NCPE Assessment

Technical Summary

Tezepelumab (Tezspire®)

HTA ID: 23025

01 July 2025

Applicant: AstraZeneca

Add-on treatment for adults and adolescents 12 years and older with severe asthma with blood eosinophil levels < 300 cells per microlitre, who are inadequately controlled despite high-dose inhaled corticosteroids plus another maintenance treatment. This is a subpopulation of the licensed population.

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of tezepelumab (Tezspire®).

Following assessment of the Applicant's submission, the NCPE recommends that tezepelumab (Tezspire®) not be considered for reimbursement, as an add-on treatment for adults and adolescents 12 years and older with severe asthma with blood eosinophil levels < 300 cells per microlitre, who are inadequately controlled despite high-dose inhaled corticosteroids plus another maintenance treatment (subpopulation of the licensed population)*.

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (AstraZeneca) Health Technology Assessment of tezepelumab (Tezspire®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In June 2024, AstraZeneca submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of tezepelumab (Tezspire®) as add-on treatment for adults and adolescents 12 years and older with severe asthma with blood eosinophil (EOS) levels < 300 cells per microlitre, who are inadequately controlled despite high-dose inhaled corticosteroids (ICS) plus another maintenance treatment. This is a subpopulation of the licensed population. AstraZeneca is seeking reimbursement of tezepelumab on the High-Tech Drug Arrangement.

Tezepelumab is a first-in-class monoclonal antibody directed against thymic stromal lymphopoietin (TSLP), preventing interaction with the TSLP receptor. It is available as a pre-filled pen, which contains 210mg tezepelumab for subcutaneous injection. It should be administered once every four weeks. Tezepelumab is intended for long-term use. A decision to continue the therapy should be made at least annually based on the patient's level of asthma control.

The subpopulation under evaluation is those with EOS < 300 cells per microlitre. Clinical opinion, obtained by the Review Group, highlighted the diurnal variation associated with EOS levels, and the suppressive impact of maintenance oral corticosteroids (mOCS) on these levels. This subpopulation therefore encompasses patients with true, sustained EOS < 300 cells per microlitre (in the absence of mOCS use), and those with EOS < 300 cells per microlitre whose EOS levels are suppressed by mOCS use. The Review Group considered that both patient cohorts would be considered for treatment with tezepelumab in Irish clinical practice. The prevalence of true, sustained EOS < 300 cells per microlitre (in the absence of mOCS use) was expected, by clinicians, to be rare, particularly if there is no associated allergic mechanism. The proposed comparator of relevance for patients with true, sustained EOS < 300 cells per microlitre (in the absence of mOCS use) is standard high-dose ICS, plus at least one additional maintenance agent, which may include mOCS. This was the comparator included by the Applicant. Biologic therapies, including dupilumab and mepolizumab, are reimbursed in Ireland for patients on long-term mOCS with a blood EOS of < 300 cells per microlitre, provided a blood EOS level taken prior to commencement of long-term mOCS is

provided to confirm the eosinophilic phenotype of asthma. Biologic therapies are therefore a relevant comparator for this cohort of patients. These therapies were not included as a comparator. The Review Group acknowledged that clinical data pertaining to the use of these biologic comparators in this cohort was not identified. As such, they were not included as comparators. However, the exclusion of these comparators in a relevant patient population is a key limitation.

1. Comparative effectiveness of tezepelumab

Two trials provided efficacy and safety data of tezepelumab in participants with severe uncontrolled asthma and EOS < 300 cells per microlitre; NAVIGATOR (pivotal trial) and SOURCE (supportive trial). Both trials were phase III, double-blind, randomised, and placebo-controlled. Participants were permitted to enrol in these trials irrespective of EOS level. Data pertaining to those with EOS < 300 cells per microlitre were presented in the Applicant submission. These data are presented below. Participants who completed the NAVIGATOR or SOURCE trials had the opportunity to enrol in DESTINATION, a long-term extension study. However, as data for participants, in DESTINATION, with EOS < 300 cells per microlitre were not provided by the Applicant, details of the DESTINATION study are not reported here.

NAVIGATOR

NAVIGATOR was a 52-week trial designed to assess the effect of tezepelumab on asthma exacerbations in adult and adolescent participants with severe, uncontrolled asthma. Participants in NAVIGATOR were required to have been receiving medium- or high-dose ICS for at least 12 months, plus one additional asthma maintenance controller for at least 3 months. Participants were also required to have poorly controlled asthma (defined by ACQ-6 score ≥ 1.5) and to have experienced at least two exacerbations in the previous 12 months. Participants in the tezepelumab arm (n=309) received tezepelumab at a dose of 210mg administered via subcutaneous injection once every four weeks. Participants in the control arm (n=309) received placebo administered via subcutaneous injection once every four weeks. Participants in both the tezepelumab and control arms received medium- to high-dose ICS plus at least one additional controller medication with or without mOCS. The primary endpoint of NAVIGATOR was annualised asthma exacerbation rate ratio (AAER)

measured at week 52. Change from baseline in pre-bronchodilator FEV1 and change from baseline in ACQ-6 score were key secondary endpoints.

Results of NAVIGATOR indicated that tezepelumab resulted in a statistically significant reduction in the rate of asthma exacerbations over 52 weeks (primary endpoint) compared with placebo (AAER rate ratio 0.59; 95% CI 0.46 to 0.75, p<0.001). Change from baseline in pre-bronchodilator FEV1 was 0.13 (standard error (SE) 0.02) in the tezepelumab arm and 0.06 (SE 0.02) in the placebo arm; difference 0.07 (95% CI 0.00 to 0.13). The change from baseline in the ACQ-6 score was -1.36 (SE 0.06) in the tezepelumab arm and -1.15 (SE 0.06) in the placebo arm; difference -0.21 (SE -0.37 to -0.05). For all key secondary and other endpoints no statistical testing was performed, p-values are therefore not available.

SOURCE

SOURCE was a 48-week trial designed to evaluate the effect of tezepelumab in reducing the prescribed mOCS dose in participants with severe, OCS-dependent asthma. The eligibility criteria were generally aligned with NAVIGATOR. However, participants in SOURCE were required to have been receiving mOCS for asthma for at least six months. Additionally, participants who experienced one asthma exacerbation in the previous 12 months were permitted to enrol. There was no minimum requirement regarding ACQ-6 score. Dosing of tezepelumab and placebo was aligned with that of the NAVIGATOR trial. These were administered in addition to high-dose ICS plus long-acting beta agonist with mOCS with or without another controller medication. The primary endpoint of SOURCE was the categorised percent reduction from baseline in the daily mOCS at week 48 while not losing asthma control. AAER measured at week 48 and change from baseline in ACQ-6 score were secondary endpoints.

Results of SOURCE indicated that the primary endpoint of odds of reaching a category of greater percent mOCS reduction was numerically lower with tezepelumab versus placebo; this difference was not statistically significant (odds ratio 0.70; 95% CI 0.33 to 1.47). Additionally, a treatment benefit for AAER was not demonstrated for tezepelumab in this trial (AAER rate ratio 1.12; 95% CI 0.64 to 1.95). The change from baseline in the ACQ-6 score was -0.80 (SE 0.16) in the tezepelumab arm and -0.53 (SE 0.15) in the placebo arm;

difference -0.26 (95% CI -0.70 to 0.17). Note, statistical testing was not performed for secondary endpoints in SOURCE.

Both NAVIGATOR and SOURCE included participants with true, sustained EOS < 300 cells per microlitre (in the absence of mOCS use), and those with EOS < 300 cells per microlitre whose EOS levels are suppressed by mOCS use. The treatment effect of tezepelumab in patients with true, sustained EOS < 300 cells per microlitre (in the absence of mOCS use) is unknown.

2. Safety of tezepelumab

The Applicant presented safety data for participants with EOS < 300 cells per microlitre in the NAVIGATOR and SOURCE trials. In NAVIGATOR, the overall incidence of adverse events (76.4% versus 81.9%) and serious adverse events (11.7% versus 13.6%) were lower in the tezepelumab versus placebo arms. Adverse events leading to discontinuation of treatment were experienced by 1.3% of participants in the tezepelumab arm and 3.9% of participants in the placebo arm. Findings were similar in the SOURCE study, in which the proportion of participants experiencing a serious adverse event (17.4% versus 19.2%) or adverse event leading to discontinuation (2.2% versus 3.8%) were also lower in the tezepelumab arm than in the placebo arm.

In the long-term extension study, DESTINATION (inclusive of all participants irrespective of EOS level), there was a numerical imbalance in cardiac disorders with a higher proportion of serious adverse event reported in those receiving tezepelumab versus placebo (NAVIGATOR: 1.5% versus 0%; SOURCE: 5.4% versus 0%). These were not considered to be causally related to study treatment by the investigator.

Overall, the EPAR concluded that tezepelumab has an acceptable safety profile. Most adverse events were mild to moderate in severity, and reversible. However, the summary of product characteristics outlines that patients should be advised 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.

3. Cost effectiveness of tezepelumab

Methods

A cohort state transition Markov model comprised five health states: controlled asthma (defined by ACQ-6 score < 1.5), uncontrolled asthma (defined by ACQ-6 score ≥ 1.5), uncontrolled asthma with exacerbation, controlled asthma with exacerbation, and the death state. All patients entered the model in the uncontrolled asthma health state and received treatment with tezepelumab or standard of care (SoC, defined as high-dose ICS, plus at least one additional maintenance agent, which may include mOCS for a proportion of patients). Three types of exacerbations were modelled according to severity, and defined by the treatment required; OCS burst (defined as the administration of systemic corticosteroids or a temporary escalation in a stable mOCS dose for at least 3 days), accident and emergency visit or hospitalisation.

The Review Group had several concerns regarding the model structure. The ACQ-6 score, used to define the controlled and uncontrolled asthma health states, is not commonly used in Irish clinical practice for this purpose. Furthermore, the threshold of < 1.5, used to define controlled asthma, included patients with partially controlled asthma (i.e., patients with ACQ-6 score between 0.75 and 1.5). There was also no clinical justification for separate health states for controlled and uncontrolled exacerbations. These factors were considered to potentially induce an overestimation of the treatment effect.

The treatment effects modelled were the reduced risk of exacerbation and corresponding exacerbation-associated mortality, and reduction in mOCS usage. The Review Group had several concerns regarding the modelling of treatment effects. These included a high degree of uncertainty in the sources and estimates used to inform mortality, and uncertainty regarding long-term transition probabilities in the tezepelumab arm. Of note, no evidence was provided by the Applicant that tezepelumab reduces mortality.

The primary health outcome of the model was the quality adjusted life year (QALY). Health-related quality of life data were collected in NAVIGATOR and SOURCE trials using the EQ-5D-5L. Of note, the data collected corresponded to the full severe asthma population, and included patients with EOS ≥ 300 cells per microlitre. The patient response outcome data

were then mapped to EQ-5D-3L. NAVIGATOR and SOURCE data were pooled and analysed using a mixed regression model. This model included covariates for type of exacerbation, asthma control status (controlled/uncontrolled) and being on tezepelumab treatment. The estimate for being on tezepelumab treatment was not statistically significant. There was no clear clinical rationale for this utility increment. Additionally, inclusion of the asthma control status covariate resulted in an implausible combination of utility values. Adverse events due to mOCS usage were accounted for as utility decrements.

The model included costs for drug acquisition, administration, management of exacerbations, healthcare services, and adverse events due to mOCS use. Healthcare resource use costs were stratified by the treatment arm and health state.

The Review Group noted a number of limitations to the Applicant's base case, which were addressed, via changes, in the NCPE-adjusted base case. These included removing the utility benefit associated with tezepelumab treatment and employing an alternative utility value for the uncontrolled asthma health state.

Results

The results of the Applicant's and NCPE-adjusted base case deterministic cost-effectiveness analysis are presented in Tables 1 and 2, respectively.

Table 1 Applicant base case incremental cost-effectiveness results versus SoC[a,b]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
SoC	43,305	12.67	-	-	-
Tezepelumab	143,753	13.31	100,448	0.63	159,142

ICER: Incremental cost-effectiveness ratio; **QALY:** Quality-adjusted life year; **SoC:** Standard of care.
[a] Corresponding probabilistic ICER using 1000 iterations =**€**159,241/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Cost and outcomes discounted at 4%.
[b] A commercial in confidence PAS is proposed for tezepelumab, not included in this table.

Table 2 NCPE-adjusted base case incremental cost-effectiveness results versus SoC[a,b]

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
SoC	43,305	13.11	-	-	-
Tezepelumab	143,753	13.37	100,448	0.27	379,494

ICER: Incremental cost-effectiveness ratio; **QALY:** Quality-adjusted life year; **SoC:** Standard of care.
[a] Corresponding probabilistic ICER using 1000 iterations =€374,082/QALY. Figures in the table are rounded, and so calculations may not be directly replicable. Cost and outcomes discounted at 4%.
[b] A commercial in confidence PAS is proposed for tezepelumab, not included in this table.

Sensitivity analysis

The probability of cost-effectiveness in the Applicant and NCPE-adjusted base cases was 0% at thresholds of €20,000 per QALY and €45,000 per QALY. Deterministic one-way sensitivity analysis indicated that the most influential parameters in the model for both the Applicant and the NCPE-adjusted base case related to utilities associated with controlled asthma, age, and transition probabilities of tezepelumab from uncontrolled asthma state to exacerbation state.

A price-ICER analysis, conducted using the NCPE-adjusted base case, indicated that a 96% reduction on the price-to-wholesaler of tezepelumab was required to meet the €45,000 per QALY threshold. It was not possible to generate a price reduction that met the €20,000 per QALY threshold.

4. Budget impact of tezepelumab

The price-to-wholesaler per pack (one x 210mg injection) of tezepelumab is €1,146.47. The total cost per pack to the HSE, inclusive of rebate and VAT, is €1,419.79.

The prevalence of severe asthma was informed by data from the Asthma Society of Ireland and the literature. The prevalence of patients with true, sustained EOS < 300 cells per microlitre (in the absence of mOCS use) is highly uncertain. It was assumed that 3.5% of all patients with severe asthma have true, sustained EOS < 300 cells per microlitre, based on Clinical Opinion obtained by the Applicant. Of all potentially eligible patients, the Applicant assumed that 10% in Year One, increasing to 25% by Year Five, would receive treatment with tezepelumab. The Review Group considered this to be an underestimate, given that there is no other licensed treatment for this subpopulation. The proportion of patients discontinuing tezepelumab each year (8.92%) was informed by a weighted annual probability obtained from the cost-effectiveness model. Uncertainties in the cost-effectiveness model, as described in Section 3, are therefore also applicable to the budget impact model. The cumulative five-year net-drug budget impact, based on the Applicant preferred assumptions, was estimated to be €9.2 million (including VAT).

The budget impact model was highly sensitive to the estimate used to inform the prevalence of patients with true, sustained EOS <300 cells per microlitre (in the absence of mOCS use). Data from a randomised controlled trial conducted in the United Kingdom, indicated that 10% of patients had an EOS < 300 cells per microlitre. This was considered to include both patients with true sustained EOS < 300 cells per microlitre and those with EOS < 300 cells per microlitre whose EOS levels are suppressed by mOCS use. In the absence of mechanisms to ensure that only patients with true sustained EOS < 300 cells per microlitre are considered for treatment, the Review Group considered that both groups might be considered for treatment in Irish clinical practice. The NCPE-adjusted base case, considering the impact of treating both patient cohorts, was estimated to be €26.2 million (including VAT). Uncertainty with regards to the proportion of patients receiving treatment was explored in scenario analyses, whereby the market shares of tezepelumab were assumed to double, resulting in a cumulative five-year net drug-budget impact of €52.4 million (including VAT).

5. Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment.

6. Conclusion

Following assessment of the Applicant's submission, the NCPE recommends that tezepelumab (Tezspire®) not be considered for reimbursement as add-on treatment for adults and adolescents 12 years and older with severe asthma with blood eosinophil levels < 300 cells per microlitre, who are inadequately controlled despite high-dose inhaled corticosteroids plus another maintenance treatment (subpopulation of the licensed population)*.

*This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.