

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Appraisal consultation document

**Dupilumab for treating severe asthma with
type 2 inflammation**

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

This document has been prepared for consultation with the consultees.

It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the [committee papers](#)).

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

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

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

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal document.
- Subject to any appeal by consultees, the final appraisal document may be used as the basis for NICE's guidance on using dupilumab in the NHS in England.

For further details, see NICE's [guide to the processes of technology appraisal](#).

The key dates for this appraisal are:

Closing date for comments: 31 March 2020

Second appraisal committee meeting: 15 April 2020 Details of membership of the appraisal committee are given in section 4.

1 Recommendations

- 1.1 Dupilumab as add-on maintenance therapy is not recommended, within its marketing authorisation, for treating severe asthma with type 2 inflammation that is inadequately controlled in people aged 12 years and over, despite maintenance therapy with high-dose inhaled corticosteroids and another maintenance treatment.
- 1.2 This recommendation is not intended to affect treatment with dupilumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Severe asthma is usually treated with inhaled corticosteroids plus another drug, such as a long-acting beta-agonist. Oral corticosteroids may also be needed to prevent exacerbations (asthma attacks), but they cause long-term side effects. These treatments may not work well enough for severe asthma with type 2 inflammation, which can be difficult to control. Some people who have another type of severe asthma called eosinophilic asthma can have mepolizumab, reslizumab or benralizumab. These drugs, like dupilumab, are biological agents but work in a different way.

Clinical trial results show that having dupilumab plus standard asthma treatment reduces exacerbations and the use of oral corticosteroids more than placebo in people with severe asthma with type 2 inflammation. There are no trials directly comparing dupilumab with mepolizumab, reslizumab or benralizumab. Comparing these drugs indirectly suggests a reduction in asthma exacerbations with dupilumab but no difference in other asthma symptoms.

The company's population of people with type 2 inflammation is not suitable for considering the cost effectiveness of dupilumab compared with standard care. This

is because it combines people eligible for biologicals (mepolizumab, reslizumab or benralizumab) with people not eligible for biologicals who can only be offered standard care. The cost-effectiveness estimates for dupilumab vary depending on whether people are eligible for mepolizumab, reslizumab or benralizumab, and what their individual treatment options are. Regardless, the cost-effectiveness estimates for dupilumab are higher than what NICE usually considers a cost-effective use of NHS resources. Dupilumab cannot be recommended for treating inadequately controlled severe asthma with type 2 inflammation.

2 Information about dupilumab

Marketing authorisation indication

2.1 Dupilumab (Dupixent, Sanofi) has a marketing authorisation ‘in adults and adolescents 12 years and older as an add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO [fractional exhaled nitric oxide]...who are inadequately controlled with high dose ICS [inhaled corticosteroid] plus another medicinal product for maintenance treatment’. The definition of type 2 inflammation is as in the [Global Initiative for Asthma](#) guideline.

Dosage in the marketing authorisation

- 2.2 The recommended starting dose of dupilumab is 400 mg, followed by 200 mg every other week, administered subcutaneously. For people with severe asthma on oral corticosteroids, or for people with severe asthma and co-morbid moderate-to-severe atopic dermatitis, a starting dose of 600 mg followed by 300 mg every other week can be administered. Dupilumab is intended for long-term treatment. Treatment should be reviewed by the specialist at least annually.
- 2.3 For full details of dosage schedules, see the summary of product characteristics.

Price

- 2.4 The list price of dupilumab is £1,264.89 for 2 prefilled syringes of either the 200 mg per 1.44 ml or 300 mg per 2 ml dose (excluding VAT; British National Formulary online accessed January 2020).
- 2.5 The company has a commercial arrangement. This makes dupilumab available to the NHS for all indications with a discount and it would have also applied to this indication if the technology had been recommended. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The appraisal committee (section 4) considered evidence from several sources. See the [committee papers](#) for full details of the evidence.

New treatment option

An additional treatment option that lowers the risk of exacerbations and may reduce the need for oral corticosteroids would be welcome

- 3.1 Severe asthma is a distressing and socially isolating condition. The patient expert explained that exacerbations can happen without warning, be life threatening, cause fear and result in hospitalisation. People are often unable to work or start a family, and may need help with day-to-day activities because of their symptoms. The clinical expert explained that, in addition to optimised inhaled treatment, standard treatment for severe asthma is oral systemic corticosteroids or, if the patient has eosinophilic asthma and depending on the blood eosinophil count, NICE recommended interleukin-5 inhibitors biologicals [benralizumab](#), [mepolizumab](#) and [reslizumab](#). Dupilumab is the only licensed treatment for severe asthma with type 2 inflammation. Although asthma can respond to systemic corticosteroids, the treatment can be associated with long-term complications (such as diabetes mellitus, weight gain, bone loss,

immunosuppression and a negative effect on mental health). The patient expert explained that patients would welcome treatment options that replace the need for corticosteroids. The clinical expert explained that a blood eosinophil count and fractional exhaled nitric oxide (FeNO) are used to help define subtypes of severe asthma and help predict the people with severe asthma who are at highest risk of a future exacerbation. In people with severe asthma with type 2 inflammation, their condition does not respond to interleukin-5 inhibitors but can respond to interleukin-13 inhibitors such as dupilumab. The committee concluded that there is a need for new treatments with a different mode of action for people with severe asthma with type 2 inflammation whose asthma does not respond with current standard care, and for people not eligible for current NICE recommended biologicals.

Clinical management

Severe asthma with type 2 inflammation is a subtype of asthma

3.2 Severe asthma with type 2 inflammation is associated with allergy, higher risk of exacerbations, hospitalisation, dependency on oral corticosteroids and increased risk of dying. The [Global Initiative for Asthma \(GINA\) guideline on difficult to treat severe asthma](#) (2019) lists 5 criteria in its definition of severe asthma with type 2 inflammation that are prognostics markers:

- a blood eosinophil count of 150 cells per microlitre or more
- FeNO of 20 parts per billion or more
- sputum eosinophils of 2% or more
- asthma that is clinically allergen driven
- the need for maintenance oral corticosteroids.

GINA suggests that 1 or more criterion can be used to make a diagnosis. The clinical expert explained that raised blood eosinophils and FeNO are risk predictors for future exacerbations. That is, the higher these

biomarkers, the more likely you are to have an exacerbation. The committee concluded that this subtype of severe asthma exists.

Blood eosinophil count and FeNO are common biomarkers for diagnosis

3.3 The clinical expert explained that blood eosinophil counts and FeNO levels are routinely measured in clinical practice. They also explained that, while blood eosinophils counts are raised in both eosinophilic asthma and asthma with type 2 inflammation, raised FeNO is more specific to type 2 inflammation. The committee noted the response of stakeholders during technical engagement that a blood eosinophil count of 150 cells per microlitre or more, FeNO of 20 parts per billion or more, or both, could be used for identifying people with type 2 inflammation. The committee acknowledged the complexity of diagnosing asthma subtypes, and the potential for overlap or misclassification between them, despite the use of blood eosinophil counts and FeNO levels.

Dupilumab as add-on treatment is an option for managing uncontrolled severe asthma with type 2 inflammation

3.4 The clinical expert explained that treatment for asthma in clinical practice follows the [NICE guideline on diagnosis, monitoring and chronic asthma management](#) and the GINA 2019 guideline (which includes the use of biologicals). If the asthma is still uncontrolled despite optimised inhaled therapy that includes corticosteroids, then low-dose oral corticosteroids or biologicals are added. The clinical and patient experts explained that biologicals are preferred over oral corticosteroids because they have fewer debilitating side effects. The choice of biological depends on the subtype of asthma. For severe eosinophilic asthma, according to NICE technology appraisal guidance for [benralizumab](#), [mepolizumab](#) and [reslizumab](#), the treatment of choice depends on the blood eosinophil count (300 cells per microlitre or more, or 400 cells per microlitre or more) and the number of exacerbations (3 or 4, or more) or the use of systemic corticosteroids. [Omalizumab](#) is another biological used for treating severe persistent allergic asthma. However, it is not used for eosinophilic asthma

(see section 3.6). There are currently no NICE recommended biologicals for treating severe asthma with type 2 inflammation. The committee concluded that dupilumab as add-on treatment is an option for managing uncontrolled severe asthma with type 2 inflammation.

Populations

It is challenging to define which populations should be used for decision making

3.5 There are several subgroups to consider when deciding which population to use for decision making. The committee considered whether the population would need to have a raised eosinophil count, raised FeNO or both based on the 'and/or' wording in the marketing authorisation and GINA recommendations for these biomarkers. The committee also acknowledged that there are subgroups on or off maintenance oral corticosteroids, or both (mixed proportions on and off oral corticosteroids), and populations eligible or not eligible for biologicals. In addition, it acknowledged the overlap between the populations in the marketing authorisation, trials and company decision problem:

- The marketing authorisation population is broad, consisting of people with uncontrolled severe asthma with type 2 inflammation on high-dose inhaled corticosteroids plus 1 maintenance treatment and with a blood eosinophil count and FeNO as described by GINA.
- The clinical trials (DRI12544, QUEST and VENTURE) recruited people with 1 or more exacerbation in the previous year and no restrictions on blood eosinophils and FeNO.
- The company's decision problem (base case) was in a subpopulation of people based on a posthoc analysis of the QUEST data (that is, a blood eosinophil count of 150 cells per microlitre or more, FeNO of 25 parts per billion or more, 3 or more exacerbations in the previous year and no maintenance oral corticosteroids). The company considered that this represented people with more severe asthma, who

it considers will get the most benefit from dupilumab.

The committee agreed that it was challenging to define the populations because they overlapped. It acknowledged that a mixed population on and off oral corticosteroids is not suitable for decision making. The clinical expert explained that maintenance treatment with oral corticosteroids is declining in clinical practice because it has been displaced by the increased use of biologicals. Therefore, there is uncertainty about the proportion of people having oral corticosteroids in clinical practice. This had an effect on the cost effectiveness of dupilumab in the mixed population. Also, the company's decision-problem population included both people who were and were not eligible for biologicals, for which the comparators would differ. The committee concluded that, if standard care is the comparator chosen, the population not eligible for biologicals would be the most suitable for decision making.

Comparators

Benralizumab, mepolizumab and reslizumab are appropriate comparators for dupilumab

3.6 The clinical trial populations included people with differing severity of asthma (defined by eosinophil level and the number of exacerbations in the previous year). These populations therefore included people who would be offered different treatment options in the NHS:

- People with a blood eosinophil count of 300 cells per microlitre or more, who have had at least 4 exacerbations in the previous 12 months or who are taking oral corticosteroids, can have mepolizumab or benralizumab.
- People with a blood eosinophil count of 400 cells per microlitre or more, who have had at least 3 exacerbations in the previous 12 months, can have reslizumab or benralizumab.

- People not eligible for biologicals (defined below) are offered standard care:
 - a blood eosinophil count of between 150 and 299 cells per microlitre and 4 or more exacerbations
 - a blood eosinophil count of between 150 and 399 cells per microlitre and 3 or more exacerbations
 - a blood eosinophil count of less than 150 cells per microlitre and FeNO of 25 parts per billion or more.

The committee highlighted that omalizumab was not considered to be a relevant comparator. This was because dupilumab does not have a specific indication for IgE-mediated asthma and IgE has not been shown to be a predictor of response to dupilumab. It concluded that benralizumab, mepolizumab, reslizumab and standard of care were appropriate comparators for dupilumab.

Clinical evidence

The evidence on clinical effectiveness is relevant to NHS clinical practice

3.7 The company's clinical evidence came from 3 randomised-controlled trials, DRI12544, QUEST and VENTURE. These compared dupilumab with placebo in people aged 12 years and over (except DRI12544, which only included people aged 18 years or over) with persistent asthma who had 1 or more exacerbations in the previous year. None of the trials had restrictions on blood eosinophils or FeNO. DRI12544 and QUEST included people with moderate-to-severe asthma not on maintenance oral corticosteroids. VENTURE included people with severe corticosteroid-dependent asthma (on maintenance corticosteroids). The 3 trials were conducted globally, and QUEST was the only trial that included people from the UK. The trial populations were based on use of moderate-to-high doses of inhaled corticosteroids. This was because they included people from countries like the US and Japan, where the clinical expert stated that there is reluctance to use high-dose inhaled corticosteroids. The

committee concluded that there were some caveats, but that all 3 trials included were relevant to NHS clinical practice.

Dupilumab is more clinically effective than standard care in the clinical trial populations and is a relatively safe treatment

3.8 All primary outcomes were reported for the intention-to-treat population in all 3 trials. In QUEST, the first coprimary outcome was annualised rate of severe exacerbations. There was a 47.7% (95% confidence interval [CI] 33.8% to 58.7%, $p < 0.0001$) lower rate of severe exacerbations in the dupilumab group compared with placebo. Change from baseline in the forced expiratory volume in 1 second (FEV1) at 12 weeks was the second coprimary outcomes in QUEST and the primary outcome in DRI12544. There was an increase in FEV1 at 12 weeks when dupilumab was compared with placebo in DRI12544 (least squares [LS] mean difference 0.14 litre, 95% CI 0.08 to 0.19, $p < 0.0001$) and QUEST (LS mean difference 0.20 litre, 95% CI 0.11 to 0.28, $p < 0.0001$). In VENTURE, the primary outcome was the percentage reduction in oral corticosteroid dose from baseline. There was a greater reduction in oral corticosteroid use with dupilumab compared with placebo (LS mean difference 28 mg, 95% CI 16 to 41, $p < 0.0001$) at 24 weeks. The proportion of people with treatment-related adverse events was similar within each trial between those having dupilumab and placebo. In DRI12544 and QUEST, the proportion of people with any treatment-related adverse events ranged from 74.7% to 84.1%. In VENTURE, a smaller proportion experienced any treatment-related adverse events (64.5% and 62.1% in the placebo and dupilumab arms respectively). The committee concluded that dupilumab was more clinically effective than standard care in the clinical trial populations and is a relatively safe treatment.

Dupilumab is clinically effective as an addition to standard care in the post hoc subpopulation

3.9 The company's decision-problem subgroup analyses focused on the annualised rate of severe exacerbations for the posthoc population (that

is, people with a blood eosinophil count of 150 cells per microlitre or more, FeNO of 25 parts per billion or more and 3 or more exacerbations in the previous year) from QUEST and VENTURE. Dupilumab reduced the rate of severe exacerbations when compared with placebo within this subpopulation in QUEST and VENTURE, although in small posthoc subgroups with 101 and 152 people respectively. There were improvements in the placebo groups for the primary outcomes of these trials. This was possibly because of regression to the mean and the placebo effect. The committee concluded that dupilumab is clinically effective and safe as an addition to standard care in people with a blood eosinophil count of at least 150 cells per microlitre or FeNO of 25 parts per billion or more and 3 or more exacerbations in the previous year who may or may not be taking maintenance oral corticosteroids.

The clinical-effectiveness estimates for dupilumab are uncertain in the subgroup of people who are not currently eligible for biologicals

3.10 The results for the clinical effectiveness of dupilumab in people who would not currently be eligible for a biological were only available from QUEST for the annualised rate of severe exacerbations, and in a very small population (29 people randomised to 200 mg dupilumab). Dupilumab reduced the rate of severe exacerbation compared with placebo. The committee concluded that these results were uncertain.

The clinical effectiveness of dupilumab compared with reslizumab, benralizumab and mepolizumab is uncertain

3.11 There are no head-to-head data comparing dupilumab with current biologicals. The company provided 2 methods to compare them indirectly: the Bucher indirect treatment comparison for the company's base case and in a scenario analysis, and the matched adjusted indirect treatment comparison. Both these methods matched people in the dupilumab trials to those in the comparator trials. The committee noted the evidence review group's (ERG's) view that the results of these analyses needed to be interpreted with caution because they were exploratory analyses.

Nevertheless, the ERG considered them to be the best available options to compare dupilumab with other biologicals. The Bucher indirect treatment comparison suggested that treatment with dupilumab 200 mg leads to a lower rate of severe exacerbations than mepolizumab, benralizumab and reslizumab. It was also conducted for other outcomes, none of which showed meaningful results. The committee highlighted that there are no data on the efficacy of dupilumab in people in whom interleukin-5 inhibitor biologicals have failed to control their asthma. The committee therefore concluded that there was still uncertainty about the clinical effectiveness of dupilumab compared with mepolizumab, benralizumab and reslizumab because the results of the indirect comparisons were not robust.

The company's economic model

The model structure is appropriate for decision making

3.12 The company submitted a 4-state Markov model comparing dupilumab with standard care in people with severe asthma and type 2 inflammation. The model consisted of 4 live health states: uncontrolled asthma; controlled asthma; moderate exacerbation; and severe exacerbation. In addition, the model included states for asthma-related deaths and death from other causes. Response to treatment was defined as a 50% or greater reduction in the annual exacerbation rate, which was assessed at 52 weeks. People whose asthma responded continued on dupilumab and those whose did not transferred to standard care. The company derived the efficacy and clinical parameters in the model from the QUEST clinical trial. The committee concluded that the model structure was appropriate for decision making.

Clinical inputs to the model

Estimates of severe asthma exacerbation rates in the placebo arm of QUEST do not reflect clinical practice in the NHS

3.13 The committee noted that asthma-related mortality often drives cost effectiveness in asthma models. The annual severe exacerbation rate (2.39 exacerbations per year) in the placebo arm of the QUEST trial was lower than observed in clinical practice in the year before trial enrolment (4.46 exacerbations per year). The company estimated exacerbation rates from QUEST and VENTURE in the first year in its base case. However, it increased the number of severe exacerbations in subsequent years for both dupilumab and standard care by applying a multiplier, which the company considered confidential. The company considered that this was appropriate because it had excluded people with a recent severe exacerbation from the QUEST trial. The ERG's base case did not include an exacerbation multiplier and resulted in higher incremental cost effectiveness ratios (ICERs). The committee considered that the best measure of a difference was that seen between arms the trial. It concluded that the it was not appropriate to inflate the rates of exacerbation.

The use of an exacerbation multiplier is not the best method of adjusting severe asthma exacerbation rates

3.14 During consultation on the technical report, the ERG and clinical experts stated that an exacerbation multiplier would not necessarily give a more clinically plausible exacerbation rate for standard care. Another method of assessing the effectiveness of dupilumab could have been to use registry data for the baseline risk of exacerbations. Then, the efficacy of dupilumab could have been applied to this baseline risk. However, the registry data from the O'Neill et al. study (2015) is several years out of date. The committee would have preferred to have seen the effect of other means of adjusting for severe exacerbations, such as:

- the observed exacerbation rates from more up-to-date registry data for standard care
- the treatment effect of dupilumab from QUEST and VENTURE (or more up-to-date registry data) on the cost effectiveness of dupilumab compared with standard care.

The committee concluded that the exacerbation multiplier might not have been the best method of adjusting for the rate of severe exacerbations in standard care.

It is unclear what the best source of data is to inform the setting of treating exacerbations

3.15 The company assigned different mortality rates to severe exacerbations treated in hospital emergency care, inpatients and general practice. It based the resource use associated with severe exacerbations in its original base case on UK Difficult Asthma Registry registry data (O'Neill 2015). This assumed that 26.5% of severe exacerbations were treated in hospital (7.8% in emergency care, 18.7% in inpatients) and 74.0% in general practice. However, this was higher than the 6.7% of severe exacerbations treated in hospital in the QUEST trial (3.0% in emergency care, 3.7% in inpatients) and 93.3% in general practice. The ERG base-case model used the QUEST data for the setting of severe exacerbations. During consultation on the technical report, the ERG and clinical expert stated that the clinical trials were a more reliable source of these data. The clinical expert explained that the number of patients treated in hospital in clinical practice is likely to be higher than that seen in the trial. This was because patients in trials are well monitored on optimised treatment, are more motivated and have better adherence to treatment. The committee concluded that it would have preferred to have seen exploration of different sources of data, for the setting of treating exacerbations, to inform the model.

Additional analyses should include 10-year mortality rates for dupilumab and standard care, and show the flow of patients through different health states

3.16 The ERG explained that the original company model (using the confidential exacerbation multiplier) predicted 20% mortality over 10 years in the standard care arm. The committee questioned the clinical plausibility of this estimate because it seemed high compared with the approximate 1,300 asthma-related deaths a year in the UK. The higher death rate was a result of interaction between the exacerbation multiplier (see section 3.13) and using registry data to inform the setting of treating exacerbations (see section 3.15). The committee concluded that the model did not offer plausible estimates, and that any additional analyses presented by the company should include 10-year mortality rates for dupilumab and standard care. It also concluded that the analyses should show the flow of patients through different health states in the model for the purposes of model validation.

The population including people with an unmet need who are not eligible for biologicals is the most relevant for decision making

3.17 The population the company proposed for consideration by the committee was broad, including people who had:

- a blood eosinophil count of at least 150 cells per microlitre or
- FeNO of 25 parts per billion or more, and
- 3 or more exacerbations in the previous year and
- not been taking maintenance oral corticosteroids.

The company also provided exploratory analyses on the cost-effectiveness of dupilumab in the following 3 populations:

- A mixed population that contained 30% of people having maintenance oral corticosteroids (with a blood eosinophil count of 150 cells per microlitre or more or FeNO of 25 parts per billion or more, and 3 or more exacerbations)

- A population not eligible for biologicals in whom standard care was the only relevant comparator. This included 3 groups
 - people not eligible for mepolizumab or benralizumab (with a blood eosinophil count of 150 to 299 cells per microlitre and 3 exacerbations)
 - people not eligible for reslizumab or benralizumab (with a blood eosinophil count of 150 to 399 cells per microlitre and 4 exacerbations or more)
 - people who only had raised FeNO (with a blood eosinophil count of less than 150 cells per microlitre and FeNO 25 parts per billion or more).
- A population eligible for biologicals (either mepolizumab or benralizumab eligible: with a blood eosinophil count of 300 cells per microlitre or more and 4 or more exacerbations; or reslizumab or benralizumab eligible: with a blood eosinophil count of 400 cells per microlitre or more and 3 or more exacerbations).

The broad population proposed by the company (with a blood eosinophil count of 150 cells per microlitre or more or FeNO of 25 parts per billion, and 3 or more exacerbations in the previous year not on maintenance oral corticosteroids) was not considered by the committee to be relevant for decision making. This was because it combined both people eligible and not eligible for biologicals (mepolizumab, reslizumab or benralizumab; see section 3.5) The mixed population was also not considered to be relevant because of the declining use of maintenance oral corticosteroids in clinical practice with the rising use of NICE recommended biologicals (see section 3.5). The committee concluded that, if standard care is the comparator chosen, the population not eligible for biologicals would be the most suitable for decision making. The company provided evidence of dupilumab's clinical effectiveness in this population. The committee noted the unmet need in these patients, but highlighted that the evidence was based on

small patient numbers (see section 3.10). It also considered the evidence for the exploratory biological-eligible population, but noted that this subgroup was not part of the company's proposition.

The company's base-case economic analysis

The company's base-case ICER is £34,216 per QALY gained for dupilumab compared with standard care in the proposed population

3.18 The company's base-case deterministic ICER for dupilumab compared with standard care is £34,216 per quality-adjusted life year (QALY) gained in the broad population (that is, people with a blood eosinophil count of at least 150 cells per microlitre or FeNO of 25 parts per billion or more, 3 or more exacerbations in the previous year and not taking maintenance oral corticosteroids). This included the confidential discount for dupilumab. The ERG's base-case ICER (which did not include an exacerbation multiplier and used the QUEST trial data for the setting of treating exacerbations) was £55,348 per QALY gained. The committee concluded that this combined population, which included people who were and were not eligible for other biological treatments was not relevant for decision making. It also concluded that dupilumab is not cost effective in company's broad population.

Dupilumab cannot be recommended for treating severe asthma with type 2 inflammation

3.19 The committee considered the most relevant population for decision making to be people not eligible for other biologicals (because their eosinophil or exacerbation levels in the previous year were too low), and that this is where there is a significant unmet need. The company's combined ICER for people not eligible for reslizumab (that is, with a blood eosinophil count of 150 to 399 cells per microlitre, FeNO of 25 parts per billion and 3 or more exacerbations) and those not eligible for mepolizumab (that is, with a blood eosinophil count of 150 to 299 cells per microlitre, FeNO of 25 parts per billion or more, and 4 or more

exacerbations), which included the confidential discount for dupilumab, was £50,558 per QALY gained. The ERG's ICER for the same population was £81,676 per QALY gained). The committee concluded that dupilumab does not represent a cost-effective use of resources, so could not be recommended for treating severe asthma with type 2 inflammation

The ICERs for dupilumab compared with each biological greatly exceeded what is normally considered to be a cost-effective use of NHS resources

3.20 The cost-effectiveness estimates for the exploratory analyses of dupilumab compared with biologicals in the biological-eligible populations included the confidential discount for dupilumab and comparator biologicals so are confidential and cannot be reported. However, the ICERs for dupilumab compared with each biological greatly exceeded what is normally considered to be a cost-effective use of resources in the NHS. Furthermore, the company had not proposed comparing dupilumab with biologicals in its decision problem. There was also considerable uncertainty in the ICERs for the population eligible for biologicals. This was because the efficacy data came from an indirect treatment comparison that was based on small patient numbers. The committee concluded that dupilumab does not represent a cost-effective use of resources when compared with other biologicals.

Alternative modelling methods may more accurately estimate the cost effectiveness of dupilumab

3.21 There may have been more appropriate ways to model the exacerbations rate in the placebo arm, so that it better reflected the exacerbation rate with standard care in clinical practice. The committee would have liked to have seen alternative modelling methods for adjusting the severe exacerbation rate in the placebo arm (see section 3.13). Also, it would like to have seen the effect of alternative modelling of exacerbations, and of using QUEST or updated registry data, on the ICER in people not eligible for biologicals at different exacerbation thresholds. For example:

- people with a blood eosinophil count of 150 cells per microlitre or more, or FeNO of 25 parts per billion or more and 3 exacerbations
- people with a blood eosinophil count of 150 cells per microlitre or more, or FeNO of 25 parts per billion or more, and 4 or more exacerbations.

The committee also thought that any further analysis should be accompanied by:

- data on the 10-year modelled mortality in the dupilumab and standard care arm
- an evaluation of whether the output is consistent with the current UK asthma mortality rate.

The committee was also interested in the results for people who had raised eosinophils or FeNO, and those in whom both were raised. It concluded that any further analysis should use alternative methods of modelling exacerbations in standard care and explore different exacerbation thresholds.

Other factors

Additional benefits in people with severe asthma and type 2 inflammation, and nasal polyps or atopic dermatitis, may not have been adequately captured

3.22 The committee recognised that there is an unmet need for people with severe asthma caused by type 2 inflammation. The committee also heard that dupilumab is effective in people with comorbidities (such as nasal polyps and atopic dermatitis). It concluded that these additional benefits of dupilumab had not been captured in the QALY calculation.

There are limited data available on dupilumab for young people

3.23 Dupilumab is licensed in people aged 12 years and over. The clinical trials included a small number of people aged under 18 years (n=52, QUEST; n=3, VENTURE), and the company did not provide a subgroup analysis

for this age group. There is an unmet need in this population with uncontrolled severe asthma with type 2 inflammation. Current NICE recommended biologicals are licensed for eosinophilic asthma only, so would not routinely be used for asthma with type 2 inflammation (if defined by blood eosinophil counts). Mepolizumab is currently the only other biological that is licensed for treating children aged 6 years or over for severe refractory eosinophilic asthma. However [NICE's technology appraisal guidance on mepolizumab](#) recommends it for use in adults. The committee concluded that there are limited data available for dupilumab in young people, and acknowledged this during decision making.

Conclusion

Dupilumab is not recommended for treating severe asthma with type 2 inflammation

3.24 The committee acknowledged that dupilumab is effective for preventing exacerbations in people with severe asthma with type 2 inflammation compared with standard care. However, the cost-effectiveness estimates for dupilumab compared with standard care and people eligible for biologicals were high. The committee identified several uncertainties in the modelling assumptions, particularly about severe exacerbation rates and the source of data to inform the setting for treating exacerbations. These uncertainties resulted in uncertainty about the true ICER. Therefore, the committee was unable to recommend dupilumab as a cost-effective treatment for use in the NHS for treating severe asthma with type 2 inflammation.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based

on information gathered by NICE, and in consultation with consultees and commentators.

Sanjeev Patel

Chair, appraisal committee

March 2020

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee B](#).

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

The [minutes](#) of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

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NICE project team

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

Shelly Patel

Technical lead

Eleanor Donegan

Technical adviser

Joanne Ekeledo

Project manager

ISBN: [to be added at publication]