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)	Dupixent is indicated for the treatment of moderate-to-severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy.
Start/end date of procedure	12.07.2019 – 07.05.2020
Final decision	Rejects inclusion in Annex 1 of the Positive Drug List (PDL) for home treatment of diseases, paid for by the NHIF and in Annex 2 of the PDL for purchase from medical institutions with state and/or municipal participation and under Art. 5 of the Medical Establishments Act and payment by the NHIF beyond the value of the rendered medical services.

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

Health problem

Atopic dermatitis is a common, chronic recurrent skin disease, characterized by dryness and impaired barrier function of the skin and a familial predisposition to an IgE-mediated immune response, called atopic diathesis.

In adolescence the disease manifests itself with dryness of the skin of the whole body, the lesions most often affect the folds and are represented by lichenified plaques, and during exacerbation erosions and escoriations with exudation and crusts occur. In adulthood, the rash affects the face and neck, back, palms, and soles, and presents with limited pigmented lichenified plaques with hyperkeratosis and scars.

From the subjective symptoms, itching of varying severity, duration and location is characteristic of all variants of atopic dermatitis, caused or exacerbated by sweating, contact with wool, emotions, stress or certain foods, and is responsible for the significant deterioration of the quality of life in patients with atopic dermatitis.

Atopic dermatitis is associated in about 60-70% of cases with allergic rhinitis, bronchitis, and 30% of patients develop bronchial asthma, with this association being known as atopic triad.

The severity of the disease is measured in different ways, with criteria for this being erythema, edema, exudation, excoriation, and dryness of the skin, and the involvement by area is calculated in different anatomical areas.

The medicinal product Dupixent (dupilumab) is indicated for the treatment of moderate to severe atopic dermatitis (ICD code L20), in patients in whom:

- the disease did not respond to one or more systemic agents (cyclosporine, methotrexate, azathioprine, or mycophenolate mofetil);
- there are contraindications for standard systemic therapy and phototherapy due to a concomitant severe or life-threatening disease;
- who have developed intolerance/hypersensitivity to systemic treatment with other drugs.

Epidemiological data

Atopic dermatitis affects about 10-20% of children and 1-10% of adults. Data for Bulgaria are similar to those for Europe. The treatment of atopic dermatitis is carried out with local,

systemic and phototherapy according to international and national therapeutic guidelines and consensuses. Depending on the severity of the disease and the size of the affected area, many therapeutic agents are employed in various combinations.

Efficacy data

To evaluate the therapeutic efficacy and safety profile of the new health technology, the following clinical trials have been analyzed: SOLO 1; SOLO 2; CHRONOS.

In the SOLO 1 and 2 studies, patients were randomized into three treatment groups: Group 1 - an initial dose of 600 mg dupilumab (two 300 mg injections) on day 1, followed by 300 mg once every 2 weeks (Q2W); Group 2 - 600 mg dupilumab on day 1, followed by 300 mg once a week (QW); and group 3, placebo. Clinical trials lasted 16 weeks, after which the results were assessed.

In the CHRONOS study, in addition to dupilumab or placebo according to the above treatment regimens, patients received a topical corticosteroid or topical calcineurin inhibitors. In this study, the results were reported at 16 and 52 weeks.

Dupilumab showed a rapid onset of efficacy with a statistically significantly higher rate of improvement, both for IGA 0 or 1 (significant or complete disease response) and for the reduction of EASI 50, EASI 75 and EASI 90 compared to placebo. In studies SOLO 1 and 2, the clinical effect of dupilumab treatment in patients with atopic dermatitis was statistically significantly better ($p < 0.001$) than in the placebo group. The CHRONOS study confirmed the sustained efficacy and the statistically higher efficacy of dupilumab after a 52-week course of treatment.

In addition to the clinical changes, dupilumab's effects on subjective symptoms such as pruritus, effects on the sleep, and health-related quality of life were identified in the presented clinical trials.

Safety data

In dupilumab monotherapy, the percentage of patients who discontinued treatment due to adverse events was comparable to or lower than that in the placebo group (<2%). The most common side effects are local application site reactions, conjunctivitis, blepharitis and herpes simplex. Very rare cases of serum sickness or serum-like reactions as well as anaphylactic reactions have been reported.

Data on comparators

Treatment with Dupixent (dupilumab) 300 mg solution for injection is an alternative to systemic therapy with corticosteroids, azathioprin, ciclosporin, methotrexate, or mycophenolate mofetil, in patients with moderate to severe atopic dermatitis who no longer respond to therapy or who developed severe effects to the thus far conducted systemic treatment.

Pharmacoeconomic indicators

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

Three health technology assessments were performed in the UK, Sweden and Germany.

Applied analysis

A cost-utility analysis (CUA) has been employed. The main outcome measures are quality-adjusted life years (QALY) and life-year gained (LYG).

The analysis has been performed from the perspective of the paying institution – the NHIF. The time horizon is lifelong. A model has been applied, which is a combination of the "Decision Tree" and a long-term model of Markov with time-dependent transition probabilities of death. The "decision tree" has been used to model short-term treatment decisions and the initial response to treatment, while the Markov model is applied to long-term maintenance treatment of the disease. Patients with moderate to severe atopic dermatitis can be treated with dupilumab, standard care (SC) or ciclosporin. All costs and results have been discounted by 3.5%. Subgroup analysis is not applicable.

The results of the cost-effectiveness analysis show that the incremental cost-effectiveness ratio exceeds the profitability threshold in Bulgaria.

Costs for the assessed health technology

The model includes costs for:

- drug therapy with dupilumab
- drug therapy with ciclosporin
- medical services

The costs for medical services have been determined on the basis of input data on the rate of application at the micro-level in the model (annual use of medical services and unit costs).

Budget impact analysis

The analysis of the budget impact was conducted from the point of view of the paying institution – the NHIF, with a time horizon of 5 years. Assumptions in the budget impact analysis have been made with respect to a cohort of 100 patients in the first year through 450 patients in the fifth year.

The inclusion of the new technology in the PDL increases the cost of the NHIF, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

Dupixent has been shown to be highly efficacious in achieving a therapeutic response in patients with atopic dermatitis. Dupixent is currently the only alternative for the treatment of other treatment-resistant atopic dermatitis. The medicinal product has a good and manageable safety profile, and in clinical trials most of the reported side effects were comparable to those in the placebo group. The incremental cost-effectiveness ratio exceeds the break-even point in Bulgaria. Upon inclusion of the medicinal product in the PDL, an increase in the NHIF budget is expected.