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

HEALTH TECHNOLOGY ASSESSMENT

Briviact

10 mg film- coated tablet x 14

50 mg film- coated tablet x 56

Brivaracetam

Therapeutic indication(s)	Briviact is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents and children from 4 years of age with epilepsy.
Start/end date of procedure	01.06.2020 - 11.12.2020
Final decision	To include a therapeutic indication 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 Briviact

Health problem

The International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE) define epilepsy as "a brain disease characterized by a persistent predisposition to generate epileptic seizures and the neurobiological, cognitive, psychological and social consequences of the condition."

Epileptic seizures are episodes of sudden onset of quantitative and/or qualitative impairment of consciousness, sensory, motor, autonomic and mental functions. They are an expression of hypersynchronous discharges of cortical neurons. The clinical manifestation of epileptic seizures depends on the location of the discharges in the cerebral cortex and their spread in the brain. Epileptic seizures are characterized by electroencephalographic (EEG) and clinical characteristics as focal (partial), generalized and of unknown etiology. The prognosis in children with focal seizures depends on the etiology and type of epileptic syndrome. Some epileptic syndromes, such as benign idiopathic focal epilepsy with centrotemporal spikes (Roland's epilepsy), including with atypical course (pseudo Lennox syndrome) are associated with remission during adolescence, while others, such as temporal lobe epilepsy with mesial localization, require long-term or even lifelong treatment.

Epilepsy is considered to be cured in patients with age-related epileptic syndrome who have passed the typical age or patients without seizures for at least 10 years and without antiepileptic medication in the last 5 years.

Epilepsy in children is associated with comorbidities. Almost 80% of pediatric patients have ≥1 comorbidity, compared to 30% of the general population, and multiple comorbidities are common.

Childhood epilepsy affects all aspects of the social domain, including marital status, socioeconomic status of parents, educational level, employment and the use of social benefits compared to controls with no epilepsy.

The target population is pediatric patients with focal epilepsy, candidates for adjunctive therapy with antiepileptic drugs (AED).

Epidemiological data

Epilepsy is the most common chronic neurological disease, affecting 65-70 million people worldwide and is most commonly seen in children and the elderly. About 40-50% of cases are diagnosed in childhood, with childhood epilepsy being the most common serious, treatable neurological disease among children and adolescents.

The prevalence of epilepsy in the European countries in children aged ≤16 is approximately 0.45% per 1,000 people.

In Bulgaria there are about 50,000 patients with epilepsy, about 50% of them with focal epilepsy. As of December 2019, about 23,000 are receiving treatment, about 40% of epilepsy patients are drug-resistant and are being treated with polytherapy (a combination of 2-3 antiepileptic drugs). About 4,000 is the number of health-insured children under the age of 18 who receive antiepileptic drugs.

Efficacy data

Efficacy data of Briviact in the pediatric focal seizure population were extrapolated from the adult focal seizure population based on available guidance from the European Medicines Agency.

Based on the principles of extrapolation, clinical pharmacology studies have shown that the proposed dose adjustments in pediatric patients correspond to the same exposure of Briviact observed in adults.

Reduction in seizure frequency after adjunctive treatment with Briviact
From the pooled dataset, adjunctive treatment with Briviact showed a statistically significant reduction in the incidence of focal seizures compared to placebo at doses of 50 mg/day, 100 mg/day and 200 mg/day; the achieved ≥50% response rate was statistically significant for all doses of Briviact compared to placebo.

Freedom from seizures after adjunctive treatment with Briviact
In the pooled data set, the proportion of patients who were able to achieve freedom from seizures during the treatment period was more significant in those treated with 50 mg/day, 100 mg/day or 200 mg/day than in those treated with placebo. The number of seizure-free patients after treatment with Briviact 100 mg/day or 200 mg/day was statistically significant compared to placebo.

Safety data

The safety of Briviact adjunctive therapy in the treatment of focal seizures in patients ≥4 to <16 years of age has been studied in two studies. In these studies, Briviact showed a favorable safety profile in pediatric patients with focal seizures with a low rate of adverse events, serious adverse events and low discontinuation rates. The safety profile of Briviact in this patient population is very similar to the established safety profile in adult patients based on data in more than 2,000 adult patients with focal seizures. The most common adverse effects in the adult population were: drowsiness (13.0%), dizziness (12.1%), fatigue (8.9%),

headache (7.3%) and seizures (4.9%). In comparison, headache, drowsiness, and seizures were also reported in ≥10% of patients in pediatric studies with Briviact.

In the pooled data from the studies, approximately 25% of the total patient population had treatment emergent adverse events (TEAEs) associated with behavioral disorders, with irritability (11.9%), aggression (5.9%), grief (3.2%) and psychomotor hyperactivity (3.2%) being the most common. Most of the TEAEs potentially associated with behavioral disorders were mild to moderate in intensity and did not result in dose reduction or discontinuation of treatment. The data show that suicidal ideation is observed in 20% of children with epilepsy.

Data on comparators

Lacosamide was chosen as a comparator and topiramate, lamotrigine, levetiracetam were included in the analysis in line with the national therapeutic practice.

Pharmacoeconomic indicators

Published health technology assessments performed by governmental institutions for the purposes of another national health care system

Germany and France have issued a positive assessment for patients over 16 years of age, and the Swedish assessment does not provide a description of the target group of patients, but the reimbursement of Briviact was approved with certain restrictions.

Applied analysis

A cost-effectiveness pharmacoeconomic analysis was applied, with an outcome measure the quality adjusted life years (QALY). The perspective of the analysis is that of the paying institution - NHIF. The selected time horizon is 2 years. The model was initiated as a line of adjunctive therapy, which includes each patient with a set of baseline characteristics to whom brivaracetam or one of the comparator products was randomly assigned, together with a baseline AED (antiepileptic drug) with a titration period, if necessary. Clinical outcomes of the model include total seizure-free duration, seizure-free days, number of early and late ADRs, years of life, and QALY achieved. The model tracked the treatment response for each patient, and the different patients were designated as seizure-free patients, patients with ≥50% seizure reduction, and patients with <50% seizure reduction. Lacosamide was chosen as a comparator and according to the national therapeutic practice, topiramate, lamotrigine, levetiracetam were included in the analysis. Brivaracetam is more expensive and more effective than lacosamide, and Briviact therapy is cost-effective compared to lacosamide, but only if it is administered as a second-line adjunctive therapy. When comparing brivaracetam with lamotrigine, topiramate, levetiracetam, topiramate therapy was dominant in evaluating efficacy with indicators: > 50% positive response rate and no seizures.

Subgroup analyses
No subgroup analysis was applied.

Cost of the assessed health technology
Direct medical costs are included in the analysis.

Budget impact analysis
The analysis of the budget impact was conducted from the perspective of the paying institution - the National Health Insurance Fund, and the time horizon is 5 years. The estimated number of patients eligible for treatment with the assessed technology is 49 in the first year, reaching 136 in the fifth year. The reimbursement of the health technology for the population aged 4-16 will lead to additional cost for the NHIF, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

Briviact can be administered in a therapeutic dose from the first day without the need for titration, which contributes to patient cooperation and adherence to therapy. The reimbursement of the health technology for the evaluated indication will lead to an increase in the costs for the NHIF.