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

HEALTH TECHNOLOGY ASSESSMENT

Quinsair

240 mg nebulizer solution x 56 ampoules + 1 Nebuliser Handset

INN Levofloxacin

Therapeutic indication(s)	Indicated for the management of chronic pulmonary infections due to Pseudomonas aeruginosa in adult patients with cystic fibrosis.
Start/end date of procedure	29.04.2020 - 18.12.2020
Final decision	Inclusion in Annex 1 of the Positive Drug List (PDL) for home treatment of diseases, paid 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.

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

Health problem

Cystic fibrosis (CF) is a multisystem disease with an autosomal recessive inheritance. It affects the exocrine glands, causing the most serious damage to the respiratory and digestive systems, including lung infections with impaired mucociliary clearance and pancreatic insufficiency. CF reduces life expectancy and significantly impairs the health-related quality of life (HRQL) of patients.

In the course of CF, three stages are generally defined: early, intermediate and final stage with complications. Patients in the early stage of CF do not have *P. aeruginosa* infection or have intermittent infection that can be eradicated with antibiotics. Patients in the intermediate stage of disease are chronically infected with *P. aeruginosa* or others organisms, and in the final stage, in addition to chronic infection with *P. aeruginosa* they present with complications - severe hemoptysis, pneumothorax and respiratory failure. The chronic pulmonary infection with *P. aeruginosa* is the main reason for the progressive decline of lung function, increased morbidity and mortality. After the establishment of chronic infection with *P. aeruginosa*, the inclusion of long-term maintenance therapy with inhaled antibiotics is recommended to suppress infection, reduce the number of acute exacerbations and preserve lung function.

Treatment of exacerbations with antipseudomonas antibiotics causes reduction of symptoms and improves lung function. The use of inhaled antipseudomonas antibiotics, which include the assessed health technology, improve the quality of life of patients by improving the lungs function, prolonging the time until the next exacerbation, reducing the need of an additional antibiotic. All these benefits lead to improved physical capacity of patients, weight gain and less indirect expenditure.

Epidemiological data

The total number of patients with CF in Bulgaria is about 220. The probability of giving birth to a child with cystic fibrosis also shows population and geographical differences and is determined based on the carrier frequency in a given country. The frequency of *P. aeruginosa* infection in CF patients is about 1.3 per 10,000 patients in the European Union.

Efficacy data

The clinical development of Quinsair includes 10 studies, of which the main ones are MPEX 204, 207 and 209 (main phase and extension phase).

MPEX 204 is a randomized, double-blind, placebo-controlled, phase II study. *P. aeruginosa* sputum density decreased compared to baseline in patients with levofloxacin inhalation solution (LIS) on day 28, but increased in the placebo group. The average FEV1 increased with increasing dose and decreased in the placebo group. The sum of the respiratory symptoms of CFQ-R in patients in the LIS groups increased, with statistically significant changes with levofloxacin 240 mg twice daily on day 14, but not on day 28. LIS treatment reduces the need for another antipseudomonas antibiotic compared to placebo for the 56-day period of the study.

MPEX 207 is a randomized, double-blind, placebo-controlled, phase III study. The time to first pulmonary exacerbation of CF is the primary endpoint. Additional endpoints are a change in FEV1% of the projected estimate, change in the point sum of respiratory symptoms in the baseline CFQ-R questionnaire and change in the density of *P. aeruginosa* in sputum compared to baseline. During the treatment period, 55% of patients receiving LIS and 47% of patients receiving placebo showed symptoms of exacerbation. The mean time to exacerbation was 51.5 days in the LIS group and 58 days in the placebo group. The values of predicted FEV1% are similar in both groups at baseline. The average change of predicted FEV1% of day 28 was 3.66% in the LIS group (baseline 57%) and 1.24% in the placebo group (baseline 56%). The mean time to administration of a systemic and/or inhaled antipseudomonas antibiotic for patients who show respiratory symptoms, requiring additional antibiotic was 59 days in the LIS group and 58 days in the placebo group. MPEX 209 (main phase and extension) are phase III studies, multicenter, comparing levofloxacin inhalation solution (LIS) with tobramycin inhalation solution (TIS). The primary endpoint is the change in the predicted FEV1% vs baseline level to day 28. The non-inferiority of LIS compared to TIS is demonstrated by a relative change in predicted FEV1% from baseline to day 28 in favor of the LIS at the end of each treatment period, without a statistically significant difference. Pre-planned analysis of predicted FEV1 % from baseline to day 28 in the individual categories shows improvement of up to 70% in patients receiving LIS compared with 53% in patients receiving TIS.

Post-hoc analysis of MPEX 209 shows that the improvement of predicted FEV1% is confirmed at the mean of the 3 treatment cycles in the LIS versus TIS group (68.2% vs. 48.8%, respectively). In patients with LIS, a -31% risk of pulmonary exacerbation was reported during the 24-week study period leading to potentially fewer hospitalizations.

Safety data

Most of the patients included in MPEX 209 reported at least one adverse event (AE) during the study. Serious AE occurring during treatment are reported by 22% of patients receiving

LIS and 32% of patients receiving TIS. Discontinuation of treatment due to AE was low in both groups - 3.2% with LIS and 1.1% with TIS, respectively.

A significant difference in the proportion of patients reporting dysgeusia (change in taste) was found: 25% of patients treated with LIS against none of the patients receiving TIS. Other AE reported in at least 5% of patients treated with LIS versus TIS are cough (58% vs. 53%), increased sputum (52% vs. 44%), paranasal sinus hypersecretion (27% vs. 20%) and headache (19% vs. 14%).

The safety profile of parenteral levofloxacin is well known and characterized. Known classes of adverse effects of systemic fluoroquinolones such as nausea, altralgia and tendonitis were not commonly reported during the study. The most frequently reported adverse reactions are cough/productive cough (54%), dysgeusia (30%) and fatigue/asthenia (25%).

Data on comparators

The assessed health technology - Quinsair belongs to the group of inhaled antibiotics for the treatment of CF patients and chronic *P. aeruginosa* infection and accordingly these constitute the main therapeutic alternative.

Pharmacoeconomic indicators

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

HAS, France and SMC, Scotland have approved the health technology for reimbursement with certain restrictions. Sweden has included the medicinal product in the list of reimbursed products.

Applied analysis

A cost-utility pharmacoeconomic analysis (CUA) was performed with a cost-effectiveness (CEA) supporting analysis. The long - term outcomes were used (life expectancy, LYG), quality adjusted life years (QALY), followed by intermediate results (changes in clinical indicators and disease progression). The perspective of the analysis is that of the paying institution - NHIF. The time horizon of the analysis is lifelong. An annual discount factor of 3.5% is applied to costs and results. Markov's model was used. Tobramycin (TOBI) was chosen as a comparator. Quinsair is a cost-effective alternative because it falls below 3 times GDP per capita. A deterministic and probabilistic susceptibility analyses were performed for assessment of the variability, associated with the results of the baseline model.

Analysis of subgroups

Not applicable.

Costs of the assessed health technology and alternatives

Drug therapy cost is included.

Budget impact analysis

The analysis of the budget impact is conducted from the perspective of the payer. The time horizon is 5 years. The expected number of patients in the first year is 2, and for the fifth 15. Reimbursement of the health technology will lead to a generation of additional expenditure for the NHIF in the first year, which will increase over each following year, without taking into account risk - sharing agreements and patient access schemes.

Conclusion

Quinsair (levofloxacin solution for inhalation) is intended for the treatment of chronic *P. aeruginosa* infection in patients with CF ≥ 18 years. Quinsair has a good safety profile. The cost-effectiveness analysis shows that Quinsair is a cost effective alternative. The budget impact analysis shows that on inclusion of the new health technology in the PDL, the budget will increase, with the additional costs being accompanied by additional benefits for the patients.