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

HEALTH TECHNOLOGY ASSESSMENT

Galafold

123 mg capsule, hard x 14

Migalastat

Therapeutic indications	Galafold is indicated for long-term treatment of adults and adolescents aged 16 years and older with a confirmed diagnosis of Fabry disease (α-galactosidase A deficiency) and who have an amenable mutation (see the tables in section 5.1).
Start - end date of procedure	27.09.2018 – 28.04.2020
Final decision	Rejects 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 Galafold

Health problem

Fabry disease is an inherited metabolic disease in which insufficient activity of the enzyme α-galactosidase A (α-Gal A) leads to the build-up of globotriaosylceramide (GL3) and other products in the lysosomes of cells. Accumulation of these products damages cells and leads to progressive and irreversible organ damage, usually involving the nervous system, endothelium, kidneys and heart, as well as other tissues. Fabry disease is caused by a mutation in a gene, GLA, resulting in the production of an abnormal form of α-Gal A that is not functional or only partially functional. Many different GLA mutations have been identified. The specific mutation determines the level of residual α-Gal A activity and is related to the severity of the disease. The GLA gene is located on the X chromosome, and all men who inherit a pathogenic GLA mutation develop Fabry disease. Fabry disease in male patients is sometimes classified as "classic" or "variant" (also called "atypical" or "non-classical"), based on the symptoms and level of α-Gal A activity.

Most patients remain clinically asymptomatic during the first years of life. In an analysis of 1,765 patients in the Fabry registry, the median age at onset of initial symptoms was 9 years in men and 13 years in women, although there was significant variability among patients. The earliest manifestations usually involve the nervous system and the gastrointestinal tract.

Epidemiological data

Fabry disease is a rare condition occuring in people of all ethnic groups. There is a higher frequency among ethnic groups that have a high level of blood relations. The prevalence of the classic form of Fabry disease is estimated as 1:117,000 or 1:40,000 in men.

Data for Bulgaria show between 45 and 60 confirmed patients with Fabry disease. Enzyme replacement therapy in Bulgaria started 7 years ago and is associated with data for a delay and halting of organ damage and prolonging the survival of individual patients. However, the small number of patients is a limiting factor for making cardinal conclusions with respect to the Bulgarian population with Fabry disease.

Efficacy data

GALAFOLD's clinical development program covers 20 clinical trials involving 386 participants. Of these trials, 10 were phase 1 studies involving 218 healthy volunteers and 24 participants with renal impairment; 6 studies are phase 2 and 4 are phase 3 studies (2 main, 1 ongoing open extended study and 1 completed open extended study). Of the 386 patients who

were receiving GALAFOLD until June 2017, 127 were treated for at least 1 year and 3 patients were treated for 11 years.

The main studies included in the analysis of therapeutic efficacy and safety of GALAFOLD were phase 3 studies ATTRACT and FACETS. Almost all patients included in ATTRACT and FACETS had severe Fabry disease, characterized by multiorgan involvement and significant disease severity. The severity of disease is comparable to that of patients in the main studies of ERT (Enzyme Replacement Therapy), suitable for ERT according to the treatment instructions. GALAFOLD is effective in all subgroups of patients, regardless of their phenotype.

Basic clinical trial AT1001-012, ATTRACT - AT1001 therapy compared to enzyme replacement therapy in patients with Fabry disease with AT1001 amenable mutations was performed to evaluate the efficacy of GALAFOLD versus ERT in the treatment of Fabry disease in patients who had amenable mutations and had previously been treated with ERT. Composite primary efficacy endpoints assessed renal function, which is impaired in most patients with Fabry disease. Because there is a high risk of impaired renal function in patients with higher urinary protein excretion, patients are stratified by degree of proteinuria. As a secondary endpoint, renal function was also assessed by the annual change from baseline to 18 months in GFR (glomerular filtration rate), calculated by the formula for modifying the diet in renal disease (eGFRMDRD). Migalastat and ERT showed comparable beneficial effects on renal function at 18 months, using both methods to determine GFR. These effects persisted with additional 12-month therapy with migalastat. Migalastat stabilized renal function at 18 months, regardless of baseline eGFR (Estimated glomerular filtration rate).

Basic Clinical Trial AT1001-011, FACETS - Study on the efficacy, therapeutic effectiveness and safety of AT1001 chaperone therapy in Fabry disease was performed to evaluate the efficacy, safety and pharmacodynamics of GALAFOLD in patients with amenable mutations who had not been previously treated with ERT (did not receive ERT at all, or did not receive ERT for at least 6 months prior to screening). From baseline to month 24, renal function was stable in patients with amenable mutations treated with migalastat. Renal function remained stable at 36 and 48 months. Stabilization of renal function was observed regardless of baseline eGFR.

Safety data

Safety data from ATTRACT clinical trial indicate that GALAFOLD was well tolerated during the 18-month treatment period. No clinically significant effects of GALAFOLD were seen on the safety indicators and no differences were seen between patients who switched from ERT

to GALAFOLD and those who remained on ERT in terms of vital signs, physical findings, ECG indicators or laboratory tests. The percentage of patients with treatment-related adverse reactions was similar in the GALAFOLD (94%) and ERT (95%) groups.
In general, treatment-related adverse reactions (TEAEs) were mild to moderate in severity. The most common (≥25%) treatment-related adverse reactions reported in the group of GALAFOLD (nasopharyngitis and headache) were observed with a similar frequency to that in the ERT group. Serious adverse reactions (SAE), all considered unrelated to the study subjects were reported in 33% of patients in the ERT group and 19% of patients in the GALAFOLD group. There were no reported deaths in the study.

Safety data from FACETS clinical trial indicate that none of the patients discontinued the treatment with GALAFOLD due to treatment-related adverse reactions (TEAE). Data on treatment - related adverse reactions (TEAE) are: during the 6-month double-blind phase 1, headache and nasopharyngitis were reported most frequently with GALAFOLD compared with placebo; during open phase 2, the most commonly reported TEAEs were headache and pain during procedures (associated with kidney biopsies). During phase 2 (open extended trial), the most commonly reported TEAEs were proteinuria, headache, and bronchitis. Most TEAEs are mild or moderate in severity.

Comparators data

The comparative alternative is enzyme replacement therapy (ERT) with recombinant human enzyme α-Gal A administered by infusion every 2 weeks. There are two medicinal products available for ERT: Replagal (Agalsidase alfa) and Fabrazyme (Agalsidase beta).

Pharmacoeconomic indicators

Published health technology assessments, performed by state institutions serving other national health care systems

Six health technology assessments have been conducted in the United Kingdom, France, Canada, Germany, Scotland and Spain.

Applied analysis:

A cost-utility analysis (CUA) has been applied, with a basic outcome measurement being quality-adjusted life years (QALY), also data on life years gained (LYG) have been presented, which are a measure of a cost-effectiveness analysis. The analysis was made from the perspective of the paying institution - NHIF. The time horizon is lifelong.

A Markov model with 11 conditions covering the main symptoms of Fabry disease was used to assess costs and outcomes. All costs and results have been discounted by 3.5%. Subgroup analysis is not applicable.

Migalastat therapy demonstrated a higher value of acquired health benefits at a higher direct cost per patient compared to agalsidase beta. The results of cost-benefit analyzes show that the incremental cost-benefit ratio exceeds the breakeven point in Bulgaria.

Costs for the assessed health technology

In the model costs have been included for:
- drug therapy with migalastat
- drug therapy with agalsidase beta
- costs of agalsidase beta administration, diagnosis and follow-up of patients
- costs of disease control and monitoring

Budget impact analysis

The analysis of the budget impact has been conducted from the perspective of the paying institution, the NHIF, the time horizon is 5 years. The size of the target population was estimated from literature data on the incidence of Fabry disease and also from NHIF data. It is estimated that about 30% of diagnosed patients have amenable mutations, indicating 10 patients per year are eligible for Galafold therapy.

Sensitivity analysis was performed with +/- 20% key parameters variation and the budget impact was measured largely by the cost of therapies with Galafold and comparators.

Upon inclusion of the new technology in the PLC, an increase in expenses of the NHIF is expected, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

Migalastat therapy demonstrated a higher value of acquired health benefits at a higher direct cost per patient compared to the alternatives. The results of cost-benefit analyses show that the incremental ratio exceeds the breakeven point. The reimbursement of the new technology by the NHIF will increase expenses in all cases considered, without taking into account risk-sharing agreements and patient access schemes.