NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Tezepelumab for treating severe asthma

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using tezepelumab in the NHS in England. The appraisal committee has considered the evidence submitted by the company 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 age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Note that this document is not NICE's final guidance on this technology. 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 stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using tezepelumab in the NHS in England.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: 06 January 2023

Next appraisal committee meeting: 7 February 2023

Details of membership of the appraisal committee are given in section 4

1 Recommendations

1.1 Tezepelumab is not recommended, within its marketing authorisation, as an add-on maintenance treatment 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.

1.2 This recommendation is 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 long-term adverse effects. 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 oral corticosteroid dose compared with placebo. Tezepelumab has not been compared directly with other biological treatments. Its effectiveness compared with these is unclear because of uncertainties in the indirect treatment comparisons.

Whether tezepelumab is cost effective is unclear because of uncertainties in the clinical and economic evidence. The cost-effectiveness estimates are also all above the range NICE normally considers to be an acceptable use of NHS resources. So, tezepelumab is not recommended.

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 will be 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, which would have applied if tezepelumab had been recommended.

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, be life threatening, cause fear and result in hospitalisation. People are often unable to work or play, feel tired and may need help with day-to-day activities because of the symptoms. They 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 adverse effects from long-term use of standard treatments. 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 adverse 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 the choice of currently available biological treatments, such as anti-interleukin-5 inhibitors, is 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. However, 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 currently 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. The committee understood that standard treatment for severe asthma includes oral corticosteroids, and several biological treatments as an add-on to first-line treatments.

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

3.3 The clinical and patient experts explained that about 5% of people with severe asthma who are regularly having 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 for them. They noted these may have adverse 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 welcome.

The company's proposed positioning of tezepelumab as an add-on to first-line treatment may be 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:

- 12 years and over with severe uncontrolled asthma despite high-dose inhaled corticosteroids and an additional treatment (as specified in section 1.6 of the NICE guideline on asthma).
- 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), and also 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 may be 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 definition of treatment response is not appropriate

3.6 Reducing exacerbations and dose of maintenance oral corticosteroids 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 corticosteroids dose from baseline was a treatment response. The EAG considered the company's definition of response inappropriate and not clinically meaningful. It considered that a reduction between 20% and 50% 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, for example, a 20% to 50% reduction in exacerbations, would have little implication 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 corticosteroids 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 exacerbation 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. The committee concluded that a 50% reduction would be considered a clinically meaningful reduction and the company's definition of treatment response was not appropriate.

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. This was assessed as a secondary outcome in SOURCE at 48 weeks. In SOURCE, the primary outcome was percentage reduction from baseline in maintenance oral

corticosteroids dose without loss of asthma control at 48 weeks. The trials showed tezepelumab was associated with a greater reduction in annualised exacerbation rate 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 result for this outcome was similar in SOURCE (the company considers this data confidential, so it is not reported here). The committed noted that largely similar results were reported in SOURCE (the company considers this data confidential, so it is not 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 is not reported here). Largely similar results were found for other secondary outcomes. Evidence from NAVIGATOR and SOURCE also shows tezepelumab was associated with a greater improvement in quality of life measured by EQ-5D-5L when compared with placebo. No subgroup analysis (see section 3.9) was done for this outcome. The company explained that the assessment for this outcome took place at 12-week follow-up in these 2 trials. 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. However, in SOURCE, tezepelumab only reduced AAER in the anti-interleukin-5 eligible (see section 3.2) subgroup at 48 weeks. 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's critique focused on the 3 outcomes that informed the model, which were: reduction in AAER, reduction in AAER-related hospitalisations, and change in oral corticosteroid dose from baseline. Results for all were reported as RRs. The EAG noted that for the outcome of AAER, both NMAs for the intention-to-treat (ITT) population and for subpopulations defined by biological therapy eligibility were available, but only the results from the subgroup NMAs informed the model. However, 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. The EAG noted that the trials included in the NMAs had different follow-up times, which could potentially bias the results of the NMAs. The EAG also noted the mismatch between the subpopulations informing the NMA for the outcome of AAER, and the ITT population informing the outcome of AAER-related hospitalisations. 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 more effective than other biological treatments in reducing AAER and oral corticosteroid dose in the assessed subpopulations. It further noted that it appeared more effective than other biological treatments in reducing AAER-related hospitalisation in the ITT population. However, most 95%

credible intervals for the reported RRs crossed 1, which meant that it was likely that there was no difference in treatment effect between the interventions compared. Only the difference between tezepelumab and placebo was substantial in most subpopulations or the ITT population. 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 either having a blood eosinophil count of 300, or 150 cells and above per microlitre. However, 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. However, considering the uncertainties in the methods of the NMAs and the entirety of the evidence, the committee concluded that the results of the company's NMAs were highly uncertain. Because of this, tezepelumab's clinical effectiveness as an add-on treatment compared with other existing biological treatments is unknown.

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 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 cross-over 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 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. was a part of 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 the company's approach of 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 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. However, 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 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.

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 pre- and post-52 weeks to be equal in the model, and considered this approach 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 estimate is appropriate

3.15 Mortality was a driver of cost-effectiveness in the company's model. The company assumed that deaths from asthma could only occur through an exacerbation over and above background mortality rates. The EAG considered that the probabilities used by the company overestimated asthma-related mortality for people younger than 75 years. It noted that the Health Survey for England asthma report 2018 suggested that about 25% of deaths occurred in people aged 35 to 74 years. However, this was estimated at 37% in the company's model, about 12% higher than the Health Survey for England estimate. So the EAG re-estimated mortality risk for people younger than 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 of 0.0078 per 4-weekly cycle based on NICE's technology appraisal guidance on benralizumab. The company disagreed with the EAG. It explained that the EAG had misaligned the populations, because the population indicated for tezepelumab is severe asthma, but the Health Survey for England survey data covered all asthma-related deaths. The company also cited real-world evidence from a French healthcare database for people with severe asthma. This evidence suggested that the percentages of deaths in people younger than 70 and 80 years was 35.6% and 59.3%, respectively. So, it considered it was reasonable to assume the percentage of deaths for people younger than 75 years to be around 45%, which was higher than both the company's and the EAG's predictions in the model. 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 sometimes mortality does not only occur because of exacerbations but also long-term use of oral corticosteroids. The committee concluded that the company's asthma-

related mortality estimates, which were closer to the EAG's scenario analysis estimate, was appropriate for decision making.

Assuming a utility gain with biological treatments is not 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 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 3.14). 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. The committee concluded that the company's approach of assuming an additional utility gain for biological treatments was not appropriate.

Cost-effectiveness estimates

There are uncertainties in the evidence and in the company's modelling assumptions

3.17 The committee noted the high level of uncertainty in the company's clinical evidence and model assumptions, specifically:

- the definition of treatment response in its model (see section 3.6)
- uncertainty in the methods of the NMAs for subpopulations eligible for existing biological treatments (see section 3.10)
- the unknown clinical effectiveness of tezepelumab compared with other biological treatments as an add-on treatment and in relevant subpopulations (see section 3.10)
- applying an additional utility gain to biological treatments in the model (see section 3.16).

The cost effectiveness of tezepelumab is unclear, and more analyses are needed

3.18 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 incremental cost-effectiveness ratio (ICER). The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented. The committee considered that a reliable ICER could not be determined because of the uncertainties in the company's NMAs for biological treatments in eligible subpopulations, and other uncertainties in the modelling. The cost-effectiveness estimates were also all above the range NICE normally considers to be an acceptable use of NHS resources. And neither the company nor the EAG's base cases or scenario analyses included all the committee's preferred assumptions. The committee considered that further analyses are needed. It requested:

- treatment response defined as 50% reduction in exacerbations and oral corticosteroids dose and applied in the model (see section 3.6)
- uncertainties in the NMAs to be addressed (see section 3.10)
- no additional utility gain for people having biological treatments (see section 3.16).

Other factors

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

3.19 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 current standard care. The patient experts also noted that tezepelumab may improve treatment adherence for people who may find it more difficult to adhere to standard care, for example, 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 be able to plan more and have more control of their lives. But the committee also noted the uncertainties in the clinical evidence and in 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

3.20 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 asthma. The clinical experts explained that this is not fully understood because of a lack of evidence. However, 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 took those into consideration and noted that if tezepelumab were recommended, the recommendation would not restrict access for some people over others. No other equality or social value judgement issues were identified.

4 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
Technical adviser

Daniel Davies
Project manager

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