NICE National Institute for Health and Care Excellence

NICE guidance

Dupilumab for treating severe asthma with type 2 inflammation

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Dupilumab as add-on maintenance therapy is recommended as an option for treating severe asthma with type 2 inflammation that is inadequately controlled in people 12 years and over, despite maintenance therapy with high-dose inhaled corticosteroids and another maintenance treatment, only if:

- the dosage used is 400 mg initially and then 200 mg subcutaneously every other week
- the person has agreed to and follows an optimised standard treatment plan
- the person has a blood eosinophil count of 150 cells per microlitre or more and fractional exhaled nitric oxide of 25 parts per billion or more, and has had at least 4 or more exacerbations in the previous 12 months
- the person is not eligible for mepolizumab, reslizumab or benralizumab, or has asthma that has not responded adequately to these biological therapies
- the company provides dupilumab according to the commercial arrangement.

1.2 Stop dupilumab if the rate of severe asthma exacerbations has not been reduced by at least a 50% after 12 months.

1.3 These recommendations are not intended to affect treatment with dupilumab that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For young people, this decision should be made jointly by them, their clinician, and their parents or carers.

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 can cause long-term adverse effects. Also, these treatments may not work well enough for severe asthma with type 2 inflammation, which

can be difficult to control.

Clinical trial results show that adding dupilumab to standard asthma treatment is more effective than placebo plus standard treatment at reducing the frequency of severe exacerbations, and the use of oral corticosteroids in people with severe asthma with type 2 inflammation.

The company proposes dupilumab 200 mg for very severe asthma with type 2 inflammation in people not eligible for mepolizumab, reslizumab or benralizumab, or whose asthma has not adequately responded to these biological treatments. This is a narrower population than that in the marketing authorisation. It represents people with the highest unmet need and people only eligible for standard care. Dupilumab could be a valuable treatment option in these people because, without it, they will need regular oral corticosteroids.

The cost-effectiveness estimates for dupilumab plus standard care are at the higher end of what NICE usually considers an acceptable use of NHS resources. But there is an unmet need for people with very severe asthma with type 2 inflammation and dupilumab represents an additional treatment option before oral corticosteroids. Also, the benefits associated with avoiding oral corticosteroids to people with this type of asthma and to the NHS may not have been fully captured in the cost-effectiveness estimates. So, dupilumab (200 mg) is recommended for treating inadequately controlled very 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 dosage schedule is available in the summary of product characteristics.

Price

2.3 The list price of dupilumab is £1,264.89 for 2 prefilled syringes 200 mg per 1.44 ml (excluding VAT; BNF online accessed November 2020).

2.4 The company has a commercial arrangement. This makes dupilumab available to the NHS with a discount. 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 considered evidence submitted by Sanofi Genzyme, a review of this submission by the evidence review group (ERG), NICE's technical report and responses from stakeholders. 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. They further explained that 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 person has eosinophilic asthma, and depending on the blood eosinophil count, NICE recommended interleukin 5 inhibitor biologicals benralizumab, mepolizumab and reslizumab (see NICE's technology appraisal guidance on 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 people with severe asthma with type 2 inflammation 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 the highest risk of a future exacerbation. In people with severe asthma with type 2 inflammation, if their condition does not respond to interleukin-5 inhibitors it may 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 and dependency on oral corticosteroids, and increased risk of dying than in people with severe asthma without type 2 inflammation. The Global Initiative for Asthma (GINA) guideline on difficult to treat severe asthma (2021) 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 criteria can be used to make a diagnosis. The clinical expert explained that raised blood eosinophils and FeNO are predictors for future exacerbations. The committee concluded that this subtype of severe asthma can be characterised as type 2 inflammation.

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 2021 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 adverse effects. The choice of biological depends on the subtype of asthma. For severe eosinophilic asthma, according to NICE's 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 recommended by NICE (see NICE's technology appraisal guidance on omalizumab) and 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

The company's updated population is suitable for decision making

3.5 There are several subgroups to consider when deciding which population to use for decision making. At the first appraisal committee meeting, 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 at the first committee meeting:

- 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 exacerbations in the previous 12 months and no restrictions on blood eosinophils and FeNO.

  The company's decision problem (base case) was in a subpopulation of people not eligible for mepolizumab, reslizumab or benralizumab or whose asthma had not responded to these biological therapies based on a post hoc analysis of the QUEST data. They were 12 years and older and had blood eosinophils counts of 150 cells per microlitre or more, FeNO of 25 parts per billion or more, and at least 4 exacerbations in the previous 12 months. The company considered that this narrower population represented people with the highest unmet need and could be split into 3 subgroups: young people aged 12 years to 17 years, adults not eligible for mepolizumab, reslizumab or benralizumab (a blood eosinophil count 150 cells per microlitre to 299 cells per microlitre) and adults whose asthma had not responded to these biological therapies (blood eosinophil count of 300 cells per microlitre and more). The committee noted that the comparator for the updated population

was standard care and other biologicals were only recommended for adults in NICE guidance. The committee concluded that the updated population was suitable for decision making.

Comparators

Standard care is the appropriate comparator in the updated population

3.6 The clinical trial population in QUEST included people with differing asthma severity (defined by eosinophil level, FeNO and the number of exacerbations in the previous 12 months). 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, mepolizumab or benralizumab.
- People not eligible for biologicals are offered standard care, defined as:
  - a blood eosinophil count of between 150 and 299 cells per microlitre and 4 or more exacerbations in the previous 12 months (not eligible for mepolizumab or benralizumab)
  - a blood eosinophil count of between 150 and 399 cells per microlitre and 3 or more exacerbations in the previous 12 months (not eligible for reslizumab or benralizumab)
  - a blood eosinophil count of less than 150 cells per microlitre and FeNO of 25 parts per billion or more (not eligible for any other biological)
- People whose asthma had not responded to biological therapy are offered standard care.

The committee concluded that standard care was an appropriate comparator in the company's population, that is, people who are not eligible for mepolizumab, reslizumab or benralizumab or people whose asthma has not responded to these biological therapies.

Clinical evidence

The population in QUEST is generalisable to people seen in NHS clinical practice

3.7 The clinical evidence for the company's population came from a double-blind placebo-controlled randomised trial, QUEST. This trial compared dupilumab with placebo in 948 people 12 years and over with persistent asthma who had 1 or more exacerbations in the previous 12 months. It included people with moderate to severe asthma, who were not on maintenance oral corticosteroids. It was conducted globally and included people from the UK. QUEST's population was based on the use of moderate-to-high doses of inhaled corticosteroids. This was because it included people from countries such as the US and Japan where, according to the clinical expert, there is a reluctance to use high-dose inhaled corticosteroids. The committee concluded that QUEST was broadly generalisable to NHS practice and appropriate for decision making.

Dupilumab is more clinically effective than standard care in the clinical trial population

3.8 All primary outcomes were reported for the intention-to-treat population in all 3 trials. In QUEST, the coprimary outcome was annualised rate of severe exacerbations and change from baseline in the forced expiratory volume in 1 second (FEV1) at 12 weeks. 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. There was an increase in FEV1 at 12 weeks when dupilumab was compared with placebo in QUEST (least squares mean difference

0.20 litre, 95% CI 0.11 to 0.28, p<0.0001). The committee concluded that dupilumab was more clinically effective than standard care in the clinical trial population.

Dupilumab is clinically effective in the company's population, but estimates are based on a small population

3.9 The company proposed dupilumab in a small post hoc population of people from QUEST:

- with a blood eosinophil count of 150 cells per microlitre or more, FeNO of 25 parts per billion or more and 4 or more exacerbations in the previous 12 months
- who are not eligible for mepolizumab, reslizumab or benralizumab or have had biological therapy.

It explained that dupilumab reduced the rate of severe exacerbations when compared with placebo within this subpopulation but was based on small post hoc subgroups. The relative risk ratios are considered confidential by the company so cannot be reported here. The committee noted that dupilumab was clinically effective as an addition to standard care in people who had not had biological therapy and had a blood eosinophil count of at least 150 cells per microlitre, FeNO of 25 parts per billion or more, and 4 or more exacerbations in the previous 12 months. The committee concluded that the clinical-effectiveness evidence for dupilumab in the company's population was limited and based on a small number of people.

QUEST subgroup analyses support dupilumab's efficacy in the company's populations

3.10 The company presented additional subgroup analyses from QUEST on different severities of asthma based on exacerbation level in the previous 12 months, and blood eosinophil and FeNo levels. It did this to support its definition of the population with the highest unmet need. One analysis of the dupilumab's clinical

effectiveness showed that, in people randomised to placebo, the adjusted annualised severe exacerbation rate increased with an increasing number of exacerbations in the 12 months before QUEST baseline from 0.871 in people with 1 or more exacerbations to more than 2.563 in those with 4 or more exacerbations. There was also a statistically significant reduction in the adjusted annualised severe exacerbation rate with dupilumab, ranging from a 48% (0.456) reduction compared with placebo in the 1 or more exacerbation group to a 77% (0.571) reduction compared with placebo in the 4 or more exacerbations group. Another analysis assessed adjusted annualised severe exacerbation rate by baseline levels of blood eosinophil count and FeNO. In this, the subgroup with a blood eosinophil count of 150 cells per microlitre or more and FeNO of 20 parts per billion or more (48% of the QUEST population) had the highest adjusted annualised exacerbation rate in people randomised to placebo and the most pronounced treatment effect (66%, $p<0.001$ rate reduction compared with placebo). The ERG agreed that a raised blood eosinophil count of 150 cells per microlitre or more and FeNO of 20 parts per billion or more represented the group with the highest baseline exacerbation rate and response to dupilumab. The committee considered the additional company analyses were sufficient to support the company's definition of severe asthma with type 2 inflammation, that is, 4 exacerbations or more, a blood eosinophil count of 150 cells per microlitre or more, and FeNO of 20 parts per billion or more. The committee concluded that adding dupilumab to standard care is clinically effective in people with the highest unmet need defined by a blood eosinophil count of 150 cells per microlitre or more and FeNO of 25 parts per billion or more and 4 or more exacerbations in the previous 12 months.

The proportion of people who have had biological therapy whose asthma will respond to dupilumab is uncertain

3.11 The committee had concerns about the company's assumption of equal efficacy with dupilumab in people who have and have not had a biological therapy. In response to its second appraisal consultation document, the company presented real-world evidence on the clinical effectiveness of dupilumab from the UK, Europe and US for people who had mepolizumab, reslizumab or benralizumab. The committee noted that the company's real-world evidence from the UK showed a similar response in people who had and had not had biological therapy.

The details of the company's observational evidence are confidential so cannot be reported here. The company's real-world evidence from Europe and the US showed that dupilumab improved asthma control and reduced asthma exacerbations in people with severe asthma who had mepolizumab, reslizumab or benralizumab. The ERG noted several differences in the observational studies from the EU. People had had the 300 mg dose of dupilumab, which is only recommended in people on oral corticosteroids. Also, a high proportion of people had oral corticosteroids compared with people in QUEST who had 200 mg dupilumab. The committee noted that, based on limited retrospective studies with small sizes, dupilumab was effective in improving asthma control and reducing exacerbations in people with severe asthma who had mepolizumab, reslizumab or benralizumab. The committee concluded that dupilumab is likely to be effective in some people whose asthma has not responded to mepolizumab, reslizumab or benralizumab. However, it concluded that the proportion of people who have had mepolizumab, reslizumab or benralizumab whose asthma will respond to dupilumab is uncertain.

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 asthma did not respond were transferred to standard care. The company derived the efficacy and clinical parameters in the model from QUEST. The committee concluded that the model structure was appropriate for decision making.

The evidence for the company's population is limited because it is based on clinical-effectiveness estimates from small sample sizes

3.13 The committee noted that the company's population included young people aged 12 years to 17 years, adults not eligible for mepolizumab, reslizumab or benralizumab (blood eosinophil count of 150 cells per microlitre to 299 cells per microlitre) and adults who had biological therapy but whose asthma had not responded (a blood eosinophil count of 300 cells per microlitre or more). The committee noted that the clinical-effectiveness evidence available for the company's populations was limited because the number of people included in QUEST was small (see section 3.11). The trial only included 2 people corresponding to the young-people subgroup and 14 people corresponding to the subgroup of adults not eligible for biologicals. Also, the QUEST protocol excluded people who had had biological therapy but 1 person was included who had had a biological. The ERG noted that the estimates of transition probabilities for the company's population were highly uncertain because of the small sample sizes. The company assumed that clinical effectiveness was the same for each subgroup based on trial estimates for the company's population. The company provided clinical expert opinion that switching from other biologicals (the interleukin-5 inhibitors: mepolizumab, reslizumab, benralizumab) to dupilumab (a interleukin-4/13 inhibitor) was acceptable because the mechanisms of action were different enough. The committee considered that the assumption of equal efficacy of dupilumab regardless of whether people had mepolizumab, reslizumab or benralizumab was uncertain. This was because it considered assuming that the response rate would be as good in people not eligible for mepolizumab, reslizumab or benralizumab was optimistic. In response to its second appraisal consultation document, the company provided additional data on the effectiveness of dupilumab in people with asthma that had not responded to mepolizumab, reslizumab or benralizumab. The committee concluded that, because the evidence for dupilumab's clinical effectiveness in the company's population was based on a small number of people, it was limited.

Clinical inputs to the model

The company's updated base case does not include a multiplier for long-term severe exacerbation rates

3.14 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 QUEST was lower than that seen in clinical practice in the year before trial enrolment (4.46 exacerbations per year). The company's model after technical engagement used the exacerbation rates from QUEST and VENTURE in the first year of the model. Also, it increased the number of severe exacerbations in subsequent years for both dupilumab and standard care by applying a multiplier. The ERG considered the trial to be the best source of exacerbation data. It did not include an exacerbation multiplier in its base-case model, which resulted in higher incremental cost-effectiveness ratios (ICERs). The company provided evidence on severe exacerbation rates from 3 cohorts with severe asthma: WATCH (Wessex Asthma Cohort of Difficult Asthma), U-BIOPRED (Unbiased Biomarkers in Prediction of respiratory disease outcomes) and the Sanofi Real World Evidence (RWE) study. It also accepted the committee's and ERG's concerns about the uncertainty of using a multiplier. The exacerbation rates in the company's updated base-case model were taken from QUEST for the duration of the model without an exacerbation multiplier. The committee concluded that the updated base-case model without the exacerbation multiplier was appropriate.

Real-world evidence is an appropriate source of data to inform the treating severe exacerbations setting

3.15 The company assigned different mortality rates to severe exacerbations treated in hospital emergency care, inpatients and general practice based on the UK Difficult Asthma Registry data (O'Neill et al. 2015). In QUEST, 6.7% of severe exacerbations were treated in hospitals (3.0% in emergency care, 3.7% in inpatients and 93.3% in general practice). In the UK Difficult Asthma Registry data, this was 26.5% (7.8% in emergency care, 18.7% in inpatients and 74.0% in general practice), which it thought was a more appropriate estimate of resource

use in the NHS. The ERG base-case model used the QUEST data for the setting of severe exacerbations. The clinical expert explained that the number of people treated in hospitals in clinical practice is likely to be higher than that seen in QUEST. This was because people in trials are well monitored on optimised treatment, more motivated and adhere better to treatment. The committee requested further exploration of different sources of data to inform the setting of treating exacerbations to inform the model. The company then submitted data on the setting of treating severe exacerbation rates from 3 different sources (WATCH, U-BIOPRED and the Sanofi RWE study). The definition of severe exacerbation in the Sanofi RWE study was based on case notes from severe asthma centres in the NHS to match the definition in QUEST. The data for setting exacerbations from the Sanofi RWE study was used in the company's updated model. The ERG considered the Sanofi RWE study to be of reasonable quality and that it produced results consistent with other sources. The committee concluded that the Sanofi RWE study on the setting of severe exacerbations was appropriate for use in the company's base case.

The company's mortality estimates are appropriate for decision making but uncertain

3.16 The company's original 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 estimated 1,300 asthma-related deaths a year in the UK. The higher death rate was because of interaction between the exacerbation multiplier (see section 3.14) and using registry data to inform the setting of treating exacerbations (see section 3.15). The committee noted that the model did not offer plausible estimates and asked that additional analyses presented by the company:

- include 10-year mortality rates for dupilumab and standard care and
- show the flow of patients through different health states in the model for the purposes of model validation.

The company updated its model and removed the exacerbation multiplier (see section 3.15), which reduced 10-year mortality with standard care to

16.7%. The ERG considered that this still probably overestimated mortality, but that the plausibility of model survival projections was difficult to judge without UK data. The committee was concerned that mortality could have been overestimated because asthma-related mortality was one of the drivers of the model. It also noted that alternative methods had been used in NICE's technology appraisal guidance on benralizumab for treating severe eosinophilic asthma to adjust for high mortality. So, at its second meeting, the committee concluded that the mortality rates were still uncertain. It asked the company to explore alternative scenarios to assess the effect of mortality on the ICER. To address the committee's concern, the company explained that the modelled mortality rates (73 years for standard care and 75 years with dupilumab) were consistent with published literature. It provided data from a French asthma study. When it adjusted its model to a mean starting age of 61 years, the mortality was 7.1% at 3 years compared with a modelled output of 7.6% at 3 years. The ERG did not consider this to reduce the uncertainty about whether the modelled mortality was overestimated for current UK clinical practice. This was because of differences in the population, treatments and setting. The company also applied a correction to the case fatality rate (1.81% rather than 0.85%) for people aged 55 years to 64 years admitted to hospital with a severe asthma exacerbation. The ERG noted that this increased the ICER from £28,156 to £28,929 per quality-adjusted life year (QALY) gained. The committee noted that this correction was not in the company's base case. To further address committee concerns, the company presented a scenario using NICE's technology appraisal guidance on mepolizumab for treating severe refractory eosinophilic asthma exacerbation settings. The committee noted that this only reduced the ICER to £27,257 per QALY gained. It appreciated the company's attempt to explore uncertainty. It concluded that the company's mortality estimates were appropriate for decision making and that the mortality rates were still uncertain.

Cost-effectiveness estimates

The company's updated base-case ICER is £28,156 per QALY gained for dupilumab compared with standard care

3.17 At consultation, the company updated the confidential discount for dupilumab and provided additional evidence for dupilumab's efficacy. It also explored scenarios for the uncertainties identified by the committee, including:

- varying the 1-year response rate for dupilumab
- varying the relative risks of severe exacerbations for dupilumab compared with standard care alone
- using settings of exacerbation from NICE's technology appraisal guidance on mepolizumab for treating severe refractory eosinophilic asthma
- using a lower mortality estimate for people aged 55 years to 64 years who were hospitalised.

The company's revised base-case deterministic ICER for dupilumab compared with standard care was £28,156 per QALY gained in people with a blood eosinophil count of 150 cells per microlitre or more and FeNo of 25 parts per billion or more, who have had at least 4 or more exacerbations in the previous 12 months, and who are not eligible for mepolizumab, reslizumab or benralizumab or whose asthma has not responded adequately to these biological therapies. The committee was aware that all the explored scenarios had minimal effect on the cost-effectiveness results. It noted, however, that the base-case model should have included the mortality correction (see section 3.16), which increased the ICER to £28,929 per QALY gained. The committee noted that this was at the higher end of what NICE usually considers a cost-effective use of NHS resources. However, it considered dupilumab to be innovative as an additional treatment for people with severe asthma with type 2 inflammation and a high unmet need. It also noted that the model did not take into account the costs and disutilities associated with long-term oral corticosteroid use (that is, obesity, diabetes, osteoporosis, cataracts, hypertension, adrenal suppression, anxiety and depression). Also, some people with comorbidities such as nasal polyps and

atopic dermatitis would get additional benefits from dupilumab. The committee considered dupilumab to be a step change for people with severe asthma with type 2 inflammation. Therefore, it concluded that the ICER of £28,929 per QALY was likely to represent the upper estimate of the cost effectiveness of dupilumab.

Other factors

Additional benefits in people with nasal polyps or atopic dermatitis may not be adequately captured in the QALY calculation

3.18 The committee recognised that there is an unmet need for people with severe asthma with type 2 inflammation. It 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 adequately captured in the QALY calculation and took them into consideration in its decision making.

There is limited data available on dupilumab for young people

3.19 Dupilumab is licensed in people 12 years and over. The company provided an analysis for the subgroup of people aged 12 years to 17 years. The committee noted that QUEST only included 2 people under 18 years that met the criteria for the base-case population. There is an unmet need in this population with uncontrolled severe asthma with type 2 inflammation. Mepolizumab is the only other biological that is licensed for treating severe refractory eosinophilic asthma in children (6 years or over). However, NICE's technology appraisal guidance on mepolizumab only recommends it for use in adults. No other biologicals are recommended by NICE for severe asthma in people under 18 years. The committee concluded that there is limited data available for dupilumab in young people and acknowledged this during decision making.

There are no equality issues relevant to the recommendations

3.20 No equality or social value judgement issues were identified.

Conclusion

Dupilumab is recommended for treating severe asthma with type 2 inflammation

3.21 The committee acknowledged that dupilumab is effective for preventing exacerbations in people with severe asthma with type 2 inflammation compared with standard care. The cost-effectiveness estimates for dupilumab are within what NICE usually considers a cost-effective use of NHS resources. The committee identified several uncertainties in the modelling assumptions, particularly about estimates of mortality and response rates in adults whose asthma did not respond to biological therapy. These uncertainties resulted in uncertainty about the true cost effectiveness of dupilumab. To address the committee's concerns, the company presented further analyses to support the population with a high unmet need and further increased the discount for the 200 mg dose of dupilumab (see section 3.17). The committee noted that all scenarios presented by the company had minimal effect on the cost-effectiveness results and considered the ICER of £28,929 per QALY a plausible estimate of cost effectiveness. It also noted that the additional benefits of dupilumab may not have been fully captured in the QALY calculation. Therefore, it recommended dupilumab as a cost-effective treatment for use in the NHS for treating severe asthma with type 2 inflammation that is inadequately controlled in people 12 years and older, despite maintenance therapy with high-dose inhaled corticosteroids and another maintenance treatment, only if:

- the dosage used is 400 mg initially and then 200 mg subcutaneously every other week
- the person has agreed to and follows an optimised standard treatment plan
- the person has a blood eosinophil count of 150 cells per microlitre or more and FeNo of 25 parts per billion or more, and has had at least 4 or more

exacerbations in the previous 12 months

- the person is not eligible for mepolizumab, reslizumab or benralizumab, or the asthma has not responded adequately to these biological therapies.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has asthma and the doctor responsible for their care thinks that dupilumab is the right treatment, it should be available for use, in line with NICE's recommendations.

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.

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.

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Accreditation