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	27.07.2020 – 22.12.2020
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 Galafold

Health problem

Fabry disease is an inherited, chronic and progressive disease. Patients suffering from Fabry disease have a significantly reduced quality of life in regard to their health. The classic clinical picture of Fabry disease, a lysosomal metabolic X-linked disorder, is mainly observed in men. In women, disease manifests later in life and in a milder form, compared with men. Up to 18% of children with Fabry disease (under the age of 18) may already have proteinuria as a first presenting symptom. Nephropathy signifies unfavorable prognosis, regardless of gender. First presenting symptoms (acroparesthesias, chronic joint pain, gastrointestinal symptoms, sensitivity to heat, tinnitus) usually appear during childhood or adolescence. Angiokeratomas and nonspecific telangiectasias, sweat secretion disorders, sensorineural hearing loss and damage to the vestibular system are additional manifestations. Obstructive respiratory disease, osteopenia and anemia can also be seen. Because of the heterogeneity of the clinical picture, Fabry disease is often diagnosed many years after the onset of first symptoms. A common ophthalmology finding is *cornea verticillata*.

If Fabry disease is suspected, the diagnosis is made by enzymatic and/or molecular genetic testing. Commonly employed tests assess the activity of the enzyme AGLA in leukocytes in men and analyse gene GLA mutations in women. Mutations in the GLA gene are usually private, family-specific mutations. The main cause of Fabry disease is a mutation in the GLA gene, which encodes AGLA and is located in the long arm of the X chromosome. A large number of different GLA mutations are known.

Enzyme replacement therapy (ERT) in patients with Fabry disease may stop development of disease. No differences were observed between children and adults in the tolerance profile of ERT. Two enzyme replacement medicinal products have been approved so far: Agalsidase alfa and Agalsidase beta.

Galafold (migalastat) is a novel, orally active drug that provides personalized targeted therapy for patients with Fabry disease. Unlike ERT, migalastat allows the mutated enzyme to function on its own, providing steady and effective drug levels in body tissues. Migalastat is indicated for long-term treatment of adults and adolescents aged 16 years and older with a confirmed diagnosis of Fabry disease who have a mutation that responds to treatment.

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. Studies related to the incidence of Fabry disease have shown a prevalence ranging from 1:40,000 to 1:117,000 live

births. The frequency varies in different countries. Fabry disease primarily affects men. Women may also suffer from this condition, but they present with a milder clinical picture and may have a better prognosis. The average age of disease onset in male patients is between 3-10 years. In female patients it is between 6-15 years. If left untreated, renal failure, cerebrovascular disease and cardiomyopathy shorten patients' life expectancy.

Efficacy data

The clinical development program of migalastat, used as monotherapy, involves nine studies; for the purposes of this analysis, two of them have been described and analyzed.

ATTRACT Clinical Trial (AT1001-012) – A Phase 3, 18-month, active-controlled clinical trial, followed by 12-month open-label extension study (OLE). Comparative alternatives - ERT (agalsidase alpha or agalsidase beta).

FACETS clinical trial (AT1001-011) - a double-blind, placebo-controlled, 6-month clinical trial, followed by a 6-month OLE and a 12-month OLE. For the 6-month double-blind study (phase 1), 67 patients were randomized to receive: migalastat 150 mg once every other day and placebo once every other day. Then, in the 6-month open-label extension study (phase 2), all patients received migalastat. It was followed by 12 months open-label extension study in which patients and researchers were blinded to therapy received during phase 1. After a 12-month open-label extension study patients were able to continue in the long-term OLE study 041.

Schiffmann et al., study, 2020 - The aim of this study was to examine lyso-Gb3 profiles in patients receiving migalastat in phase 3 clinical trials and to evaluate the relationship between changes in lyso-Gb3 and changes in disease progression outcomes over time. The assay included ERT-untreated and ERT-treated patients from FACETS (NCT00925301) and ATTRACT (NCT01218659) studies, who were included in a long-term open-label extension with migalastat (AT1001-042, NCT02194985). Initiation of migalastat treatment was selected as baseline (month 0). For patients not treated with ERT, randomized to receive placebo in FACETS, month 6 of the study was selected as baseline. ERT-treated patients were randomized. The results show a significantly lower incidence of the composite endpoint of renal, cardiovascular, cerebrovascular events or death with migalastat compared to ongoing ERT. Compared to ERT, Galafold was equivalent in stabilizing renal function and significantly reduced left ventricular mass index (LVMI). Galafold was also associated with a low incidence of adverse effects. The most common adverse reaction during migalastat treatment was headache, which was experienced by approximately 10% of patients. Migalastat also has the benefit of the more convenient for the patient oral therapy.

Analysis of data reported by patients

Significant improvements in vitality and overall health were observed compared to baseline level. Results for other domains remained unchanged.

No significant changes were observed at 6 months and no deterioration in pain scores was observed. Data from a registry of patients (so-called "followME") treated with migalastat or ERT, which aims to assess the long-term safety and efficacy of migalastat in patients taking the drug in real world conditions showed that the median duration of the period between the earliest symptom and time of establishing the diagnosis in the groups was 1.2 years in men and 1.4 years in women.

In the migalastat cohort, the median duration of the period between the earliest symptom and time of establishing the diagnosis was 2.4 years in men and 1.8 years in women. In the cohort with ECT median duration was 0.6 years in men and 9.6 years in women.

Safety data

The most common adverse drug reaction during treatment with migalastat is headache, experienced by approximately 10% of patients taking migalastat. Therapy with Migalastat has a good tolerability profile. No clinically relevant effects of migalastat on safety indeces were observed; no differences between patients, who have switched from ECT to migalastat and those who remain on ECT were reported in terms of vital signs, physical findings, ECG parameters or laboratory test results. No cases of treatment discontinuation due to treatment-related adverse reactions have been identified. Serious adverse reactions, all considered unrelated to study treatment, were reported in 33% of patients in the ERT group and 19% of patients in the migalastat group. No death cases have been identified.

Comparators data

Currently available treatment for Fabry disease includes ERT, the only etiologic treatment, and concomitant therapies for the treatment of organ manifestations and symptoms.

1. Agalsidase alfa is produced in a human cell line and administered at a dose of 0.2 mg/kg body weight
2. Agalsidase beta is produced recombinantly in CHO cells (CHO = Chinese hamster ovary) and administered at a dose of 1.0 mg/kg body weight.

Bulgarian National Consensus for the treatment of patients with Fabry disease defines enzyme replacement therapy (ERT) as the primary treatment of paramount importance for the course of disease.

Pharmacoeconomic indicators

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

Galafold health technology has been evaluated by NICE (UK), HAS (France), GB-A (Germany), CADTH (Canada), SMC (Scotland), AEMPS (Spain), NCPE (Ireland), where all these institutions have approved the product for reimbursement in the treatment of Fabry disease in patients who have an amenable mutation.

Applied analysis

A cost-utility analysis (CUA) was applied and health benefits for patients were measured as life-year gained (LYG) and quality-adjusted life years gained (QALY). The perspective of analysis is that of the paying institution - the National Health Insurance Fund. The time horizon is lifelong, health benefits and costs are discounted with an annual discount factor of 3.5%. The only alternative is agalsidase beta. Agalsidase alfa therapy was not included in the analysis as an alternative, as according to data from the public registers of the National Health Insurance Fund there are no patients in Bulgaria on the respective treatment.

A modified Markov model has been applied in the analysis, in which the patient progression in 10 mutually exclusive health conditions were monitored. Kaplan-Meier survival analysis has been applied to determine the median time to transition to the next health condition. Of any given condition it is possible for the patient to enter an absorbing state (death). The initial age of patients who enter the model is based on an ATTRACT clinical trial.

The cost-benefit analysis shows that migalastat therapy demonstrated a higher value of acquired health benefits at a higher direct cost per patient compared to agalsidase beta, with therapy not falling within the breakeven point.

In order to analyze the cost-benefit sensitivity to stochastic changes in the values of migalastat health technology, a probabilistic (PSA) and unidirectional (DSA) sensitivity analysis was conducted. Results of these analyses confirm the main outcome of the cost-effectiveness analysis.

Costs for assessed health technology

Direct medical costs have been included in the model, namely those for drug therapy with comparative alternatives, costs for using agalsidase beta, costs for disease control and monitoring. Costs to control adverse drug reactions and indirect costs (such as loss of work productivity) have not been included in the analysis, as they are perceived as similar in both arms and thus can be neglected.

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 estimated number of patients eligible for treatment with Galafold is two in the first year, expected to increase to three in the fifth year. The analysis shows that the reimbursement of health technology in patients with Fabry disease, who have an amenable mutation will lead to an increase in the expenses of the NHIF, without taking into account risk-sharing agreements and patient access schemes.

Conclusion

Galafold has a once every other day oral regimen, thus allowing patients to avoid the burden and risks of infusion therapy and to improve adherence to therapy, and its standalone administration could have a positive effect on patients' quality of life and reduce missed time from work or study. Compared to ERT, Galafold demonstrated equivalence in terms of renal function stabilization and significantly reduced the mass index of the left ventricle (LVMI). Galafold was also associated with a low incidence of adverse events. The reimbursement of the new health technology will lead to additional expenses for the paying institution, while at the same time bringing additional benefits to the patients.