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

HEALTH TECHNOLOGY ASSESSMENT

Dupixent
300 mg solution for injection x 2 prefilled syringes
300 mg solution for injection x 2 prefilled syringes with needle shield
dupilumab

Therapeutic indication(s)	Indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised fraction of exhaled nitric oxide (FeNO), who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment.
Start/end date of procedure	27.05.2020 – 07.01.2021
Final decision	Rejects inclusion in Annex № 1 of the Positive Drug List (PDL) for home treatment of diseases paid by the National Health Insurance Fund (NHIF) and Annex 2 of the PDL for purchase by medical establishments with state and/or municipal participation and under Art. 5 of the Medical Establishments Act.

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

Health problem

Bronchial asthma is a heterogeneous disease characterized by chronic airway inflammation and respiratory symptoms associated with variable bronchial obstruction. Symptoms and airflow limitation vary by time and intensity. The diagnosis of "asthma" is based on the identification of both characteristic pattern of respiratory symptoms such as wheezing, difficulty breathing, tightness in chest or cough, and the variable restriction of expiratory air flow.

Recognizable groups of patients with certain demographic, clinical and/or pathophysiological characteristics form "asthma phenotypes". The individual phenotypes do not correlate with specific pathological processes or treatment responses. The most common asthma phenotypes include: Allergic asthma; Non-allergic asthma; Asthma in adults (late onset); Asthma with persistent airflow limitation; Asthma in obesity.

The bronchial asthma treatment strategy derives from disease control, with pharmacological and non-pharmacological therapy set up in a continuous cycle that includes assessment, treatment and control.

Epidemiological data

Bronchial asthma is the most common chronic disease in childhood (0-18 years) and one of the most common chronic diseases worldwide. The disease affects 10-15% of children and 5-10% of adults with different frequency in different regions of the world, being higher in developed countries. The age distribution of asthma severity has peaks at 10-14 years and at the age of 75-79 years. The lowest burden is in the age group of 30-34 years.

There are no rigorous studies conducted in Bulgaria, but according to the Association of Patients with Bronchial asthma approximately 350,000 people have the disease in Bulgaria, of which approximately 40,000 are children. Only 50% of asthma patients in Bulgaria have been diagnosed, mainly due to limited access to specialists.

Dupixent (Dupilumab) is a monoclonal antibody that inhibits the signaling of IL-4 and IL-13, which is thought to be involved in the inflammatory processes of asthma. This helps reduce inflammation, results in fewer asthma attacks, increases the quality of life, reduces the cost of treatment, hospitalizations. It is indicated for adults and adolescents (over 12 years) as an adjunct to maintenance treatment of patients with severe asthma with type 2 inflammation characterized by high levels of Eo in the blood and/or elevated FeNO levels - nitric oxide

fraction in exhaled air with insufficient control despite the high dose of inhaled corticosteroids in combination with another drug for maintenance therapy (step 5 according to GINA). Monoclonal antibodies are recommended by GINA for inclusion at step 5 in severe asthma, in inadequate effect of prior treatment, with about 10% of asthma patients having severe, insufficiently controlled asthma. Monoclonal antibody therapy increases the quality of life of patients and reduces the need for hospitalization and emergency visits.

Efficacy data

The clinical efficacy and safety of dupilumab in the treatment of patients 12 years of age and older as adjunctive and supportive therapy for severe type 2 asthma inflammation is based on data from 5 studies of a clinical program:

1. Two phase 2 studies, one of which is principal:
ACT11457 – a 12-week randomized double-blind, placebo-controlled study, in patients with persistent moderate to severe eosnophilic asthma.
DRI12544 – a principal 24-week double-blind, randomized, placebo-controlled study to determine the dose, efficacy and safety in patients with moderate to severe uncontrolled asthma.

2. Three phase 3 studies, two of which are principal:
QUEST – a principal 52-week randomized, placebo-controlled phase 3 study in patients with persistent moderate to severe uncontrolled asthma, a study to confirm efficacy and safety.
VENTURE – a principal 24-week double-blind, placebo-controlled phase 3 study, to determine the efficacy of dupilumab in patients with severe corticosteroid-dependent asthma.
TRAVERSE - open-label phase 3 study with continued treatment (open-label extension) for long - term monitoring of safety and tolerability in patients from previous asthma studies.

The results of the studies show that Dupixent statistically significantly reduces the incidence of severe exacerbations in patients with moderate to severe asthma - 48% - 46% compared with placebo, and the incidence of severe exacerbations requiring hospitalization or emergency visits by 47%. The frequency of exacerbations decreases significantly in all patients regardless of the blood level of Eo.

An increase in the lung function was observed two weeks after the first administration of Dupixent. The effect of Dupixent is fast and stable for 52 years weeks. Dupixent statistically significantly increased asthma control in terms of ACQ-5 assessment towards week 24 compared with placebo, has good tolerability and safety. Efficacy does not depend on the baseline values of biomarkers of inflammation such as level of Eo in the blood and FeNO.

Dupixent statistically significantly reduced oral use of corticosteroids compared with placebo at week 24 of treatment in total population by 70.1% on average.

Analysis of patient-reported data

The degree of response with respect to the predetermined secondary endpoint ACQ-5 Asthma Control Questionnaire and AQLQ Asthma Quality of Life Questionnaire was analyzed at week 24 and week 52. The degree of response is defined as a score improvement of 0.5 or more (scale range 0-6 for ACQ-5 and 1-7 for AQLQ). Improvement in ACQ-5 and AQLQ was observed as early as week 2, which persisted until week 24 in study DRI12544 and week 52 in study QUEST. Similar results were observed in VENTURE.

Safety data

The most common side effect is injection site reaction. Anaphylactic reaction has been reported very rarely in the asthma development program. In studies DRI12544 and QUEST, the percentage of patients who discontinued treatment due to adverse events was 4.3% in the placebo group, 3.2% in the group of dupilumab 200 mg every two weeks and 6.1% in the group of dupilumab 300 mg every two weeks.

The most common adverse reactions are arthralgia and general disorders and application site effects - erythema, swelling, pain, and itching at the injection site.

Like all therapeutic proteins, dupilumab has immunogenic potential. Anti-drug antibody (ADA) responses are generally not associated with an effect on exposure, safety or efficacy of dupilumab.

Less than 0.4% of patients had a high titer of ADA-related responses resulting in reduced exposure and efficacy. A total of 107 adolescents aged 12 to 17 years with asthma were included in the 52-week QUEST study. The observed safety profile is similar to that in the adults.

Data on comparators

First choice therapy for the treatment of asthma are inhaled corticosteroids, alone and in combination with other drugs (long-acting beta agonists, short-acting beta agonists, leukotriene receptor antagonists, Tiotropium). With depletion of the clinical effect oral corticosteroids are included, which have significant side effects with prolonged use. This includes therapies with monoclonal antibodies (anti-IgE, anti-IL-5, anti-IL-4/IL-13, etc). which displace or reduce oral corticosteroid therapy.
Alternatives to Dupixent are:

- Anti-IgE-Omalizumab (Xolair)
- Anti-IL-5-Mepolizumab (Nucala) and Benralizumab (Fasenra)

Pharmacoeconomic indicators

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

The assessments by governmental institutions of France and Sweden are positive, both recommending reimbursement. In Germany, the assessment is negative.

Applied analysis

A cost-benefit analysis with QALY outcome measure is attached. The analysis is conducted from the perspective of the NHIF. The time horizon is lifelong (30 years). The cost-effectiveness ratio is modeled via Markov's model. As comparators, the three biological products with reimbursement in this country - Omalizumab, Benralizumab and Mepolizumab are included. Both costs and results are discounted with 3.5% per year when presented for a period longer than one year.

The results show that all products, including dupilumab dominate benralizumab, which has the lowest efficacy and highest cost. Mepolizumab and omalizumab dominate dupilumab because they are more effective (number of QALYs acquired) and with lower costs. In terms of cost effectiveness, mepolizumab leads, followed by omalizumab.

A sub-analysis for groups with > 300 eosinophils was performed. The results show again that benralizumab is cost-ineffective and dupilumab is dominated by both other alternatives - omalizumab and mepolizumab.

Costs of the assessed health technology

Only the cost of drug therapy is considered for a period of one year and after modeling - for 30 years thereafter.

Budget impact analysis

The budget impact analysis is conducted from the perspective of the paying institution, the NHIF with a time horizon of 5 years. The estimated number of patients is 59 the first year, rising to 698 in the fifth year. The inclusion of the new health technology leads to a positive budget impact, not taking into account risk-sharing agreements and patient access schemes.

Conclusion

Dupixent (Dupilumab) is a monoclonal antibody that inhibits the signaling of IL-4 and IL-13, which is thought to be involved in the inflammatory processes of asthma. This helps reduce inflammation, results in fewer attacks of asthma, increases quality of life, reduces the cost of treatment, hospitalizations.

Dupilumab is a cost-ineffective alternative. It is less efficacious and has a higher cost compared to two of the alternatives included in the PDL. The budget impact is associated with an additional cost for the paying institution.