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

HEALTH TECHNOLOGY ASSESSMENT

Vpriv

400 U powder for solution for infusion x 1 vial

Velaglucerase alfa

Therapeutic indication(s)	Indicated for long-term enzyme replacement therapy (ERT) in patients with type 1 Gaucher disease.
Start/end date of procedure	03.04.2020 – 18.12.2020
Final decision	Inclusion in: - Annex № 1 of the Positive Drug List (PDL) for home treatment of diseases paid by the 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 Vpriv

Health problem

Gaucher disease is a rare genetic lysosomal disease with autosomal recessive inheritance. Gaucher disease is the most common lysosomal storage disease. It is characterized by a deficiency of the lysosomal enzyme glucocerebrosidase, which leads to the accumulation of glucocerebroside in macrophages. Gaucher disease is an autosomal recessive disorder due to mutations in the GBA gene that results in a deficiency of the lysosomal enzyme beta-glucocerebrosidase. This enzyme deficiency causes accumulation of glucocerebroside mainly in macrophages, causing the formation of foam cells (so-called "Gaucher cells"). In this lysosomal storage disease clinical manifestations reflect the distribution of Gaucher cells in the liver, spleen, bone marrow, skeleton, and lungs. The accumulation of glucocerebroside in the liver and spleen causes organomegaly. Bone involvement leads to skeletal abnormalities and deformities, as well bone pain crises. Deposits in the bone marrow and splenic sequestration cause clinically significant anemia and thrombocytopenia.

Depending on whether the central nervous system is involved, three main phenotypes of the disease are known - non-neuronopathic form or Gaucher type I disease, acute, neuronopathic form, Gaucher type II disease and chronic neuronopathic form Gaucher type III disease. Gaucher type I disease is the most common lysosomal disease and the most common Gaucher phenotype. It is characterized by an extremely heterogeneous clinical picture and the lack of a strict genotype-phenotype correlation. Asymptomatic forms are known, which are probably the most frequently missed, and those with extreme organomegaly, severe manifestations of hypersplenism and severe damage to the skeletal system. Clearly, early disease onset in childhood is associated with a severe clinical picture.

Enzyme replacement therapy (ERT) has been considered the gold standard in the treatment of Gaucher disease for nearly two decades. The treatment is safe and effective, with reversal of a number of symptoms and prevention of severe bone manifestations.

Epidemiological data

According to the European reference portal for rare diseases Orphanet, the prevalence of Gaucher disease is between 1-9 per 100,000.

Epidemiological data from Bulgaria for Gaucher disease show 17 treated patients by 2019. With a morbidity of 1 in 40,000 to 1 in 60,000 births, the expected number of new cases per year should be in the range of 1-1.3.

Efficacy data

The main clinical trials evaluating Vpriv in Gaucher type 1 disease are: TKT025 (extension TKT025EXT), TKT032, TKT034, HGT-GCB-039, HGT-GCB-044 (long-term follow-up of participants in TKT032, TKT034 and HGT-GCB-039) and HGT-GCB-058.

The studies included only patients with a confirmed diagnosis of Gaucher type 1 disease. TKT025, TKT025EXT, TKT032, HGT-GCB-044 and HGT-GCB-058 are single-arm clinical trials. HGT-GCB-039 assessed the comparison with Cerezyme and TKT034 assessed a switch from ERT with Cerezyme to ERT with Vpriv. HGT-GCB-044 is an open extension of TKT032, TKT034 and HGT-GCB-039. HGT-GCB-058 is an early access program, the study included 205 patients switched from Cerezyme to Vpriv, as well as 6 previously untreated.

The main goal of treatment is stopping the progression, reversal of disorders, prevention of irreversible and life-threatening complications (such as avascular necrosis, pathological fractures, skeletal deformities, pulmonary hypertension, life-threatening bleeding, progressive liver damage), improvement of the quality of life. The main results of clinical trials with Vpriv in type 1 Gaucher disease showed clinically significant improvements in spleen and liver volume after 6 months and platelet count and hemoglobin concentration after 3 months. All patients achieved the long-term therapeutic goals regarding skeletal pathology, spleen and liver volume, platelet count, and hemoglobin concentration within 48 months of VPRIV enzyme replacement therapy. Clinically significant improvements in spleen and liver volume, platelet count, hemoglobin concentration, and plasma biomarkers persisted throughout the 7-year period, despite dose reduction at months 15-18 of the study. The quality of life of patients improved. Clinically significant improvements were reported in all key clinical parameters after 12 months in patients who had not been treated with ERT. VPRIV enzyme replacement therapy in Gaucher type 1 disease achieves clinically equivalent results compared to Cerezyme enzyme replacement therapy. The most serious adverse drug reactions in patients in clinical trials were hypersensitivity reactions. The most common side effects are related to the infusion. The most commonly observed symptoms of infusion-related reactions are: headache, dizziness, hypotension, hypertension, nausea, fatigue/asthenia and pyrexia/fever. The only adverse reaction that resulted in discontinuation of treatment was infusion-related. Most side effects are mild to moderate. The most commonly reported side effects are headache, arthralgia and nasopharyngitis. No patient developed anti-velaglucerase alfa antibodies.

Patient-reported data

Patient satisfaction and quality of life after ERT with Vpriv were assessed in Germany and Austria. A statistically significant proportion of patients, 66.7%, reported greater satisfaction

with home infusions versus 0 patients with less satisfaction. The degree of adherence to treatment is extremely high - 98%. The results for the generalized physical and mental components of SF-36 increased by 3.0 ± 7.2 and 1.3 ± 9.0, respectively. The trend of improvement of the quality of life is maintained throughout the observation period.

Safety data

The results of 40 patients switching from imiglucerase ERT to velaglucerase alpha in a phase II/III TKT034 clinical trial, where safety was the main endpoint, showed that only one patient discontinued treatment due to a serious adverse event. There are no other patients who discontinued their participation due to an adverse event or drug-related adverse reaction. No patients developed antibodies to velaglucerase alfa.

The main objective of the extended study HGT-GCB-044 was to evaluate the long-term safety of weekly intravenous infusions of velaglucerase alfa in patients with type 1 GD. The study confirmed the safety and efficacy profile of velaglucerase alfa reported in previous studies and the low long-term frequency of anti-drug antibodies production and hypersensitivity reactions. Clinically stable patients can safely switch from imiglucerase to velaglucerase alpha ERT while preserving/achieving good results.

Data on comparators

Clinically employed therapeutic alternatives for Gaucher disease include:

- *Cerezyme (imiglucerase) (ERT)*

Cerezyme (imiglucerase) is indicated for long-term enzyme replacement therapy (ERT) in patients with a confirmed diagnosis of non-neuronopathic (type 1) or chronic neuronopathic (type 3) Gaucher disease who demonstrate clinically significant non-neurological manifestations of the disease.

- *Cerdelga (eliglustat) (SRT)*

is indicated for long-term substrate-reduction therapy (SRT) in adult patients with type 1 Gaucher disease who are weak, intermediate or extensive metabolisers of CYP2D6.
According to the NHIF Requirements for the Treatment of Gaucher Disease in outpatient care from late 2019, Cerezyme and Cerdelga are the only health technologies used for the treatment of patients with Gaucher disease that are paid by the NHIF.

Pharmacoeconomic indicators

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

A positive assessment of the Vpriv health technology carried out by HAS, France, has been published. HAS recommends Vpriv for the treatment of patients with Gaucher disease, stating a number of advantages and benefits of the product, one of which is that Vpriv is a first-line therapy. The product is recommended for reimbursement for hospital use. Another assessment was done by TLV, Sweden, which states that Vpriv achieves non-inferior, clinically equivalent results compared to Cerezyme at lower costs.

Applied analysis

A cost-minimisation pharmacoeconomic analysis was applied to evaluate the cost effectiveness of Vpriv for the treatment of type 1 Gaucher disease. Cerezyme ERT was selected as comparator in view of the international and national pharmacotherapeutic guidelines for the treatment of patients with Gaucher disease and reflects the clinical practice in Bulgaria. The purpose of the cost-minimisation analysis is to compare the costs of treatment with the alternatives from the perspective of the payer under conditions of achieving equivalent results. The results obtained from HGT-GCB-039 show that Vpriv achieves non-inferior, clinically equivalent results compared to Cerezyme with respect to all major therapeutic goals in type 1 Gaucher disease. The perspective is that of the NHIF, with only the medication-related direct medical costs being calculated. The use of Vpriv is associated with a higher cost compared to Cerezyme.

Budget impact analysis

The budget impact analysis was conducted from the perspective of the paying public institution. The time horizon of the budget impact analysis is 5 years. The target population includes patients with type 1 Gaucher disease.

The payment of Vpriv with public funds leads to additional costs, which are expected to increase every following year, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

Vpriv achieves similar, clinically equivalent results compared to Cerezyme with respect to all major therapeutic goals in type 1 Gaucher disease. The two ERT medicinal products (Vpriv and Cerezyme) have a similar safety profile, with Vpriv achieving more favorable results as regards immunogenicity. Vpriv has a significantly lower likelihood of antibody formation and more favorable results as regards immunogenicity. The use of the medicinal product Vpriv will generate additional costs for the paying institution, without taking into account risk-sharing agreements and patient access schemes.