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

HEALTH TECHNOLOGY ASSESSMENT

Flutiform

pressurised inhalation, suspension 50 mcg/5mcg per actuation (120 впръсквания) x 1

Fluticasone, Formoterol

Therapeutic indication(s)	Indicated for the treatment of asthma in children and adolescents aged 5 years and above.
Start/end date of procedure	15.04.2020 - 15.10.2020
Final decision	Inclusion in: - Annex № 1 of the Positive Drug List (PDL) for home treatment of diseases paid by the National Health Insurance Fund (NHIF); - 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 Flutiform

Health problem

Bronchial asthma (BA) is a heterogeneous disease, characterized by a chronic inflammation of the respiratory tract. It is defined as a history of prior respiratory symptoms (wheezing, shortness of breath, chest tightness and cough), which vary in time and intensity, accompanied by a variable expiratory airflow limitation. The episodes are often triggered by factors such as physical exertion, exposure to allergens or irritants, climate change or viral respiratory infections.

The disease is usually associated with airway hyperresponsiveness to direct or indirect stimuli and with chronic inflammation that usually persists in the off-seizure period.

Establishing the diagnosis of "asthma" is based on identification of a characteristic model of respiratory symptoms such as wheezing, dyspnoea, chest tightness or cough, and a variable expiratory restriction of the air flow. The diagnosis of asthma in young children is based largely on recurrent patterns of symptoms combined with accurate clinical assessment of family history and physical findings with careful consideration of differential diagnostic capabilities.

The clinical picture of bronchial asthma includes the following symptoms: shortness of breath, chest tightness, wheezing and cough. These are manifested as daily episodes, disrupting patients' normal activity or nocturnal attacks of shortness of breath, disturbing sleep and rest. The most characteristic manifestation is a sudden attack of shortness of breath, most frequently at night. The patient wakes up with heaviness in the chest, adopts orthopneic position with painful, irritating cough or wheezing. Children can present with nonspecific symptoms as well, such as self-limitation in physical exertion, general fatigue.

Epidemiological data
Data on patients with bronchial asthma in Bulgaria show that their number is over 500 000, with more than 150,000 children with asthma, i.e. every tenth child suffers from asthma. In almost 80% of cases, BA begins before the age of six.

Efficacy data

The therapeutic efficacy and safety profile of fluticasone propionate/formoterol (FP/FORM), indicated for the treatment of asthma in patients aged 5-12 years have been evaluated in three clinical trials.
Clinical trial FLT3506 is a double blind, double-dummy, parallel groups, multicentre study. Fluticasone/formoterol is more effective than fluticasone with respect to change from pre-

dose FEV1 at baseline to 2 h post-dose FEV1 over the 12-week treatment period. Fluticasone/ formoterol is non-inferior to fluticasone/salmeterol. Fluticasone/formoterol is more effective compared to fluticasone for FEV1 AUC0–4h at week 12. A greater effect was observed with fluticasone/formoterol compared to fluticasone. All endpoints show greater changes before and 2 hours after dosing with fluticasone/formoterol and fluticasone/salmeterol than fluticasone monotherapy. Therapeutic effects of the two combination therapies are generally similar. The differences between fluticasone/salmeterol and fluticasone, as well as between fluticasone/formoterol and fluticasone/salmeterol are not statistically significant.

Clinical trial FLT3502 is a 12-week open-label, randomized, controlled trial with a 24-week extension to evaluate the effectiveness and safety of fluticasone propionate/formoterol in children with asthma. In the basic analysis of efficacy based on the change in pre-dose FEV1 from day 0 to day 84, it was found that Fluticasone propionate/formoterol is non-inferior to fluticasone/salmeterol. The analysis of the change in pre-dose FEV1 on day 0 to 2 hour post-dose FEV1 on day 84 also showed non-inferiority of Fluticasone propionate/formoterol. On day 84 (end of the main study) the mean predose FEV1 is similar in both groups and then increased in the extended phase (Fluticasone propionate/formoterol) between day 84 and day 252. The values of pre-dose PEFR and 2 hour post-dose PEFR are higher on days 0, 14, 42 and 84 compared with pre-dose PEFR on day 0 in both groups in the main study. The results are preserved in the open extension of this study.

Safety data

Studies with fluticasone propionate/formoterol have shown similar safety and tolerability profile compared to fluticasone monotherapy in children aged 5-12 years and fluticasone/salmeterol in children aged 4-12 years. Possible systemic effects, including Cushing's syndrome, Cushingoid manifestations, suppression of the adrenal glands and growth retardation in children and adolescents have been reported. The children may also experience anxiety, sleep disturbances and behavioral effects, including hyperactivity and irritability.

Data on comparators

The available therapeutic alternative is Seretide Diskus 50 µg/100 µg/dose inhalation powder, pre-dispensed. Seretide Diskus is indicated for regular treatment of asthma when administration of a combination product (long-acting ß2-agonist and inhaled corticosteroid) is considered appropriate:

• patients with unsatisfactory control on the background of treatment with inhaled corticosteroids and with a short-acting ß2-agonist on demand, or

• patients with adequate control with co-administered inhalation corticosteroid and a long-acting ß2-agonist.

Pharmacoeconomic indicators

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

HAS (France) recommends the combination Fluticasone propionate/formoterol for inclusion in the list of medicinal products subject to reimbursement. TLV (Sweden) also recommends reimbursement.

Applied analysis

A pharmacoeconomic analysis of cost-minimisation type was used. The perspective of the analysis is of the paying institution - the NHIF. The time horizon is one year. Discounting is not applied. A decision tree type model was created with included Markov model for evaluation of pMDI inhaler devices (dosing pressurized inhaler, for Flutiform) and DPI (dry powder inhalers, for Seretide diskus) and the associated costs as a result of their misuse. Seretide Diskus, 50 μg/100 μg/dose, was chosen as comparator. The assessment of the pharmacoeconomic indicators of Flutiform versus Seretide Diskus presents both therapies as having similar therapeutic efficacy. The results show that therapy with Flutiform shows a higher annual cost than Seretide Diskus. The conclusions are confirmed by the conducted sensitivity analyzes.

Subgroup analyzes

Not applied.

Costs of the assessed health technology

Costs of the evaluated therapies and costs for preventive examinations and dispensarisation have been applied.

Budget impact analysis

The analysis was conducted from the point of view of the paying institution – the National Health Insurance Fund. The time horizon is 5 years. The expected number of patients in the first year is 118, and in the fifth it is 339. The reimbursement of the health technology Flutiform for regular treatment of asthma in adolescents and children aged 5 years and older will add cost to the NHIF, not taking into account risk - sharing agreements and patient access schemes.

Conclusion

Bronchial asthma is the most common chronic disease in childhood globally. Flutiform (fluticasone propionate/formoterol 50μg/5 μg) improves asthmatic symptoms and lung function, and reduces attacks. It exerts powerful anti-inflammatory effect in the lungs and

thanks to the inhalational administration has fewer side effects. The reimbursement of the health technology Flutiform leads to an increase in the NHIF costs, not taking into account risk-sharing agreements and patient access schemes.