NICE National Institute for Health and Care Excellence

NICE guidance

Tezepelumab for treating severe asthma

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 Tezepelumab as an add-on maintenance treatment is recommended as an option for severe asthma in people 12 years and over, when treatment with high-dose inhaled corticosteroids plus another maintenance treatment has not worked well enough. It is recommended only if people:

- have had 3 or more exacerbations in the previous year, or
- are having maintenance oral corticosteroids.

Tezepelumab is recommended only if the company provides it according to the commercial arrangement.

1.2 Stop tezepelumab if the rate of severe asthma exacerbations, or the maintenance oral corticosteroid dose, have not been reduced by at least 50% at 12 months.

1.3 These recommendations are not intended to affect treatment with tezepelumab 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 maintenance treatment. Oral corticosteroids are sometimes used to prevent exacerbations (asthma attacks), but they may have negative effects in the long-term. Some people with severe asthma can have biological treatments. Tezepelumab is another biological treatment.

Clinical trial results show that tezepelumab, when added to usual treatment, reduces exacerbations and the dose of oral corticosteroids needed, compared with placebo. An indirect comparison of tezepelumab with other biological treatments suggests similar clinical effectiveness, but this is uncertain.

The cost-effectiveness estimates show that tezepelumab as an add-on maintenance therapy is cost effective compared with standard care and other biological treatments. So, tezepelumab is recommended when treatment with high-dose inhaled corticosteroids plus another maintenance treatment has not worked well enough, for people who have had 3 or more exacerbations in the previous year or who are having maintenance oral corticosteroids.

2 Information about tezepelumab

Marketing authorisation indication

2.1 Tezepelumab (Tezspire, AstraZeneca) is indicated as 'an add-on maintenance treatment in adults and adolescents 12 years and older with severe asthma who are inadequately controlled despite high-dose inhaled corticosteroids plus another medicinal product for maintenance treatment'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for tezepelumab.

Price

2.3 The list price for tezepelumab is £1,265 per 210 mg prefilled syringe per vial (company submission, May 2022). The company has a commercial arrangement. This makes tezepelumab 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 AstraZeneca, a review of this submission by the evidence assessment group (EAG), and responses from stakeholders. See the committee papers for full details of the evidence.

Condition background

Living with severe asthma is physically and emotionally challenging

3.1 Severe asthma is a distressing and socially isolating condition. Patient experts commented that exacerbations can happen without warning, causing fear. Exacerbations may result in hospitalisation and can be life threatening. The symptoms of severe asthma mean that people often feel tired and unable to work or play, and they may need help with day-to-day activities. The patient experts explained that severe asthma can also affect mental health. The committee understood that people with severe asthma often have difficulties doing day-to-day tasks. People may also have negative effects, including bone damage, from long-term use of standard treatments. People may go on to require surgery because of weak bones. The committee concluded that living with severe asthma is physically and emotionally challenging.

Treatment pathway

Standard care includes oral corticosteroids and biological treatments as add-ons to first-line treatments

3.2 Asthma treatment in clinical practice follows the NICE guideline on asthma and the Global Initiative for Asthma (GINA) guideline (which includes the use of biological treatments). If asthma becomes uncontrolled despite inhaled corticosteroids (usually offered with another treatment), then low-dose oral corticosteroids or biological treatments

are added. The clinical and patient experts explained that biological treatments are preferred to oral corticosteroids because they have fewer negative effects. Biological treatments may be offered as add-on options if asthma is not controlled well enough with maintenance treatment with high-dose inhaled corticosteroids plus a long-acting beta-agonist or another treatment. The committee noted that, when it met, the choice of available biological treatments, such as anti-interleukin-5 inhibitors, was based on the phenotype and biomarker profile of asthma. See NICE's technology appraisal guidance on benralizumab, mepolizumab, reslizumab, dupilumab and omalizumab. Patient experts highlighted that biological treatments have been life changing for some people. But not all people with severe asthma can have them because of the specific eligibility criteria. The clinical experts explained that immunoglobulin E, blood eosinophil count and fractional exhaled nitric oxide (FeNO) levels are used to assess and manage severe asthma. They noted that blood eosinophil count and FeNO levels are routinely measured in clinical practice. They also explained that most people with severe asthma usually have 1 or 2 of these biomarkers, but relatively few people have all 3 biomarkers. The committee understood that standard treatment for severe asthma includes oral corticosteroids and several biological treatments as add-ons to first-line treatments.

A treatment option without the need for biomarker assessment would be welcomed

3.3 The clinical and patient experts explained that about 5% of people with severe asthma who have regular treatment cannot have existing biological treatments. The patient experts added that long-term use of oral corticosteroids could suppress people's biomarkers, meaning they cannot have existing biological treatments. Both the clinical and patient experts explained that there is an unmet need for treatments that reduce exacerbations and improve asthma control. The patient experts explained that for many people with severe asthma that does not respond to standard treatments (including biological treatments), long-term oral corticosteroids are the only option. They noted these may have negative effects, including osteoporosis, cataracts, glaucoma, skin conditions, reflux oesophagitis, non-alcoholic fatty liver, and weight gain. The clinical expert noted that, in practice, people can switch to a

different biological treatment if there was no response to the previous one. But in this situation people would need to have biomarker assessment again. So, a new treatment without the need for biomarker assessment would benefit people. The committee understood that there is an unmet need for people with severe asthma who cannot have existing biological treatments because of their biomarker profiles. So, it concluded that a new treatment option without the need for biomarker assessment would be welcomed.

The company's proposed positioning of tezepelumab as an add-on to first-line treatment is appropriate

3.4 Tezepelumab has a marketing authorisation as an add-on maintenance treatment in people 12 years and over with severe asthma that is inadequately controlled despite high-dose inhaled corticosteroids plus another maintenance treatment. The company proposed tezepelumab for a narrower population than in the marketing authorisation. This was people:

- who had 3 or more exacerbations in the year before, or
- who are having maintenance oral corticosteroids.

The company explained that the existing biological treatments target specific biomarkers (see section 3.3). People with severe asthma often have a biomarker that overlaps with other phenotypes or fluctuates, and some people have no defined inflammation. The company explained that tezepelumab has a unique mechanism of action, which could make it effective for different asthma phenotypes regardless of biomarker profiles. It proposed tezepelumab as an add-on treatment to first-line standard care regardless of biomarker profiles or eligibility. If recommended, tezepelumab would be an alternative option for people with low biomarkers (not eligible for existing biological treatment), as well as those with high biomarkers (eligible for existing add-on biological treatments). The committee noted that there were several subpopulations to be considered based on biomarker eligibility at different positions in the treatment pathway. It concluded that the company's positioning of tezepelumab is appropriate, and it considered the evidence presented for these subpopulations in its decision making.

Comparators

Relevant comparators are standard care plus add-on biological treatments, and standard care alone

3.5 The company provided evidence on tezepelumab compared with standard care with or without add-on biological treatments (see section 3.2). The committee agreed that standard care plus add-on biological treatments, and standard care alone, were relevant comparators for tezepelumab.

Treatment response

The company's updated definition of treatment response is appropriate

3.6 Reducing exacerbations and the dose of maintenance oral corticosteroids taken are primary outcomes in the company's pivotal clinical trials (see section 3.8). The EAG noted that the tezepelumab trials did not define treatment response. The company assumed that any reduction in exacerbations or maintenance oral corticosteroid dose from baseline was a treatment response. The EAG considered the company's original definition of response inappropriate and not clinically meaningful. It considered that a reduction of between 20% and 50% in exacerbations was an appropriate treatment response, which was in line with the clinical advice it had received. The EAG also noted that using an alternative definition of response, for example, a 20% reduction in exacerbations, was likely to affect the post-assessment transition probabilities in the model. The company explained that using an alternative definition for treatment response of 20% reduction in exacerbations would have little effect on a person's eligibility to continue treatment after 52 weeks (see section 3.14). This is because it would only affect people with 6 or more exacerbations in the previous year. The patient expert explained that for severe asthma, any reduction in exacerbations or maintenance oral corticosteroid dose may not be seen as clinically meaningful in clinical practice. But it could mean qualitative

improvement in quality of life. The committee noted the wide spectrum of asthma phenotypes and symptoms (see section 3.2) and queried how the reduction would be meaningfully measured in practice. The clinical expert explained that a holistic view would be needed in practice when response is assessed. People may have natural variation in symptoms or biomarkers from year to year, but these would be relatively small. A reduction in exacerbations may be associated with symptom improvement, but there needs to be a threshold in practice, and this is usually set at 50%. This allows quicker switching to another biological treatment if a person's asthma does not respond. At the first meeting, the committee concluded that a 50% reduction in exacerbations would be more appropriate. In response to consultation, the company explained that it had obtained a clinical opinion from severe asthma specialists who confirmed that they would consider an appropriate definition of response to be:

- for people not having maintenance oral corticosteroids: 50% reduction in exacerbations
- for people having maintenance oral corticosteroids: 50% reduction in their dose.

The company explained that the committee's requested scenario of 50% reduction in exacerbations and maintenance oral corticosteroid dose use in people already having oral maintenance corticosteroids was not in line with clinical practice. It was also not consistent with previous NICE technology appraisal guidance on mepolizumab, benralizumab and reslizumab for treating severe asthma. Stakeholder comments in response to the consultation, and the clinical expert at the second appraisal committee meeting, agreed with the company's updated definition of response. The committee concluded that the company's updated definition of treatment response was appropriate for decision making.

Clinical-effectiveness evidence

Populations in the company's trials reflect the NHS

3.7 The clinical evidence came from 3 multicentre, randomised, double-blind,

placebo-controlled trials: PATHWAY (n=550), NAVIGATOR (n=1,059) and SOURCE (n=150). These trials compared 210 mg tezepelumab every 4 weeks with placebo for people 18 years and over (except NAVIGATOR, which included people 12 years and over). People in the trials had severe asthma with 2 or more exacerbations in the previous year (except SOURCE, which included people with 1 or more exacerbations in the previous year). This included people having medium-to-high doses of inhaled corticosteroids. The 3 trials were done globally; NAVIGATOR was the only trial that included people from the UK. The EAG noted that the baseline characteristics of the trial populations were well balanced in the 2 arms. The clinical experts and the EAG considered that the populations of PATHWAY, NAVIGATOR and SOURCE reflected those with severe asthma seen in the NHS. The committee concluded that the trial populations were generally representative of people in the NHS.

Tezepelumab is clinically effective compared with placebo for severe asthma

3.8 The primary outcome was annualised asthma exacerbation rate (AAER) at 52 weeks in PATHWAY and NAVIGATOR. In SOURCE this was a secondary outcome at 48 weeks. The primary outcome in SOURCE was percentage reduction from baseline in maintenance oral corticosteroid dose without loss of asthma control at 48 weeks. The trials showed tezepelumab was associated with a greater reduction in AAER at 52 weeks compared with placebo. In PATHWAY, the rate ratio (RR) was 0.29, (95% confidence interval [CI] 0.16 to 0.51); in NAVIGATOR the RR was 0.44, (95% CI 0.37 to 0.53). The committee noted that largely similar results were reported in SOURCE (the company considers this data confidential, so it cannot be reported here). The 3 trials assessed multiple secondary outcomes. The committee focused on AAER-related hospitalisations or emergency department visits, which also informed the model. The results from PATHWAY and NAVIGATOR suggested that tezepelumab was more effective than placebo at reducing AAER-related hospitalisations at 52 weeks. The difference in AAER-related hospitalisations was not statistically significant in SOURCE (the company considers this data to be confidential, so it cannot be reported here). Largely similar results were found for other secondary outcomes. Evidence from NAVIGATOR and SOURCE also shows that tezepelumab

was associated with a greater improvement in quality of life as measured by EQ-5D-5L when compared with placebo. No subgroup analysis (see section 3.9) was done for this outcome. The committee concluded that tezepelumab is clinically effective in severe asthma compared with placebo.

Tezepelumab is generally more effective than placebo for severe asthma in pre-planned and post-hoc subgroups

3.9 The company also presented clinical trial evidence assessing tezepelumab's clinical effectiveness compared with placebo in pre-planned subgroups. The company also presented post-hoc subgroup analysis based on eligibility for biological treatments (see section 3.2). For the pre-planned subgroups, results from PATHWAY and NAVIGATOR suggested that tezepelumab was more effective than placebo in reducing AAER. This was in subgroups stratified by:

- baseline blood eosinophil count (at least 300 cells per microlitre or less than 300 cells per microlitre [PATHWAY and NAVIGATOR])
- baseline FeNO level (24 [PATHWAY] or 25 [NAVIGATOR] and above parts per billion, or less than 24 [PATHWAY] or 25 [NAVIGATOR] parts per billion)
- baseline inhaled corticosteroid dose (medium or high-dose [PATHWAY])
- number of exacerbations in the previous 12 months (1 to 2, or 3 or more exacerbations in the previous 12 months [PATHWAY])
- baseline FeNO status (positive or negative [NAVIGATOR]) at 52 weeks.

In SOURCE, tezepelumab was more effective than placebo in reducing maintenance oral corticosteroid dose in subgroups with a higher baseline blood eosinophil count (defined as 150 or 300 cells per microlitre and above) at 48 weeks. Largely similar results for AAER reductions were also reported from NAVIGATOR for most post-hoc subgroups at 52 weeks. In SOURCE, tezepelumab reduced AAER in the anti-interleukin-5-eligible and omalizumab-eligible subgroups but not in the non-biologic eligible subgroup (see section 3.2) at 48 weeks. But the number of events captured in the subgroup analyses was small. The results are academic in confidence so cannot be

reported here. The committee concluded that the clinical trial evidence suggested that tezepelumab is generally more effective than placebo in reducing AAER or maintenance oral corticosteroid dose in pre-planned or post-hoc subgroups.

Network meta-analysis

The company's indirect treatment comparisons are highly uncertain

3.10 There was no direct comparison between tezepelumab and existing biological treatments including omalizumab, reslizumab, benralizumab, mepolizumab and dupilumab. So, the company did a series of network meta-analyses (NMAs) comparing the clinical effectiveness of tezepelumab with these biological treatments in the NICE-recommended subpopulations. It also compared tezepelumab with standard care alone in the subpopulation who cannot have existing biological treatments. The NMAs were done for several outcomes. The EAG noted that for the outcome of AAER, NMAs for both the intention-to-treat (ITT) population and for subpopulations defined by biological therapy eligibility were available. But it was only the results from the subgroup NMAs that informed the model. For the outcome of reduction in AAER-related hospitalisations, the only NMA available was done in the ITT population. For reduction in oral corticosteroid dose, NMAs were done in both the ITT population and subpopulations, and the company used the NMA results for the subpopulation with a baseline blood eosinophil count of at least 300 cells per microlitre. It highlighted that the results of the NMAs based on different populations were blended in the model. The EAG also explained that not all of the biomarkers that defined relevant biological treatment-eligible subpopulations (see section 3.2) were consistently available across trials included in the NMAs. The uncertainty about this meant that its impact on the NMA results was unknown. The committee noted that the company's NMA results suggested that tezepelumab appeared to be more effective than other biological treatments in reducing AAER and oral corticosteroid dose in the assessed subpopulations. It further noted that it appeared to be more effective than other biological treatments in reducing AAER-related hospitalisation

in the ITT population. But most 95% credible intervals for the reported RRs crossed 1, which meant that it was possible that there was no difference in treatment effect between the interventions compared. In most subpopulations and in the ITT population the only substantial difference was between tezepelumab and placebo. For the subgroups defined by baseline blood eosinophil count, the committee noted that the results suggested that tezepelumab was associated with a greater reduction in AAER than placebo when the subpopulation was defined as having a blood eosinophil count of either 300 or 150 cells and above per microlitre. But this was not the case for this same outcome when the subpopulation was defined as having a blood eosinophil count of less than 300 cells per microlitre. The committee understood that the biomarker evidence in the trials (which informed the NMAs) did not all match the biomarkers used for the NICE-recommended treatments. The committee understood that there were challenges in evidence generation. At the first meeting, the committee concluded that the results of the company's NMAs were highly uncertain, and it would like to see uncertainties addressed. In response to consultation, the company updated its base-case NMA inputs in the population who were eligible for reslizumab. This was so that the NMA data for the subgroup with a baseline blood eosinophil count of at least 300 cells per microlitre informed all NMA-based comparisons in the economic model (this included comparisons with reslizumab, mepolizumab and benralizumab). The EAG agreed with these changes and incorporated them in its updated base case because they reflect the relevant guidance for these treatments. For the comparison with dupilumab the company used NMA data relating to the 200 mg dose. This corrected an error in their previous NMA that had used a higher dose (300 mg) not used in clinical practice. The EAG was concerned that the company provided no additional information to clarify the impact of the error. The EAG preferred to use the subgroup with baseline blood eosinophil count of at least 150 cells per microlitre to inform its updated base-case analyses for the duplimumab comparison. The results of the updated subgroup analyses suggested that tezepelumab was associated with a greater reduction in AAER compared with other biological treatments. The company also provided scenarios based on a simulated treatment comparison and a comparison to published NMAs. The EAG considered that the uncertainty that related to matching exact subgroups to data

from comparator trials was still not fully resolved by the company's scenarios presented. The committee considered that the company's original and updated NMAs both had considerable uncertainty. This was because of the unresolvable limitations in the evidence, and because the biomarker evidence in the trials did not all match the biomarkers used for the NICE-recommended treatments. The committee was satisfied that the company had explored the uncertainty in its updated NMAs and that there were unresolvable challenges in matching exact subgroup data because of the lack of evidence. The committee concluded that tezepelumab is likely to have a similar clinical effectiveness compared with existing biological treatments, but that this is highly uncertain.

Economic model

The company's model structure is appropriate for decision making

3.11 The company used a 5-state Markov model comparing tezepelumab with standard care in people with severe asthma. The model included 5 health states: controlled asthma, uncontrolled asthma, uncontrolled asthma with exacerbation, controlled asthma with exacerbation, and dead. Controlled asthma was defined as an asthma control questionnaire (ACQ)-6 score of less than 1.5. Uncontrolled was defined as an ACQ-6 score of more than 1.5. An exacerbation was defined as a worsening of asthma needing oral corticosteroids for at least 3 consecutive days, an emergency department attendance or hospitalisation. The model had a lifetime horizon (60 years) and a cycle length of 4 weeks. The EAG considered the model structure appropriate but it noted the uncertainty about the company's approach of modelling exacerbations as controlled and uncontrolled (see section 3.13). The committee concluded that the company's model structure was appropriate for decision making.

It is appropriate to use an ACQ-6 score of 1.5 as a cut-off to define asthma status in the model

3.12 The committee noted that the company used an ACQ-6 cut-off score of 1.5 to define asthma control status as either uncontrolled (more than 1.5)

or controlled (less than 1.5) in the model. The EAG preferred using a cut-off of 1 to define the health states. It noted that the NAVIGATOR trial defined an ACQ-6 score of between 0.75 and less than 1.5 as 'partially controlled' asthma. It considered that using the cut-off of 1.5 rather than 1 would misclassify some asthma that was not well controlled as well controlled, and overestimate the treatment effectiveness in the model. The EAG explained that a study by Juniper et al. (2006) suggested that the crossover point between well controlled and not well controlled asthma was close to an ACQ-6 score of 1. The EAG noted that a cut-off of 1.5 was used in the recommendations in NICE's technology appraisal guidance on dupilumab, benralizumab and reslizumab. But it considered that aligning with previously accepted assumptions was not sufficient justification. The company explained that it had considered using partially controlled asthma as a third health state, but did not implement it because of the multiple subgroups being considered. So, the subgroup would have been informed by a small population. The company and clinical experts noted that Juniper et al. (2006) was part of a larger study (GOAL), which included very mild asthma. This is different from the population indicated in tezepelumab's marketing authorisation. It explained that GOAL included 3 cohorts; people:

- who have not had inhaled corticosteroids
- having low-dose inhaled corticosteroids
- having medium-dose inhaled corticosteroids.

The clinical expert agreed with the company's approach of using an ACQ-6 score of 1.5 as a cut-off to define asthma control status. The committee concluded that using the ACQ-6 score of 1.5 as cut-off to define asthma control states was appropriate for decision making.

The company's approach of modelling asthma exacerbations as controlled and uncontrolled is acceptable for decision making

3.13 The company's model prohibited the transitions from controlled asthma to uncontrolled asthma with exacerbation and from uncontrolled asthma to controlled asthma with exacerbation. The EAG considered it inappropriate and noted that the transition probabilities from both the

asthma exacerbation health states to the controlled asthma state may have been overestimated in the company's model. According to the EAG, this was because people who transition from the controlled asthma exacerbation health state are more likely to return to the controlled rather than the uncontrolled asthma state in the model. But clinical opinion received by the EAG suggested that people can have exacerbations in any health state. But the risk of having an exacerbation will be different, so the transition probability will be different depending on which health state they started in. Clinical opinion received by the EAG also noted that if people were in an uncontrolled asthma state and having an exacerbation, they may be more likely to go back to having uncontrolled asthma than having controlled asthma. The company explained that its approach was in line with the recommendations in NICE's technology appraisal guidance on benralizumab. It also disagreed that the transition probabilities from exacerbation states to the controlled asthma health state were overestimated, because they were derived from the trials. It explained that distinguishing between exacerbations in previously controlled asthma from asthma not previously controlled could capture the differences in health-related quality of life, costs and mortality between the 2 states. But a single health state for exacerbation would not. The clinical expert explained that there is no fundamental difference in exacerbations regardless of the previous asthma state. He also noted that it is not common to have an exacerbation if the asthma is well controlled. In practice, an exacerbation would last for about a week and people having an exacerbation would be considered to have uncontrolled asthma. The clinical expert considered that the company's approach to modelling exacerbations was reasonable. The committee agreed that the company's approach of modelling exacerbations was acceptable for decision making.

The company's approach of using different transition probabilities after 52 weeks is appropriate

3.14 The company included a one-off stopping at 52 weeks in the model. After 52 weeks, it implemented a different set of transition probabilities for people whose asthma was considered to have responded. The EAG considered that this overestimated the treatment effect in the model because the stopping had been accounted for. Because of the lack of

data, the EAG was unable to implement different transition probabilities in the model. So, it set the transition probabilities before and after 52 weeks to be equal in the model, and considered this approach to be conservative. The company explained that the one-off stopping at 52 weeks reflected the stopping rules in previous NICE technology appraisals for other add-on biological treatments. It considered it was appropriate to have a different set of transition probabilities for people with response after 52 weeks. This was because people whose asthma does not respond would stop treatment at this point. Only those whose asthma had responded would remain in the model. The committee concluded that the company's approach was acceptable.

The company's mortality estimates are appropriate

3.15 Mortality was a driver of cost effectiveness in the company's model. The company originally assumed that deaths from asthma could only occur through exacerbations. The EAG considered that the probabilities used by the company overestimated asthma-related mortality for people under 75 years. The EAG re-estimated mortality risk for people under 75 years based on 2020 Office of National Statistics mortality data for England, which resulted in an average probability of 0.001 for death per cycle (4-weekly) for its base case. The EAG also did a scenario analysis using an asthma mortality estimate based on NICE's technology appraisal guidance on benralizumab. The clinical expert noted that asthma mortality might be higher than both the company's and the EAG's estimates in clinical practice. He also explained that death can occur not only because of exacerbations but also because of long-term use of oral corticosteroids. At the first committee meeting, the committee accepted the company's asthma-related mortality estimates for decision making. In response to consultation, the company did a UK-based real-world study of all-cause mortality in people not eligible for biological treatment to inform its updated base case. This study explored electronic health records (2012 to 2017) from the Clinical Practice Research Datalink (CPRD) for people who had 3 or more exacerbations in the previous year or who were having maintenance oral corticosteroids and were ineligible for biological treatments based on NICE's recommendations. It highlighted that it had selected a population not eligible for biological treatment, to calibrate mortality in the standard care arm of its model.

The results suggested that all-cause mortality for people with severe asthma was substantially higher than that predicted by its model. The results were also in line with Roche et al. (2022), a study based on French real-world evidence. The EAG explained that the real-world study was well done and reduced some uncertainty in the mortality estimates. It noted, however, that the results were only applicable to a subset of people who were ineligible for biological treatment, but had been applied across all subgroups in the company's model. The EAG considered that it would have been more appropriate to apply the overall population estimates across all subgroups to get more precise estimates. Alternatively, mortality rates by subgroup could have been estimated and then applied to their respective populations individually in the model. The EAG also considered that the multiplier used by the company to adjust the mortality rate to match the CPRD rates was uncertain because of the limited sample size of the CPRD data. The EAG also noted that calibrating exacerbation-related mortality to all-cause mortality may have overestimated mortality in the model. It also noted that a recent multinational cohort study by Engelkes et al. (2020) on severe asthma reported lower all-cause mortality rates in the UK than in the company's CPRD analysis. But it acknowledged that the study population was not the population of interest for this appraisal and had a lower disease burden. The committee noted that the company's original base-case asthma-related mortality estimates were more appropriate but that its CPRD analysis was informative for the non-biological eligible group. It concluded that it would consider cost-effectiveness scenarios using both the company's original base-case asthma-related mortality estimates and the all-cause mortality CPRD data (only in the non-biological eligible subgroup) in its decision making.

The company's updated approach to utility gain with biological treatments is appropriate

3.16 The company assumed a utility increment for people who had a biological treatment, which was not associated with any health state in the model. The committee questioned the face validity (that is, the clinical plausibility) of using this utility increment. The company explained that it applied this utility gain in the model because the benefits of the treatment were not fully captured. This was because its model structure

considered asthma as either controlled or uncontrolled and that a third health state, partially controlled, was considered but not implemented (see section 3.13). The company explained that it did a regression analysis based on the EQ-5D-5L data collected in the tezepelumab clinical trials. The results suggested the regression coefficient was statistically significant. The company considered its approach in line with NICE's technology appraisal guidance on benralizumab and omalizumab, in which an effect of biological treatment on utility over and above treatment effect was accepted by the committee. The EAG explained that the effectiveness of biological treatments should be reflected in the modelled health states. It considered that adding an additional utility increment with borderline statistical significance over and above the asthma control and exacerbations was not appropriate. The EAG also noted that in NICE's technology appraisal guidance on benralizumab and omalizumab, the biological treatment effect-related utilities were attached to the health states in the model. At its first meeting the committee concluded that the company's approach of assuming an additional utility gain for biological treatments was not appropriate. In response to consultation, the company explained that it had identified an error in its original regression analysis and had corrected its base case. The updated results suggested that the regression coefficient was no longer statistically significant for biological-specific utility, so it removed the additional utility gain for biological treatments in its updated base case. The committee agreed that the company's updated base case was appropriate.

Cost-effectiveness estimates

The committee's preferred base case included the company's updated treatment response definition

3.17 The committee considered the results for all the relevant comparators. For those eligible for biological treatments the relevant comparators are: anti-interleukin-5 inhibitors (mepolizumab and benralizumab), omalizumab, reslizumab, and dupilumab. For people for whom biological treatments are unsuitable a comparison with standard care was made. The committee noted its preferred assumptions, which it updated after

the first committee meeting. The committee preferred base-case assumptions that were aligned to the EAG's, and these included:

- For people not having maintenance oral corticosteroids: 50% reduction in exacerbations (see section 3.6).
- For people having maintenance oral corticosteroids: 50% reduction in their dose (see section 3.6).
- The company's updated NMA using the subgroup with baseline blood eosinophil count of at least 300 cells per microlitre (for reslizumab, mepolizumab, benralizumab) and the EAG's preferred subgroup with baseline blood eosinophil count of at least 150 cells per microlitre for the comparison with dupilumab (see section 3.10).
- The company's original base-case mortality estimates, with a scenario using the updated estimates for the non-biological eligible group only (see section 3.15).
- The company's updated approach to utility gain (see section 3.16).

Tezepelumab is cost effective for treating severe asthma when biological treatments are suitable

3.18 For the subgroups eligible for biological treatments, the committee's preferred base-case incremental cost-effectiveness ratios (ICERs) were all below £20,000 per quality-adjusted life year (QALY) gained. The results included the confidential prices for other biological treatments, which means they cannot be reported here. The committee reiterated the uncertainty associated with the NMAs. But it agreed that the most plausible ICER was unlikely to be above what NICE normally considers an acceptable use of NHS resources in all subgroups eligible for biological treatments. The committee concluded that tezepelumab is cost effective compared with the biological treatments mepolizumab, benralizumab, resilizumab, dupilumab and omalizumab.

Tezepelumab is cost effective for treating severe asthma when biological treatments are not suitable

3.19 For the subgroup not eligible for biological treatments, the committee's preferred base-case ICER was at the higher range of what NICE usually considers a cost-effective use of NHS resources. But the committee noted that when the CPRD mortality rates were applied (see section 3.15) the ICER was below £20,000 per QALY gained. The results included the confidential prices for standard care treatments, which means they cannot be reported here. Section 6 of NICE's guide to the methods of technology appraisal notes that judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee recalled that there is a high unmet need for people with severe asthma who cannot have existing biological treatments. It also considered that tezepelumab may have uncaptured benefits. Further, the committee understood that the updated mortality estimates using the CPRD data reduced the ICER substantially, and only a small movement between the original and revised company mortality estimates brought the ICER below the threshold. The committee concluded that tezepelumab is cost effective compared with standard care in people not eligible for biological treatments.

Other factors

There may be additional benefits of tezepelumab not captured, but this is uncertain

3.20 The company considered tezepelumab to be innovative because of its mechanism of action, making it suitable for the broader severe asthma subtype population. The clinical experts noted that tezepelumab has the potential to be used for various severe asthma subtypes. They noted that if tezepelumab was approved, people would have another treatment option if their asthma does not respond to standard care. The patient experts also noted that tezepelumab may improve treatment adherence for people who find it more difficult to adhere to standard care. An

example is people with mental health issues. The committee recalled the patient expert comments on biological treatments also improving people's quality of life (see section 3.6), because they can provide stability. This allows people to plan more and have more control of their lives. But the committee also noted the uncertainties in the clinical evidence and the model. It concluded that tezepelumab may have additional benefits that have not been captured in the cost-effectiveness analysis, but these are difficult to untangle because of the uncertainties in the evidence and around some of the company's model assumptions.

Equality issues

3.21 The committee noted that severe asthma and its subtypes disproportionately affect women, with about 60% of people with severe asthma being women. The committee considered whether this was partly because of the potential effect of hormone levels on immunity and consequently on asthma. The clinical experts explained that this is not fully understood, because of a lack of evidence. But it is known that hormonal stress can affect immunity and as such people's health. They also noted that there is no evidence that suggests that biological treatments affect people differently based on sex. The committee considered that the recommendation would not restrict access for some people over others. No other equality or social value judgement issues were identified.

Conclusion

Tezepelumab is recommended for treating severe asthma

3.22 The committee concluded that tezepelumab as an add-on maintenance treatment is recommended for routine commissioning for treating severe asthma in people 12 years and over, when treatment with high-dose inhaled corticosteroids plus another maintenance treatment has not worked well enough. It is recommended only if:

- people have had 3 or more exacerbations in the previous year or are having maintenance oral corticosteroids

- the company provides tezepelumab according to the commercial arrangement.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this 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 severe asthma and the doctor responsible for their care thinks that tezepelumab 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 A.

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.

Chair

Radha Todd
Chair, technology appraisal committee A

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.

Harsimran Sarpal
Technical lead

Yelan Guo and Victoria Kelly
Technical advisers

Daniel Davies

Project manager

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