Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2541

tezepelumab solution for injection in pre-filled syringe (Tezspire®)

AstraZeneca plc

07 July 2023

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

tezepelumab (Tezspire®) is accepted for restricted use within NHSScotland.

Indication under review: 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.

SMC restriction: in adults and adolescents 12 years and older who either (i) experienced at least three exacerbations in the previous year and are not receiving maintenance treatment with oral corticosteroids or (ii) have blood eosinophils ≥150 cells/microlitre and are receiving maintenance treatment with oral corticosteroids.

Compared with placebo, the addition of tezepelumab to inhaled corticosteroids and at least one additional controller medicine, significantly reduced the annual asthma exacerbation rate in patients with inadequately controlled severe asthma.

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

Vice Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Tezepelumab is a human monoclonal antibody directed against thymic stromal lymphopoietin (TSLP) preventing its interaction with the TSLP receptor. In asthma, both allergic and non-allergic triggers induce TSLP production. Blocking TSLP with tezepelumab reduces a broad spectrum of biomarkers and cytokines associated with airway inflammation but the mechanism of action of tezepelumab in asthma has not been definitively established.[1]

Tezepelumab is the first human monoclonal antibody to block TSLP. It is administered subcutaneously at a dose of 210mg every 4 weeks as a long-term treatment with a recommended review at least annually to consider treatment continuation based on patient's asthma control.[1]

1.2. Disease background

Asthma is a common and potentially serious, chronic, heterogeneous, inflammatory lung condition, which is characterised by bronchial hyper-responsiveness, wheezing, breathlessness, chest tightness and cough and variable expiratory airflow limitation. Asthma can be effectively treated and most patients can achieve good asthma control, which includes avoiding troublesome symptoms day and night, little or no need for reliever medication, normal or near normal lung function, avoiding serious asthma exacerbations or attacks and having productive, physically active lives.[2, 3]

The severity of asthma is determined based on the treatment needed to control symptoms and exacerbations. Severe asthma is defined as asthma that requires high-dose inhaled corticosteroids and long-acting beta-agonists to prevent it from becoming uncontrolled or asthma that remains uncontrolled despite adherence to this optimised treatment.[2, 3]

1.3. Company proposed position

The submitting company has requested that tezepelumab is restricted for use in adults and adolescents 12 years and older with severe asthma who are inadequately controlled despite high-dose corticosteroids plus an additional medicinal product for maintenance treatment, who either (i) experienced at least three exacerbations in the previous year and are not receiving maintenance treatment with oral corticosteroids or (ii) have blood eosinophils ≥150 cells/microlitre and are receiving maintenance treatment with oral corticosteroids.

1.4. Treatment pathway and relevant comparators

Patients whose asthma remains uncontrolled or with exacerbations despite medium- to high-dose inhaled corticosteroid and a long-acting beta-agonist should be assessed for inflammatory phenotypes (for example eosinophilic or allergic asthma) and for use of potential add-on treatments. Biologics can be considered in patients with severe asthma to achieve control and reduce the use of oral corticosteroids.[2-4] There are five other monoclonal antibodies licensed for the treatment of severe asthma. Omalizumab, benralizumab and mepolizumab have been accepted by SMC with various restrictions and are considered relevant comparators by the submitting company. For benralizumab and mepolizumab, the restriction for patients not receiving oral corticosteroids is for those with at least four exacerbations in the previous year. Dupilumab was accepted for restricted use in patients who have received previous biologic

treatment and was not considered a relevant comparator by the submitting company. Reslizumab was not recommended for use by SMC and was not considered a relevant comparator. Within the company's proposed positioning for tezepelumab, there are also some patients who would not be eligible for currently accepted biologic treatment in line with SMC advice and would be treated with standard of care (without biologic) which was considered a relevant comparator for these patients.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of tezepelumab comes from one main study (NAVIGATOR). Details are summarised in Table 2.1

Table 2.1. Overview of relevant studies

Criteria	NAVIGATOR (NCT03347279)[4-6]
Study design	An international, double-blind, randomised, phase III study
Eligible patients	• Aged 12 to 80 years with physician-diagnosed asthma for ≥12 months • Received medium- or high-dose inhaled corticosteroids for ≥12 months and documented treatment with daily dose of fluticasone propionate ≥500 micrograms or equivalent plus at least one additional controller medicine for ≥3 months before screening • History of at least two asthma exacerbations in 12 months before screening • Asthma Control Questionnaire-6 item omitting forced expiratory volume in 1 second (FEV_1) (ACQ-6) score of ≥1.5 at screening and randomisation • At least one of the following during the 7 days before randomisation: ≥2 days with a daytime or night-time symptoms score ≥1; use of short acting beta-agonist on >2 days; at least one awakening due to asthma • Previous treatment with biologics was allowed provided this was ≥4 months or at least five half-lives before screening.
Treatments	Tezepelumab 210mg or placebo subcutaneously every 4 weeks for 1 year
Randomisation	Patients were randomised equally with stratification for age (adult or adolescent) and geographical area.
Primary outcome	Annualised rate of asthma exacerbations (events per patient per year) over the 52-week treatment period.
Secondary outcomes	• Annualised asthma exacerbation rate in patients with baseline eosinophils <300 cells/microlitre • Change from baseline in pre-bronchodilator FEV_1 at week 52 • Change from baseline at week 52 in: Asthma Quality of Life Questionnaire standardised for ≥12 years (AQLQ[S]+12); and, ACQ-6Change from baseline in weekly mean Asthma Symptom Diary (ASD) score at week 52
Statistical analysis	A hierarchical statistical testing strategy was applied to the primary and key secondary outcomes in the study in the order listed above. There was no formal testing of outcomes after the first non-significant outcome in the hierarchy. Therefore the results reported for these outcomes are descriptive only and not inferential (no p-values reported).

The annualised asthma exacerbation rate was significantly reduced in the tezepelumab group compared with the placebo group. The key secondary outcomes, which were tested in the hierarchical order presented in Table 2.2, also all significantly favoured tezepelumab over placebo.[4-6] Details are presented in Table 2.2.

Table 2.2: results for the primary and key secondary outcomes in the FAS of the NAVIGATOR study[4, 6]

	Tezepelumab (n=528)	Placebo (n=531)
Primary outcome: annualised rate of asthma exacerbations		
Number of exacerbations	425	878
AAER, (95% CI)	0.93	2.10
Absolute difference versus placebo, (95% CI)	-1.17 (-1.47 to -0.88)	
Rate ratio (95% CI)	0.44 (0.37 to 0.53), p<0.001	
Key secondary outcome: pre-bronchodilator FEV_1		
Mean at baseline, litre	1.8	1.9
LSM change to week 52, litre	0.23	0.09
LSM difference versus placebo (95% CI), litre	0.13 (0.08 to 0.18), p<0.001	
Key secondary outcome: ACQ-6 score		
Mean at baseline	2.8	2.8
LSM change to week 52	-1.53	-1.20
LSM difference versus placebo (95% CI)	-0.33 (-0.46 to -0.20), p<0.001	
Key secondary outcome: AQLQ(S)+12 overall score		
Mean at baseline	3.9	3.9
LSM change to week 52	1.48	1.14
LSM difference versus placebo (95% CI)	0.33 (0.20 to 0.47), p<0.001	
Key secondary outcome: ASD overall score		
Mean at baseline	1.4	1.4
LSM change to week 52	-0.70	-0.59
LSM difference versus placebo (95% CI)	-0.11 (-0.19 to -0.04), p=0.004	

FAS=full analysis set; AAER=annualised asthma exacerbation rate; CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LSM=least square mean; ACQ-6=Asthma Control Questionnaire, omitting 6; AQLQ(S)+12=Asthma Quality of Life Questionnaire (standardised) for patients ≥12 years; ASD=Asthma Symptom Diary

2.2. Evidence to support the positioning proposed by the submitting company

The submitting company presented results from post hoc analyses for the primary and key secondary outcomes of NAVIGATOR. Results for this subpopulation reflective of the proposed positioning were considered confidential by the company.

2.3. Health-related quality of life outcomes

Health Related Quality of Life (HRQoL) was assessed as a key secondary outcome using AQLQ(S)+12, which was significantly improved in the tezepelumab group compared with the placebo group. Patient reported outcomes on asthma symptoms were assessed as key secondary outcomes, ACQ-6 and ASD, and both were significantly improved in the tezepelumab group compared with the placebo group; details are presented in Table 2.2.[4, 6]

General health was assessed as an additional secondary outcome using the European quality of life-5 dimensions-5 levels (EQ-5D-5L) questionnaire. The least square mean change from baseline

to week 52 was 16.6 in the tezepelumab group (n=448) compared with 11.9 in the placebo group (n=435) corresponding to a least square mean difference of 2.8 (95% CI 0.8 to 4.8).[4, 6]

2.4. Supportive studies

PATHWAY was a randomised, double-blind, parallel group, phase IIb, dose-ranging study which evaluated the efficacy and safety of subcutaneous tezepelumab 70mg (n=138), 210mg (n=137) or 280mg (n=137) compared with placebo (n=138) every 4 weeks in 550 adults with inadequately controlled severe asthma. Patients were receiving stable treatment with medium- or high-dose inhaled corticosteroids plus a long-acting beta-agonist with or without additional controller medicines, and/or oral corticosteroids who had at least two asthma exacerbations or at least one severe asthma exacerbation resulting in hospitalisation within the previous 12 months. As in NAVIGATOR, the primary outcome was annualised asthma exacerbation rate. This was tested hierarchically from highest to lowest tezepelumab dose versus placebo and was significant at each dose group. The annualised asthma exacerbation rate was 0.20 in the tezepelumab 210mg group (licensed dose) compared with 0.72 in the placebo group; rate ratio 0.29 (95% CI 0.16 to 0.51), p<0.001. Results presented for the subpopulation reflective of the proposed positioning were considered confidential by the company.[4, 8, 9]

SOURCE was a double-blind, randomised, phase III study which compared the efficacy of tezepelumab with placebo in reducing oral corticosteroid maintenance dose in 150 adult patients who were receiving a stable dose of oral corticosteroid (prednisolone 7.5 to 30mg daily or equivalent), medium- or high-dose inhaled corticosteroids and a long-acting beta-agonist. They could also be receiving additional controller medicines and had at least one asthma exacerbation event within 12 months before screening. Eligible patients entered an oral corticosteroid optimisation phase without loss of asthma control for ≥2 weeks before randomisation to tezepelumab 210mg (n=74) or placebo (n=76) subcutaneously every 4 weeks, for 48 weeks. After a 4-week induction phase with stable oral corticosteroid dosing, the oral corticosteroid doses were titrated downwards according to a defined schedule. The primary outcome was the categorised percentage reduction from baseline in daily oral corticosteroid dose at week 48 while not losing asthma control. Categories of oral corticosteroid reduction were: ≥90% to 100%; ≥75% to <90%; ≥50% to<75% and >0 to <50% and no change or any increase. At week 48, there was no significant improvement in oral corticosteroid reduction in patients treated with tezepelumab compared with placebo; odds ratio of 1.28 (95% CI: 0.69 to 2.35), p=0.43. Results presented for the subpopulation reflective of the proposed positioning were considered confidential by the company. [4, 10, 11]

The DESTINATION study was a phase III, multicentre, randomised, double-blind, placebo-controlled long-term extension study. Patients (n=951) were enrolled from the NAVIGATOR (n=827) and SOURCE (n=124) studies. Patients who were initially randomised to receive tezepelumab in NAVIGATOR and SOURCE continued to receive tezepelumab 210mg every 4 weeks in DESTINATION; those initially randomised to receive placebo were re-randomised equally to receive tezepelumab 210mg or placebo every 4 weeks. Treatment was continued for a further 52 weeks to 104 weeks. This was primarily a safety study but efficacy was assessed as a secondary outcome using the annualised asthma exacerbation rate which was reduced over 104 weeks in the tezepelumab group compared with placebo. In patients from the NAVIGATOR study, the annualised asthma exacerbation rate ratio between tezepelumab and placebo over 104 weeks was

0.42 (95% CI 0.35 to 0.51) and in patients from the SOURCE study was 0.61 (95% CI 0.38 to 0.96). There was no formal statistical analysis.[4, 12]

2.5. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing tezepelumab with benralizumab, mepolizumab and omalizumab, the submitting company presented indirect treatment comparisons. The company consider that tezepelumab was at least as effective as other biologics and used these results to support a cost minimisation analysis versus biologics in the economic base case.

Table 2.3: Summary of indirect treatment comparison

<table>
<tr><th>Criteria</th><th>Overview</th></tr>
<tr><td>Design</td><td>Bayesian network meta-analyses (NMAs)</td></tr>
<tr><td>Population</td><td>Adults and adolescents ≥12 years with severe asthma who are inadequately controlled despite high dose corticosteroids plus another medicinal product for maintenance therapy. Where possible, the company performed the NMAs in subpopulations of patients with eosinophils ≥150 cells/microliter; at least three exacerbations in the previous 12 months; or allergic asthma to align most closely with the SMC recommendations for comparators.</td></tr>
<tr><td>Comparators</td><td>Benralizumab, mepolizumab and omalizumab</td></tr>
<tr><td>Studies included</td><td>Overall 22 studies were included in the NMAs. The networks included studies of dupilumab and reslizumab to increase the power of the analyses but results were not reported since these medicines were not considered relevant for Scotland.</td></tr>
<tr><td>Outcomes</td><td>NMA included five outcomes:
reduction in annualised asthma exacerbation rate (AAER)
reduction in AAER leading to hospitalisation
change from baseline in asthma control questionnaire (ACQ) score
change from baseline in OCS use by predefined categories
change from baseline in pre-bronchodilator FEV_1</td></tr>
<tr><td>Results</td><td>Results for NMAs for tezepelumab versus comparator[13]
<table>
<tr><th>Population used for each outcome</th><th>Benralizumab</th><th>Mepolizumab</th><th>Omalizumab</th></tr>
<tr><td colspan="4">Reduction in AAER; rate ratio (95% CrI)</td></tr>
<tr><td>High EOS ≥150</td><td>0.63 (0.49 – 0.82)</td><td>0.94 (0.68 – 1.3)</td><td>NR</td></tr>
<tr><td>Allergic asthma</td><td>NR</td><td>NR</td><td>0.61 (0.24-1.16)</td></tr>
<tr><td colspan="4">Reduction in AAER leading to hospitalisation; rate ratio (95% CrI)</td></tr>
<tr><td>ITT Population</td><td>0.35 (0.08-1.16)</td><td>0.54 (0.13-2)</td><td>0.4 (0.1-1.55)</td></tr>
</table>
CrI=credible interval; EOS=eosinophil; ITT=intention to treat; OCS=oral corticosteroid; pre-BD=pre-bronchodilator; FEV_1=forced expiratory volume in 1 second; NR=not reported.
*results presented for the outcome reduction in AAER for the subpopulation of at least three exacerbations and for the outcomes reductions of OCS ≥50%, ≥75% and ≥90%, change in ACQ score and change in pre-BD FEV_1 were considered confidential by the company.</td></tr>
</table>

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

3. Summary of Safety Evidence

In the NAVIGATOR study, any treatment-emergent adverse event (AE) was reported by 77% (407/528) of patients in the tezepelumab group and 79% (422/531) in the placebo group. In the tezepelumab and placebo groups respectively, patients with a reported serious AE were 9.8% versus 14%, and patients discontinuing therapy due to an AE was 2.1% versus 3.6%. The most frequently reported treatment-emergent AEs of any grade in the tezepelumab group versus the placebo group respectively were: nasopharyngitis (21% in both groups), upper respiratory tract infection (11% versus 16%), headache (8.1% versus 8.5%), asthma (5.1% versus 11%), bronchitis (4.7% versus 6.2%), bacterial bronchitis (4.5% versus 3.2%), urinary tract infection (4.2% versus 4.1%), hypertension (4.4% versus 4.1%) and back pain (4.0% versus 2.8%).

Severe infections were reported by 8.7% of patients in each treatment group. Injection site reactions were reported in 3.6% of patients in the tezepelumab group and 2.6% of patients in the placebo group. Antidrug antibodies were detected in 4.9% of tezepelumab and 8.3% of placebo patients and one patient in each treatment group tested positive for neutralising antidrug antibodies but there was no evidence that this impacted observed efficacy or safety.[1, 6]

In the long-term DESTINATION extension study, the incidence of adverse events and serious adverse events were assessed as the primary outcome. In patients who had initially been in the NAVIGATOR study, the incidence of adverse events over 104 weeks in the tezepelumab and placebo groups were 49.6 and 62.7 per 100 patient-years respectively (difference -13.0 [95% CI -17.8 to -8.2]). The incidence of serious adverse events was 7.8 and 12.4 per 100 patient-years respectively (difference -4.6 [95% CI -7.7 to -1.6]). In patients who had initially been in the SOURCE study, incidence of adverse events over 104 weeks in the tezepelumab and placebo groups were 47.2 and 70.0 per 100 patient-years (difference -22.8 [95% CI -34.8 to -10.0]) and the incidences of serious adverse events were 13.1 and 18.0 per 100 patient-years respectively (difference -4.9 [95% CI -14.9 to 4.5]).[4, 12]

During the DESTINATION study, there was an imbalance in serious cardiac AEs; incidence of 0.87 versus 0 per 100 patient-years in the tezepelumab and placebo groups respectively in patients initially in NAVIGATOR and 3.09 and 0 per 100 patient-years respectively in patients initially in SOURCE. There was also an imbalance in the number of deaths of 0.80 per 100 patient-year in all patients treated with tezepelumab and 0.58 per 100 patient-years in all patients treated with placebo. No deaths were considered to be causally related to tezepelumab by the independent review committee.[4, 12]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Tezepelumab is the first monoclonal antibody to target TSLP, which works early in the asthma inflammatory cascade and may have a broader effect than targeting individual cytokines making it suitable for more patients. It has been suggested that 37% of patients with severe asthma have an inadequate response to or are ineligible for currently licensed biologics.[1, 4]

- In two randomised, double-blind studies, the annualised asthma exacerbation rate was significantly reduced in patients treated with tezepelumab compared with placebo. The reductions of 56% in the NAVIGATOR study and 71% in the PATHWAY study were considered clinically relevant.[4, 6, 8]
- In the NAVIGATOR study, there were also significant improvements with tezepelumab compared with placebo in the key secondary outcomes which assessed lung function, patient reported outcomes on asthma symptom control and quality of life.[4, 6]
- In NAVIGATOR and PATHWAY, the treatment effect of tezepelumab on asthma exacerbation rate was evident regardless of the baseline levels of blood eosinophils and other inflammatory biomarkers including fractional exhaled nitric oxide (FeNO) and immunoglobulin E (IgE). In NAVIGATOR, there were smaller reductions in the asthma exacerbation rate in patients with lower baseline levels. In patients with baseline blood eosinophil count <150 cells/microlitre and baseline FeNO <25 parts per billion (ppb), the rate ratio was 0.71 (95% CI 0.50 to 1.00) but this was still considered clinically meaningful. The size of the treatment effect increased with increasing levels of eosinophils and FeNO; in patients with both baseline blood eosinophil count ≥300 cells/microlitre and baseline FeNO ≥25 ppb, the rate ratio was 0.23 (95% CI 0.16 to 0.33).[1, 4, 6]

4.2. Key uncertainties

- The treatment effect in PATHWAY was larger than in NAVIGATOR with a 71% reduction in the annualised asthma exacerbation rate in PATHWAY compared with a 56% reduction in the NAVIGATOR. This difference between the size of the treatment effect may be the result of differences in the study population as suggested by the annualised asthma exacerbation rates in the placebo groups (2.1 in NAVIGATOR and 0.72 in PATHWAY) suggesting that patients in NAVIGATOR had more severe disease.[4, 6, 8]
- Tezepelumab may reduce the need for or dose of oral corticosteroids, but when assessed in the SOURCE study, the difference between tezepelumab and placebo did not reach statistical significance. In NAVIGATOR and PATHWAY, only 9% of study patients were receiving oral corticosteroids at baseline. [4, 6, 8, 10]
- The licensed indication for tezepelumab is for patients inadequately controlled despite high-dose inhaled corticosteroids. The study populations of NAVIGATOR and PATHWAY also included patients on medium-dose inhaled corticosteroids. Subgroup analyses suggested that the treatment effect on annualised asthma exacerbation rate was smaller with tezepelumab compared with placebo in patients receiving medium-dose than high-dose inhaled corticosteroids; in NAVIGATOR a reduction of 36% versus 60% and in PATHWAY, a reduction of 48% versus 70%. In addition, 25% of patients in the NAVIGATOR study were receiving medium-dose inhaled corticosteroids and these were considered to be at the higher end of medium-dose leading to uncertainty if the results would be generalisable to patients on a regular medium-dose. Therefore given the limited data on patients receiving inhaled corticosteroids in the full-range of medium-dose, the regulator restricted the licensed indication to high-dose only.[4, 6, 8]

- Tezepelumab is licensed for use in adult and adolescent patients. Data for adolescents are limited to 82 patients aged 12 to 17 years in NAVIGATOR. Subgroup analysis indicated that there were smaller reductions in annualised asthma exacerbation rate (rate ratio 0.70 [95% CI 0.34 to 1.46]) and improvement in FEV_1 (least square mean change 0.17litres [95% CI -0.01 to 0.35]) but these were still considered clinically meaningful. Only 15 of the 82 adolescent patients were receiving high-dose inhaled corticosteroids at baseline reflecting the licensed indication.[4, 6]
- The study populations of the NAVIGATOR, PATHWAY and SOURCE studies were broader than the company's proposed positioning for tezepelumab. In NAVIGATOR, 40% of patients had at least three exacerbations in the previous 12 months, supporting the first proposed positioning; only 9.4% of patients were receiving oral corticosteroids supporting the second proposed positioning. In SOURCE, all patients were receiving oral corticosteroids and subgroup analysis of the primary outcome (categorised reduction in oral corticosteroid dose) only favoured tezepelumab over placebo for patients with eosinophils ≥150 cells/microliter, supporting the second proposed positioning. The company provided evidence to support the proposed positioning in the "target population" based on post hoc analyses of the studies. The results suggested that tezepelumab was more effective than placebo but they should be treated with caution due to their unplanned nature and smaller numbers of study patients with potential imbalances in patient numbers and baseline characteristics between study groups.[7, 9, 11]
- The initial safety profile from the NAVIGATOR, PATHWAY and SOURCE studies was considered acceptable with generally reversible, mild to moderate adverse events reported which were comparable in the tezepelumab and placebo groups. However, subsequent data from DESTINATION raised unexpected safety issues with an imbalance in serious cardiac events and deaths. Despite a lack of known biological explanation and no established causal relationship between tezepelumab and these events, this cannot be ruled out. The company will conduct a post-authorisation safety study to further define the safety profile of tezepelumab. A warning has been included in the SPC to advise patients of signs or symptoms suggestive of a cardiac event (for example, chest pain, dyspnoea, malaise, feeling lightheaded or faint) and to seek immediate medical attention if such symptoms occur. If patients develop a serious cardiac event while receiving tezepelumab treatment, therapy with tezepelumab should be discontinued until the acute event stabilises. [1, 4, 12]
- There is no direct evidence comparing tezepelumab with other biologics in severe asthma. The submitting company presented NMAs comparing tezepelumab with benralizumab, mepolizumab and omalizumab, which they considered the most relevant comparators in Scottish practice. No indirect comparison results were presented versus dupilumab which was not considered a relevant comparator. Based on the results, the company concluded that tezepelumab was at least as effective as benralizumab, mepolizumab and omalizumab. There are a number of limitations including limited data to allow comparison with the most relevant subpopulations aligning with SMC restrictions and limited available baseline data to compare patients included when results for subgroups were available. There were differences between results in the common control arms (placebo, optimised asthma therapy and best supportive care) across the studies which suggested differences between patients. The NMA population

was broader than the licensed indication (including some patients receiving medium-dose inhaled corticosteroids) and the proposed positioning, which restricts to a number of subgroups to align with the SMC restriction. Most, but not all of the NMA results suggested that tezepelumab was at least effective as benralizumab, mepolizumab and omalizumab. Due to these limitations, there is some uncertainty in the results. However, it seems reasonable to conclude that tezepelumab has similar efficacy to other biologics in severe asthma.

4.3. Clinical expert input

Clinical experts consulted by SMC considered that tezepelumab fills an unmet need in this therapeutic area, namely to offer an alternative biologic or a first biologic when other biologics are not suitable.

They considered that tezepelumab is a therapeutic advancement due to its different mechanism of action and broader treatment effect on different types of asthma.

They considered that the proposed positioning for tezepelumab would allow an earlier place in therapy for patients with a history of fewer asthma exacerbations in the previous year (at least three compared with at least four for benralizumab and mepolizumab). However clinical experts consulted by SMC noted that the proposed positioning for patients who are receiving maintenance treatment with oral corticosteroids to have blood eosinophils ≥150 cells/microlitre would exclude use in many of these patients who would have eosinophils <150 cells/microlitre.

4.4. Service implications

The availability of another biologic which may be used in a broader group of asthmatic patients may increase the overall number of patients receiving biologic treatment and have implications for the service.

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

5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from Asthma + Lung UK, which is a registered charity.
- Asthma + Lung UK has received 2.9% pharmaceutical company funding in the past two years, including from the submitting company.
- Asthma is a long-term condition that affects the airways that carry air in and out of the lungs. It can result in coughing, wheezing, breathlessness and chest tightness. Living with uncontrolled or severe asthma can limit the daily lives of people with the condition and also impact wider health and wellbeing of them and their carer(s).
- Expanding treatment options is important to ensure that everyone with asthma can live their daily lives without exacerbating symptoms such as breathlessness, wheezing, coughing or tight chests.

- It is hoped that tezepelumab will improve the quality of life for people with severe asthma. This would include their ability to carry out everyday tasks such as housework, exercise, parental responsibilities and employment. By improving the quality of life, it would be expected that overall health and wellbeing would improve, especially around mental health. Treating the patient with tezepelumab has the potential to reduce GP and hospital visits, meaning less travelling and stress for the carer, as well as the person with asthma.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case, as described in Table 6.1

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis (CUA) and cost-minimisation analysis (CMA)
Time horizon	CUA: Lifetime (60 years); CMA: 5 years
Population	Adult and adolescent patients with severe asthma who are inadequately controlled, despite high dose inhaled corticosteroids plus an additional medicinal product, for maintenance treatment who either: • experienced ≥3 exacerbations in the previous year and are not receiving maintenance treatment with oral corticosteroids or • have blood eosinophils ≥150cells/microlitre and are having maintenance treatment with oral corticosteroids.
Comparators	CUA: Standard care (without biologics) for the biologic ineligible population. CMA: Benralizumab, mepolizumab and omalizumab as active comparators for the biologics eligible population.
Model description	The CUA used a Markov model with five health states (controlled asthma, uncontrolled asthma, uncontrolled asthma with exacerbation, controlled asthma with exacerbation, and death), applying a four-week cycle length, with patients entering the model with uncontrolled asthma. The model adopts an NHS Scotland and social care perspective.
Clinical data	The CUA is based on effectiveness and outcomes data from NAVIGATOR and SOURCE studies. This included transition probabilities informed by reductions in AAER, one year response rates, exacerbation distributions and natural attrition rate for tezepelumab. In the absence of direct evidence comparing tezepelumab with benralizumab, mepolizumab and omalizumab, the company presented indirect treatment comparisons. Overall, 22 studies were included in the NMAs assessing 5 outcomes. Results suggest that tezepelumab has similar efficacy to comparator biologics. The company used the results of the NMA as justification to conduct a CMA in the biologic population.
Extrapolation	Treatment effectiveness in terms of AAER reduction and ACQ-6 scores were incorporated through transition probabilities. The study-derived probabilities for entering exacerbation states were further adjusted to reflect real world exacerbation rates from the UK severe asthma registry. [14] Different transition probabilities were applied to patients in the tezepelumab arm before and after 12-month response assessment. This reflects the changing efficacy of tezepelumab pre-and post-assessment, and captures the reduction in need for mOCS in patients. Mortality was captured in the CUA as asthma-specific mortality and all-cause mortality.

Quality of life	Utility values were based on EQ-5D-5L data from the NAVIGATOR and SOURCE studies which were mapped onto the EQ-5D-3L UK value set. Exacerbations were incorporated as disutilities.
Costs and resource use	The CUA included acquisition and administration costs, disease management costs and adverse event costs. The CMA included acquisition costs and homecare costs. Adverse event and disease management costs were assumed to be equal across all comparators and excluded from the CMA.
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a simple discount is offered on the list price. PAS discounts are also in place for benralizumab, mepolizumab and omalizumab.

6.2. Results

The base case CUA in the non-biologic eligible population produced an ICER of £14,008 versus standard of care (SoC) at PAS price.

The base case CMA in the biologic eligible population resulted in cost savings against benralizumab mepolizumab and omalizumab at list prices.

6.3. Sensitivity analyses

In deterministic one-way sensitivity analysis for the CUA, the parameters with the greatest impact on the ICER were the probability of exacerbation in SoC treated patients whose asthma was previously controlled and the probabilities of an exacerbation resulting in hospitalisation for SoC treated patients whose asthma was previously uncontrolled/controlled. A range of scenario analyses were performed on the CUA and are presented in Table 6.4.

Table 6.4 Results of CUA scenario analysis (PAS Price)

	ICER (£/QALY)
Base case	**£14,008**
1: Alternative (Target) population: *non biologic eligible on SoC + biologic eligible receiving SoC alone*	13,935
2: Trial based transition probabilities (unadjusted)	21,760
3: Alternative utilities (mixed regression model)	£15,611
4: Alternative mortality (with exacerbation related mortality multiplier)	£13,404
5: Alternative response definition: *patients on mOCS: ≥50% reduction in mOCS dose AND ≥50% reduction in exacerbations*	£13,773
6: Time Horizon: 20 years	£16,038
7: Time Horizon: 5 years	£29,247
8: Discount rate 1.5%	£13,063

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; mOCS, maintenance oral corticosteroid treatment; PAS, Patient Access Scheme; QALY, quality-adjusted life year; SoC, standard of care.

6.4. Key strengths

The economic model was robust and structurally sound. Appropriate sources were selected to inform the model parameters and reasonable methods were used for the indirect treatment comparisons.

6.5. Key uncertainties

The main weaknesses of the economic analysis were:

- Most notably the lack of direct comparative evidence against benralizumab, mepolizumab and omalizumab. The indirect treatment comparisons, whilst well conducted, are highly uncertain. The inclusion of non-SMC approved comparators (i.e. dupilumab, reslizumab) in the networks of studies is appropriate from an evidence-based perspective, however their inclusion could potentially influence event rates or similar, which might affect model inputs, and thus cost-effectiveness. NMA results suggest that tezepelumab has similar efficacy to biologics and the company has hence performed a CMA. However due to a lack of evidence, there is unresolvable uncertainty associated with matching exact subgroups to data from comparator studies.
- The decision to use ACQ-6 score of 1.5 as a cut-off to determine asthma status is a potential source of bias. Alternative cut-offs could be used to determine the crossover point between well-controlled and not uncontrolled asthma. For example, the NAVIGATOR study defined an ACQ-6 score of between 0.75 and less than 1.5 as 'partially controlled' asthma, whereas these patients are defined as well-controlled in the model. Hence, the model could potentially overestimate the number of patients classified as having well-controlled asthma and overestimate the treatment effect of tezepelumab.

7. Conclusion

Tezepelumab is cost effective against SoC and cost minimizing when compared to benralizumab and omalizumab.

8. Guidelines and Protocols

In July 2019, the Scottish Intercollegiate Guidelines Network (SIGN) and British Thoracic Society (BTS) issued national clinical guideline number 158, British guideline on the management of asthma.[3]

In May 2022, the Global Initiative for Asthma (GINA) issued a decision tree for difficult-to-treat and severe asthma in adults and adolescents.[2]

9. Additional Information

9.1. Product availability date

5 Dec 2022

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per year (£)
tezepelumab	**210mg by subcutaneous injection every 4 weeks**	**16,445**

Costs from BNF online on 2 May 2023. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The company estimated there would be 4,049 patients eligible for treatment with tezepelumab in year 1 rising to 4,348 patients in year 5. The uptake rate was estimated to be 1.5% in year 1 (59 patients) and 6.5% in year 5 (282 patients).

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

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

References

1. AstraZeneca UK Limited. Tezepelumab 210mg solution for injection in pre-filled syringe (Tezspire) summary of product characteristics. Electronic Medicines Consortium www.medicines.org.uk/emc/ Last updated 26 September 2022.
2. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Updated 2022. Available at: https://ginasthma.org (last accessed: 26 April 2023).
3. Scottish Intercollegiate Guidelines Network 158 British guideline on the management of asthma. July 2019. Available at: https://www.sign.ac.uk/ (last accessed: 26 April 2023).
4. European Medicines Agency (EMA). European Public Assessment Report. Tezspire. 21/07/2022, EMEA/H/C/005588/0000. www.ema.europa.eu
5. Menzies-Gow A, Colice G, Griffiths JM, Almqvist G, Ponnarambil S, Kaur P*, et al.* NAVIGATOR: a phase 3 multicentre, randomized, double-blind, placebo-controlled, parallel-group trial to evaluate the efficacy and safety of tezepelumab in adults and adolescents with severe, uncontrolled asthma. Respiratory Research. 2020;21(1) 266.
6. Menzies-Gow A, Corren J, Bourdin A, Chupp G, Israel E, Wechsler ME*, et al.* Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma. New England Journal of Medicine. 2021;384(19):1800-9.
7. AstraZeneca UK Ltd. Data on file: post hoc subgroup analysis of the NAVIGATOR study. .
8. Corren J, Parnes JR, Wang L, Mo M, Roseti SL, Griffiths JM*, et al.* Tezepelumab in Adults with Uncontrolled Asthma. New England Journal of Medicine. 2017;377(10):936-46.
9. AstraZeneca UK Ltd. Data on file: post hoc subgroup analysis of the PATHWAY study. .
10. Wechsler ME, Menzies-Gow A, Brightling CE, Kuna P, Korn S etal. Evaluation of the oral corticosteroid-sparing effect of tezepelumab in adults with oral corticosteroid-dependent asthma (SOURCE): a randomised, placebo-controlled, phase 3 study. Lancet Respir Med 2022; 10: 650-60.
11. AstraZeneca UK Ltd. Data on file: post hoc subgroup analysis of the SOURCE study. .
12. Menzies-Gow A, Wechsler ME, Brightling CE, Korn S, Corren S et al. Long-term safety and efficacy of tezepelumab in people with severe, uncontrolled asthma (DESTINATION): a randomised, placebo-controlled extension study. Lancet Respir Med 2023; DOI:10.1016/S2213-2600(22)00492-1.
13. Menzies-Gow A, Steenkamp J, Singh S, Erhardt W, Rowell J et al. Tezepelumab compared with other biologics for the treatment of severe asthma: a systematic review and indirect treatment comparison. Journal of Medical Economics 2022; 25: 679-690.
14. Jackson DJ, Busby J, Pfeffer PE, Menzies-Gow A, Brown T, Gore R, et al. Characterisation of patients with severe asthma in the UK Severe Asthma Registry in the biologic era. Thorax. 2021;76(3):220-7.

This assessment is based on data submitted by the applicant company up to and including 16 June 2023.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are

therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.