REPUBLIC OF BULGARIA
NATIONAL COUNCIL ON PRICES AND REIMBURSEMENT OF MEDICINAL PRODUCTS

HEALTH TECHNOLOGY ASSESSMENT

Tezspire

210 mg /1.91 ml solution for injection x 1 (pre-filled pen (glass))

INN Tezepelumab

Therapeutic indication(s)	As an add-on to maintenance treatment in adults and adolescents aged 12 years and older with severe asthma who are inadequately controlled despite high dose inhaled corticosteroids plus another medicinal product for maintenance treatment.
Start/end date of procedure	14.03.2023 – 01.12.2023
Final decision	Inclusion in Annex 1 of the Positive Drug List (PDL) for home treatment of diseases reimbursed by the National Health Insurance Fund (NHIF). Inclusion in Annex 2 of the Positive Drug List (PDL) for purchase by the healthcare facilities with state and/or municipality ownership and under Article 5 of the Medical Establishments Act.

Summary of the report on the clinical and pharmacoeconomic assessment of the health technology of the medicinal product Tezspire

Health problem

Bronchial Asthma (BA) is a heterogeneous disease usually characterized by chronic inflammation of the airways. As a severe asthma is defined a BA requiring maximal controlled treatment at steps 4-5 according to GINA - high doses of inhaled corticosteroids (ICS) plus long-acting beta2-agonists (LABAs) over the past year, or the need for systemic corticosteroids (SCS) for more than 6 months in the previous year to maintain control, or uncontrolled asthma despite ongoing treatment.

The clinical presentation of BA includes cough (up to 92% of cases), chest tightness, shortness of breath (83%), and wheezing (90%). Patient with severe, uncontrolled BA experience significant clinical burden due to the consequences of exacerbations and poor lung function. Severe exacerbations are potentially life-threatening, and may necessitate emergency care. This includes both patients with eosinophilic asthma, for whom current treatment are not effective, and those with low levels of eosinophils, for whom no biological therapies are currently approved. Patients with severe, uncontrolled asthma are more likely to require frequent use of systemic corticosteroids (SCS) compared to other BA patients. Long- term use of SCS is also associated with an increased risk of death in asthma patient.

Tezepelumab is a new class of biological product, a monoclonal antibody (IgG2λ), targeting thymic stromal lymphopoetin (TSLP), preventing its interaction with the heterodimeric TSLP receptor. In BA, both allergic and non- allergic triggers include TSLP production. Blocking TSLP with tezepelumab reduces various biomarkers and cytokines associated with airway inflammation (e.g., blood eosinophils, submucosal airway eosinophils, IgE, FeNO, IL-5 and IL-13). It has been proved that, in addition to reducing airway inflammation, tezepelumab also affects airway hyperreactivity.

Epidemiological data

BA affects both children and adults from all ages and is one of the most widespread chronic diseases globally, defined as a socially significant condition. It is estimated that between 262 and 339 million people worldwide are affected by BA. The proportion of severe, uncontrolled asthma varies significantly, ranging from 1.8% to 49.2% of all asthma patients, depending on the region and the diagnostic criteria used. According to Bulgarian authors, approximately 3% (2.88%) of children and about 4% of adults suffer from severe asthma.

Efficacy data

The therapeutic efficacy of tezepelumab 210mg Q4W+ standard care (SoC) in reducing the frequency of asthma exacerbations and improving lung function, asthma control, and quality of life (QoL) in patients with severe, uncontrolled asthma has been evaluated in the PATHWAY (Phase IIb) and NAVIGATOR (Phase III) clinical trials. In the SOURCE (Phase III) trial, the effect of tezepelumab 210 Q4W+ SoC compared to placebo (PBO) + SoC was additionally assessed for reducing the use of oral corticosteroids (OCS) in adults with severe, corticosteroid- dependent asthma.

PATHWAY trial - determining the optimal dose of the medication. The results showed that administration of tezepelumab 210 Q4W + SoC led to statistically significant reduction in the annualized asthma exacerbation rate (AAER) by 71% compared to placebo (PBO) Q4W + SoC at week 52. Tezepelumab 210 Q4W + SoC reduced the rate of exacerbations requiring hospitalization or emergency room visits by 85% compared to PBO Q2W + SoC. Among patients hospitalized or admitted to intensive care, those treated with tezepelumab 210 Q4W + SoC (n= 8/137) reported fewer average days in the intensive care unit. AAER was reduced by 81% in the tezepelumab 210 Q4W + SoC arm (n=69) compared to the PBO Q2W + SoC arm (n=67) at week 52 in patients with eosinophils <300 cells/μL. 84.7% of patients treated with tezepelumab 210 Q4W + SoC have no exacerbations at week 52 compared to 68.8% in the PBO Q2W + SoC group. Improvement in pre-bronchodilator forced expiratory volume in one second (FEV1) was observed with tezepelumab 210 mg Q4W + SoC compared to PBO Q4W + SoC (least-squares mean difference vs. PBO Q4W + SoC: 0.13 L). The treatment effect was observed as early as week 4, remained throughout the whole trial period, and was seen regardless of baseline eosinophil status. 81.8% of patients treated with tezepelumab 210 mg Q4W + SoC achieved a clinically significant response on the Asthma Control Questionnaire (ACQ-6) compared to 69.6% with PBO Q4W + SoC (odds ratio: 1.94).

NAVIGATOR trial - Confirms the results of the previous trial. Treatment with tezepelumab 210 mg Q4W + SoC resulted in a statistically significant reduction in the exacerbation rate by 56% compared to PBO Q4W + SoC at week 52. The treatment also reduced the rate of exacerbations requiring hospitalization or emergency room visits by 79% (AAER: 0.06 vs. 0.28) over 52 weeks. The proportion of patients without exacerbations requiring hospitalization or emergency room visits was higher in the tezepelumab 210 mg Q4W + SoC group compared to the PBO Q4W + SoC group over 52 weeks (92.4% vs. 85.1%; odds ratio: 2.21). Tezepelumab 210 mg Q4W + SoC demonstrated a sustained reduction in AAER compared to PBO Q4W + SoC across all phenotypes and regardless of biomarker status over 52 weeks. The proportion of patients with no exacerbations was higher in the tezepelumab 210 mg Q4W + SoC group (56.3%) compared to the PBO Q4W + SoC group (39.9%) in the overall population over 52 weeks. The cumulative number of exacerbations in patients treated with tezepelumab 210 mg Q4W + SoC over the 52-week trial period was 52% lower than in the PBO Q4W + SoC group (tezepelumab 210 mg Q4W + SoC: 425 exacerbations; PBO Q4W + SoC: 878 exacerbations). Patients receiving tezepelumab 210 mg

Q4W + SoC showed statistically and clinically significant improvement in pre-bronchodilator FEV1 compared to PBO Q4W + SoC at week 52 (0.23 L vs. 0.09 L, least-squares mean difference: 0.13 L). Patients with exacerbations treated with tezepelumab 210 mg Q4W + SoC had fewer average days of systemic corticosteroid (SCS) use associated with exacerbations compared to patients treated with PBO Q4W + SoC (16.0 days [n=231] vs. 25.8 days [n=319]). Individual positive changes in the Asthma Symptom Diary (ASD) were observed in 58.0% of patients treated with tezepelumab 210 mg Q4W + SoC across all phenotypes and regardless of biomarkers, compared to 50.1% with PBO Q4W + SoC. The proportion of patients who achieved a clinically significant improvement on the ACQ-6 was higher with tezepelumab 210 mg Q4W + SoC (86.2%) compared to PBO Q4W + SoC (76.5%) at week 52 (odds ratio: 1.99).

SOURCE trial - Confirms the data from the previous two trials and also examines the ability of tezepelumab 210 mg Q4W + SoC to reduce dependency on systemic corticosteroids (SCS) and daily SCS dosage compared to PBO Q4W + SoC. Tezepelumab 210 mg Q4W + SoC reduced the exacerbation rate by 31% compared to PBO Q4W + SoC over 48 weeks in patients with severe, SCS-dependent asthma, despite a reduction in long-term SCS use. This represents a clinically significant improvement compared to PBO Q4W + SoC. Patients treated with tezepelumab 210 mg Q4W + SoC had a 41% reduction in exacerbations requiring hospitalization or emergency room visits compared to those taking PBO Q4W + SoC. The proportion of patients without exacerbations over the 48-week treatment period was numerically higher in the tezepelumab 210 mg Q4W + SoC group (47.3%) compared to the PBO Q4W + SoC group (34.2%). Treatment with tezepelumab 210 mg Q4W + SoC led to rapid, clinically significant, and sustained improvement in pre-bronchodilator FEV1 compared to PBO Q4W + SoC at week 48 despite the reduction in SCS dose (least-squares mean difference vs. PBO Q4W + SoC: 0.26 L).

Safety data

In the NAVIGATOR, PATHWAY и SOURCE trials, tezepelumab is well tolerated by patients with severe asthma and showed good safety profile similar to that of optimized standard therapy. The most common adverse effects associated with the use of tezepelumab were injection site reactions, pharyngitis, rash, and arthralgia. The safety profile in adolescents was generally similar to that observed in the overall trial population.

Data on comparators

The main comparative therapies are the biological products for the treatment of asthma included in the Positive Drug List: omalizumab, mepolizumab, benralizumab and dupilumab.

Pharmacoeconomic indicators

Published health technology assessments performed by governmental institutions intended for the health care systems of other countries

Three positive assessments from HTA agencies in other countries have been presented: NICE (United Kingdom), HAS (France), and TLV (Sweden). There is also one assessment that does not demonstrate additional benefit - G-BA and IQWiG (Germany).

Applied analysis
Pharmacoeconomic analyses of cost-effectiveness and cost-utility have been submitted, with outcome measures being Life Years (LY) gained and Quality-Adjusted Life Years (QALY). Comparative alternatives are the biological medicinal products included in Annex 1 of the PDL: omalizumab (Xolair), mepolizumab (Nucala), benralizumab (Fasenra) and dupilumab (Dupixent). The perspective of the analysis is that of the payer - the National Health Insurance Fund (NHIF). The time horizon in the model is lifetime. The used Markov model consist of 5 health states: controlled asthma, uncontrolled asthma, controlled exacerbation, uncontrolled exacerbation, and death. All costs and outcomes in the model are discounted at an annual rate of 3.5%.

The results off cost- effectiveness and cost utility analyses show that treatment with tezepelumab is associated with the highest costs for the payer, but also with the most benefits for the patients - more life years gained and more quality-adjusted life years. The incremental cost-effectiveness ratios (ICERs) place the new health technology tezepelumab above the favorable cost-effectiveness threshold of 60.636 BGN (3 times the GDP of Bulgaria for 2021). For the Bulgarian healthcare system, the evaluated health technology is not cost-effective.

Budget impact analysis
The budget impact analysis is conducted from the perspective of the payer - NHIF. The time horizon of the analysis is 5 years. The expected number of patients suitable for treatment with Tezspire is 56 in the first year and 325 in the fifth year.

The results of the budget impact analysis show that if patient compliance is taken into account, the inclusion of Tezspire in the Positive Drug List will lead to cost savings for the entire period of the analysis. If patient compliance is not taken into account, costs increase significantly, and the new health technology generates additional costs over the 5- year analysis period.

Conclusion

The new health technology tezepelumab is the only one biological medicinal product approved for the treatment of severe, uncontrolled asthma that has proven to be an effective therapy for the entire spectrum of patients with severe, uncontrolled asthma, regardless of biomarker profiles,

overlapping or changing phenotypes, or response to current therapies. Treatment with tezepelumab is associated with the highest costs for the payer but also with the greatest benefits for the patients, including more life years gained and more quality-adjusted life years. For the Bulgarian healthcare system, the evaluated health technology is not cost-effective. Reimbursing tezepelumab, if patient compliance is taken into account, leads to cost savings for the payer. However, if patient compliance is not considered, costs increase and the new health technology generates additional expenses over the 5-year period of the analysis.