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

HEALTH ASSESMENT TECHNOLOGY

Vabysmo

120 mg/ml - 0.24 ml solution for injection x 1 vial + 1 needle

INN Faricimab

Therapeutic indication	Treatment of adult patients with visual impairment due to diabetic macular oedema (DME).
Start- end date of procedure	21.08.2023 – 28.12.2023
Final decision	Inclusion in Annex 1 of the Positive Drug List (PDL) for home treatment of diseases reimbursed by the National Health Insurance Fund (NHIF). Inclusion in Annex 2 of the Positive Drug List (PDL) for purchase by the healthcare facilities with state and/or municipality ownership and under Article 5 of the Medical Establishments Act.

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

Health problem

Diabetic retinopathy (DR) is a common microvascular complication of diabetes that can lead to vision loss and blindness. The disease is one of the leading causes of visual impairment among the working-age population and accounts for 2.5% of all cases of blindness and 1.4% of all cases of moderate and severe visual impairment. Two forms of DR are known: proliferative and non-proliferative. Non-proliferative DR (NPDR) is characterized by swelling and weakening of the small blood vessels in the retina, which limits their ability to carry blood, resulting in fluid leakage into the retina. Proliferative DR (PDR) is characterized by the formation of abnormal new blood vessels in the retina. The early stages of DR are asymptomatic. In the later stages of the disease, bleeding from abnormal blood vessels leads to the appearance of dark "floating" spots in the visual field and can result in vision loss. Diabetic macular edema (DME) can occur at any stage of DR progression, including in patients with normal status or mild NPDR, moderate NPDR, severe NPDR, low-risk PDR, and high-risk PDR. Without treatment, approximately half of all patients with DME will lose two or more lines on the visual acuity (VA) chart within 2 years.

Currently, the standard treatment for nAMD is intravitreal (IVT) anti-VEGF injection therapy. The anti-VEGF agents currently approved for use are ranibizumab (Lucentis®), aflibercept (Eylea®), and brolucizumab (Beovu®). The use of corticosteroids is also permitted in patients who do not respond to the anti-VEGF therapy. The available intravitreal anti-VEGF therapies are associated with a significant treatment burden for patients, caregivers, physicians, and the healthcare system due to the demanding schedule of frequent injections and follow-up visits necessary to achieve and maintain optimal vision in the long term.

Vabysmo® (faricimab) is a humanized bispecific immunoglobulin G1 (IgG1), which is the first and only inhibitor of both VEGF-A and Ang-2—two key factors leading to retinal vascular disease. By dual inhibition of Ang-2 and VEGF-A, faricimab reduces vascular permeability and inflammation, inhibits abnormal angiogenesis, and restores vascular stability. Faricimab is administered intravitreally as a "treat and extend" regimen, allowing for safe extension of treatment intervals without additional follow-up visits.

Epidemiological data

Diabetes mellitus is associated with the development of ophthalmic complications such as DME. It is estimated that in 2014, a total of 422 million adults (aged ≥ 18 years) worldwide had diabetes. By 2019, this number was approximately 463 million. DR, including DME, and is one of the leading causes of vision loss worldwide, accounting for 2.5% of all cases of blindness and 1.4% of all cases of moderate and severe visual impairment. It is estimated that in 2019 there were

approximately 29 million cases of DME worldwide. It is reported that DME affects 12% of people with type 1 diabetes and 28% of people with type 2 diabetes, with a global prevalence of 7.5% among diabetic patients aged 20-79 years.

According to the Vision Health Status Report in Bulgaria, 50% of people with diabetes in Bulgaria are affected by diabetic retinopathy, and the incidence of DME among diabetics is 25%.

Efficacy data

The assessment of the therapeutic efficacy and safety profile of faricimab is based on data from two clinical trials—GR40349 (YOSEMITE) and RHINE (NCT03622593)—double-masked, multicenter, randomized, active comparator-controlled, parallel-group phase III trials evaluating the efficacy, safety, pharmacokinetics, and optimal treatment frequency of faricimab administered by intravitreal injection at 8-week intervals or PTI for approximately 100 weeks (excluding the screening period) in patients with DME.

The **GR40349 (YOSEMITE)** clinical trial demonstrated non-inferior efficacy compared to aflibercept in terms of the primary endpoint, defined as the mean change from baseline in BCVA (Best Corrected Visual Acuity) at weeks 48/52/56, measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) in patients with DME. At weeks 48/52/56, the adjusted mean change from baseline in BCVA was 10.7, 11.6, and 10.9 letters, respectively, in the faricimab arms every 8 weeks (Q8W), personalized treatment interval (PTI), and aflibercept Q8W. The difference in adjusted mean change from baseline in BCVA between the faricimab Q8W and PTI arms compared to the aflibercept Q8W arm at week 48/52/56 was 0.2 letters (97.5% CI: -2.0, 1.6) and 0.7 letters (97.5% CI: -1.1, 2.5), respectively. Clinically significant proportions of patients achieved a 2-step improvement in diabetic retinopathy severity (DRS) from baseline, as measured by the ETDRS (Early Treatment Diabetic Retinopathy Study) and DRSS (Diabetic Retinopathy Severity Scale) at week 52 in all three treatment arms (46.0%, 42.5%, and 35.8% of patients in the faricimab Q8W, PTI, and aflibercept Q8W arms, respectively).

The **RHINE (NCT03622593)** clinical trial demonstrated non-inferior efficacy compared to aflibercept in terms of the primary endpoint, defined as the mean change from baseline in BCVA at weeks 48/52/56, measured by ETDRS in patients with DME. In the ITT population, patients treated with faricimab Q8W or PTI had a non-inferior mean change from baseline in BCVA at week 48/52/56 compared to patients treated with aflibercept Q8W, as the lower bound of the 97.5% confidence interval for the adjusted mean difference between the faricimab and aflibercept arms was greater than 4 letters. At weeks 48/52/56, the adjusted mean change from baseline in BCVA was 11.8, 10.8, and 10.3 letters, respectively, in the faricimab Q8W, PTI, and aflibercept Q8W arms. The difference in adjusted mean change from baseline in BCVA between the faricimab Q8W and PTI arms compared to the aflibercept Q8W arm at week 48/52/56 was 1.5 letters (97.5% CI: -0.1, 3.2) and 0.5 letters (97.5% CI: -1.1, 2.1), respectively. In the pooled analyses, the adjusted mean change from baseline in BCVA at weeks 48/52/56 was 11.2, 11.2, and 10.5 letters in the

faricimab Q8W, PTI, and aflibercept Q8W arms, respectively; the difference between the faricimab Q8W and PTI arms compared to the aflibercept Q8W arm was 0.7 letters (95% CI: -0.4, 1.7) and 0.6 letters (95% CI: -0.4, 1.7), respectively.

YOSEMITE and RHINE are identical trials and were conducted in parallel. There is no significant imbalance in the baseline characteristics of the included patients between the two studies.

Safety data

The most commonly reported adverse reactions are cataracts (11%), conjunctival hemorrhage (7%), increased IOP (4%), vitreous floaters (4%), eye pain (3%), and retinal pigment epithelial tear (only in nAMD, 3%). The most serious adverse reactions are uveitis (0.5%), vitreitis (0.3%), endophthalmitis (0.3%), retinal tear (0.2%), and rhegmatogenous retinal detachment (< 0.1%).

Data on comparators

To reflect real clinical practice in the affected patient group and considering the possibilities for comparing efficacy, the comparative alternative to the candidate health technology faricimab includes the anti-VEGF action humanized antibodies aflibercept (Eylea) and brolucizumab (Beovu).

Pharmacoeconomic indicators

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

Five positive evaluations from HTA agencies of other countries are presented - NICE (UK), HAS (France), G-BA and IQWiG (Germany), SMC (Scotland), and CADTH (Canada).

Applied analysis

The following pharmacoeconomic analyses are applied:

- Main analysis for the inclusion of faricimab in Annex 1 of the PDL at a 75% reimbursement level: cost-utility analysis (CUA).
- Additional scenario No. 1: incomplete pharmacoeconomic analysis assessing cost differences in year 1 and year 2+ between faricimab and brolucizumab at 75% reimbursement.
- Additional scenario No. 2 for the inclusion of faricimab in Annex 2 of the PDL: incomplete pharmacoeconomic analysis of costs for the hospitalization period at 100% reimbursement.
- Additional scenario No. 3 with payer – society perspective at 75% reimbursement level.

- Additional scenario No. 4: cost-utility analysis (CUA) and cost analysis for the inclusion of faricimab in Annex 1 at 100% reimbursement level.

Health benefits for patients in the applied model are measured as quality-adjusted life years (QALY). In the main scenario, as well as in the developed additional scenarios No. 1, No. 2, and No. 4, the perspective is that of the payer - National Health Insurance Fund (NHIF). Additional scenario No. 3 includes the perspective and viewpoint of the society. The chosen time horizon is 25 years. Given the real clinical practice in Bulgaria, the comparative alternative is the anti-VEGF humanized antibody aflibercept. Since the model lacks input data for efficacy in treatment with brolucizumab (not available in network meta-analysis), this comparative alternative is not included in the main analysis but is evaluated through an incomplete pharmacoeconomic analysis of costs for year 1 and year 2+ (additional scenario No. 1 and additional scenario No. 4). Both comparative alternatives (aflibercept and brolucizumab) are considered in additional scenario No. 2 for the inclusion of faricimab in Annex 2 of the PDL. At a 75% reimbursement level, the average annual treatment costs with faricimab are lower than the average annual treatment costs with aflibercept. The results from the main analysis show that pharmacotherapy costs with faricimab per patient are lower (discounted cost) than the costs of pharmacotherapy with the alternative aflibercept. The health benefits results show that therapy with faricimab leads to more quality-adjusted life years (QALYs) compared to therapy with the alternative aflibercept. ICUR is calculated based on lower costs with higher health benefit values, and faricimab is a dominant cost-effective therapy compared to aflibercept. According to the incomplete pharmacoeconomic analysis of costs at a 75% reimbursement level, additional savings are generated with treatment with faricimab compared to treatment with brolucizumab.

Subgroup analyses
No subgroup analyses have been conducted.

Costs for the assessed health technology
The following cost components are considered: costs for drug therapy with the assessed health technology and comparative alternatives, application costs, medical service costs and services related to vision impairment, costs for disease monitoring, costs for managing adverse events, costs from the societal perspective – productivity loss, informal care costs, transportation to the hospital, and additional patient costs.

Budget impact analysis
The budget impact analysis is conducted from the perspective of the paying institution – NHIF. The time horizon of the analysis is 5 years. The projected number of patients for treatment with faricimab in the first year is 66, and in the fifth year – 175. Two options are developed: Option 1, scenario 1 – including the health technology in Annex 1 of the PDL with 75% reimbursement; Option 1, scenario 2 – including the health technology in Annex 1 of the PDL with 100% reimbursement; Option 2 – including the health technology in Annex 2 of the PDL with 100% reimbursement from NHIF. The results from the budget impact analysis show that in both options,

including Vabysmo in the Positive Drug List will lead to savings for the entire analysis period, without considering risk-sharing agreements and patient access schemes.

Conclusion

The evaluated health technology faricimab leads to improved duration of treatment effect and has the potential to significantly reduce the treatment burden for patients and caregivers, as well as allow more efficient use of health resources and long-term reduction of healthcare system costs due to fewer injections and examinations. The health benefits results show that therapy with faricimab leads to more quality-adjusted life years (QALYs) compared to therapy with the alternative aflibercept. ICUR is calculated based on lower costs with higher health benefit values, and faricimab is a dominant cost-effective therapy compared to aflibercept. The budget impact analysis results show that in both reimbursement scenarios for the health technology, including Vabysmo in the Positive Drug List will lead to savings for the paying institution for the 5-year analysis period.