maintenance OCS are likely to have the most severe disease with potentially life-threatening consequences. However, analysis provided upon request suggests that dupilumab is less cost-effective in a population requiring maintenance OCS (Table 4, Scenario 1).
- Similarly, the positioning assumes that patients will not be eligible for treatment with a biologic after previously receiving an anti-IgE or anti-IL5 treatment. However, input from clinical experts suggests that a second biologic may be considered an option in some scenarios. Therefore, comparisons with alternative biologic treatments were considered appropriate, and these suggested dupilumab is not a cost-effective alternative to the other biologic therapies (Table 4, Scenarios 2 – 4).
- The asthma-related mortality data are associated with some uncertainty. Although severe exacerbations are likely to have an increased risk of mortality versus controlled asthma, the extent of this risk may be overestimated. This is likely influenced both by the assumptions regarding mortality rate from different healthcare settings (Table 3, Scenario 10), as well as the distribution across healthcare settings (Table 3, Scenarios 3 – 4). The combination of these assumptions has the potential to overestimate the life year and QALY gain for dupilumab, and therefore potentially underestimate the ICER.
- An adjustment is applied beyond the trial period (52 weeks), which multiplies the exacerbation rate in both arms. The submitting company argues that this is warranted given the exclusion of patients experiencing a severe exacerbation within approximately 7 weeks of the baseline visit in the QUEST study, as well as the study classifying a severe exacerbation as one or more severe exacerbations within a 28 day time frame. While these arguments appear logical, there is the potential to introduce a degree of double-counting alongside an adjustment to account for disease severity, and there is also a question as to whether this multiplier will apply consistently for both treatments. Removal of this effect causes a significant increase in the ICER (Table 3, Scenario 5).
- Several alternative scenarios suggest alternative inputs regarding age, the setting of treatment exacerbation and asthma-related mortality may be more plausible, each of which have a moderate upwards effect on the ICER. When these uncertainties are combined there is a large increase in the ICER (Table 3, Scenario 12).

Despite these limitations, the economic case has been demonstrated.

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 UK and British Lung Foundation Scotland, which is a registered charity.

- Asthma UK and British Lung Foundation Scotland has received 1.7% pharmaceutical company funding in the past two years, including from the submitting company.

- People with severe asthma do not respond fully to standard treatment and require more intensive therapies. Many people with severe asthma live in constant fear of their next asthma attack. They can become caught in a vicious cycle of emergency trips to hospital, intensive care and regular doses of oral corticosteroid tablets or injections. Severe asthma can have devastating consequences on every aspect of people's lives. They may feel isolated, lonely and scared, left without hope or the right support.

- People with severe asthma may have to rely on high doses of OCS to control their symptoms, which can have toxic side effects such as osteoporosis and diabetes. The introduction of biologics for treating the condition has transformed the lives of many with severe asthma, but many may not be eligible for current treatments and even those that are eligible, may not respond to them.

- Dupilumab targets a different mechanistic pathway to the currently available biologics. It offers a new hope to those who have been unsuccessful with other biologics, and would increase the chances of someone finding a biologic that works for them.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) together with the British Thoracic Society published in 2019 a revised version of the British guideline on the management of asthma (SIGN141). It recommends that tiotropium (a LAMA, for adults only) or theophylline can be tried as add-on for patients with severe asthma not controlled with high-dose ICS (or medium dose for adolescents), and who have also been tried on or are still taking LABA, LTRA. It advised that if a trial of an add-on treatment is ineffective, it should be stopped or in the case of increased dose of ICS, the dose should be reduce to the original level. Some patients may also require frequent or continuous oral corticosteroids. It indicates that in eligible patients, with uncontrolled asthma and a high OCS burden, anti-IgE (omalizumab) and anti-IL-5 (mepolizumab, reslizumab and benralizumab) may be considered. Bronchial thermoplasty may also be considered for the treatment of adult patients with severe asthma who have poorly-controlled asthma despite optimal medical therapy. It notes that research is still needed to identify which patients with

asthma might benefit from it but that patients who remain uncontrolled despite optimal medical treatment and who have been considered for biological treatments and are either unsuitable for or fail a trial of such a treatment is likely to be an appropriate group, as other treatment options for these patients are elusive. Immunosuppressants (methotrexate, ciclosporin and oral gold) may be tried once other drug treatments have proved unsuccessful. [9]

The European Respiratory Society in liaison with the American Thoracic Society, published in 2019 the guideline 'Management of severe asthma'. It suggests using anti-IL5 as add-on therapy for adult patients with severe uncontrolled asthma with an eosinophilic phenotype and for those with severe corticosteroid-dependent asthma. It also suggests using dupilumab as add-on therapy for adult patients with severe eosinophilic asthma, and for those with severe corticosteroid-dependent asthma regardless of eosinophil levels and notes that limited data in adolescents made it not possible to provide a recommendation for this age group. For children, adolescents and adults with severe asthma uncontrolled despite treatment with high-dose ICS in combination with a LABA and a third controller such as a LTRA if the patient is treated with medium-dose ICS, it recommends the addition of tiotropium and also a trial of macrolide treatment (adult only) to reduce asthma exacerbations.[10]

In 2019, the Global Initiative for Asthma (GINA) issued an updated version of its international guidance, titled "Difficult-to-treat & severe asthma in adolescent and adult patients. Diagnosis and management". This guideline recommends for patients with severe uncontrolled asthma on high dose ICS/LABA with type 2 inflammation to consider, if eligible, add-on therapy with one of the type 2-targeted biologics, that is an anti-IgE (omalizumab), an anti-IL5/IL-5R (mepolizumab, benralizumab, reslizumab) or an anti-IL4R (dupilumab). It specifies that if there is no response to the first biologic therapy used, it should be stopped and switching to a different type 2-targeted biologic, if available and the patients is eligible, should be considered. It also mentions that responders to biologic treatment should be re-evaluated every 3 to 6 months and that for responders, a decrease/stopping of OCS first then of other add-on medication should be considered, as well as a reduction of ICS.[8]

The National Institute for Health and Care Excellence (NICE) guideline (NG80) 'Asthma: diagnosis, monitoring and chronic asthma management', published in 2017 and updated in 2020, does not cover severe, difficult-to-control asthma.[16]

Additional information: comparators

High dose ICS with at least one controller therapy (such as LABA or LTRA, LAMA [tiotropium], or a theophylline). Omalizumab, benralizumab, mepolizumab.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per year (£)
Dupilumab	**400mg (two 200mg injections) or 600mg (two 300mg injections) initially, followed by 200mg or 300mg every other week by subcutaneous injection**	**Year 1: 17,708** **Subsequent years: 16,444**

Costs from BNF online on 05/12/2020. Costs calculated using the full cost of pack assuming wastage. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The company estimated there would be approximately 2,190 patients eligible for treatment with dupilumab in year 1 and 2,222 patients in year 5. The estimated uptake rates are 1% in year 1 (22 patients) and 20% in year 5 (444 patients).

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines.

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

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This assessment is based on data submitted by the applicant company up to and including 12 February 2021.

**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: http://www.scottishmedicines.org.uk/About_SMC/Policy*

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.