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

HEALTH TECHNOLOGY ASSESSMENT

Vabysmo

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

INN Faricimab

Therapeutic indication(s)	Treatment of adult patients with neovascular (wet) age-related macular degeneration (nAMD).
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, and reimbursement by the NHIF.

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

Health problem

Neovascular (wet) age-related macular degeneration (nAMD) is a rapidly progressive, advanced form of age-related macular degeneration (AMD) that can lead to irreversible loss of central vision if left untreated. nAMD is characterized by choroidal neovascularization (CNV)—the formation of new blood vessels due to high levels of angiogenic and inflammatory factors, including angiopoietin-2 (Ang-2) and vascular endothelial growth factor (VEGF). The disease can be subdivided into early and advanced AMD. Unsuccessful treatment of AMD can lead to rapid progression of the disease, causing irreversible loss of central vision. Early-stage AMD is associated with multiple clinical signs, including drusen (extracellular deposits containing a large amount of protein and lipids that accumulate between the retinal pigment epithelium [RPE] and Bruch's membrane) and RPE disorders. Advanced stage AMD can be subdivided into atrophic (also called dry AMD) or neovascular (also called wet or exudative). Visual signs of atrophic AMD may be subtle. Advanced stage disease includes geographic atrophy and neovascular age-related macular degeneration (nAMD). The main symptoms of nAMD are decreased visual acuity, central or paracentral scotoma, pathological changes in the macular zone and metamorphopsia.

Currently, the standard treatment for nAMD is intravitreal (IVT) anti-VEGF injection therapy. Currently approved anti-VEGF agents are ranibizumab (Lucentis®), aflibercept (Eylea®) and brolucizumab (Beovu®). Corticosteroids are also allowed in patients who do not respond to anti-VEGF therapy. Currently 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 patient follow-up visits required to achieve and maintain optimal long-term vision.

Vabysmo® (faricimab) is a humanized bispecific immunoglobulin G1 (IgG1) that is the first and only inhibitor of both VEGF-A and Ang-2, the two major factors leading to retinal vascular disease. By dually inhibiting 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 safe extension of application intervals without additional follow-up visits.

Epidemiological data

Visual impairment due to nAMD is a serious public health problem that is gaining importance due to the increasing prevalence of nAMD. nAMD accounts for about 10–20% of all AMD cases. nAMD is estimated to affect approximately 14 million people worldwide. In 2019, there were 703 million people aged 65 or over worldwide. In 2020, 2,066,157 cases of nAMD were registered in

the EU5 countries (France, Germany, Italy, Spain and the UK). The annual incidence of nAMD in the EU5 in 2020 was 227,982 cases.

Efficacy data

Evaluation of the therapeutic efficacy and safety profile of faricimab is based on data from two phase 3 randomized clinical trials – **TENAYA (NCT03823287)** and **LUCERNE (NCT03823300).**

The TENAYA clinical trial (NCT03823287) was a multicenter, randomized, active-controlled, double-masked, parallel-group, 112-week phase III trial to investigate the efficacy, safety, tolerability, and pharmacokinetics of faricimab administered at intervals of up to 16 weeks in treatment-naïve patients with nAMD. The trial demonstrated non-inferiority of faricimab to aflibercept on the primary endpoint, defined as mean change from baseline in Best Corrected Visual Acuity (BCVA) at week 40/44/48 as measured by the Early Treatment of Diabetic Retinopathy Study (ETDRS), in treatment-naïve nAMD patients.

In the intention-to-treat (ITT) population, patients treated with faricimab had a non-inferior mean change from baseline in BCVA at weeks 40/44/48 compared to patients treated with aflibercept, as the lower limit of the 95% confidence interval (CI) for the adjusted mean difference between the faricimab and aflibercept arms was greater than 4 letters. At week 40/44/48, the adjusted mean change from baseline in BCVA was 5.8 and 5.1 letters in the faricimab and aflibercept arms, respectively. The difference in adjusted mean change from baseline in BCVA between the faricimab arm compared with the aflibercept arm at weeks 40/44/48 was 0.7 letters (95% CI: -1.1 to 2.5).

The LUCERNE clinical trial was a multicenter, randomized, active-controlled, double-masked, parallel-group, 112-week phase III trial to investigate the efficacy, safety, tolerability, and pharmacokinetics of faricimab administered at intervals of up to 16 weeks in treatment-naive patients with nAMD. The trial also demonstrated non-inferiority of faricimab to aflibercept on the primary endpoint, defined as mean change from baseline in BCVA at week 40/44/48, measured on the ETDRS, in patients with treatment-naïve nAMD. In the ITT population, patients treated with faricimab had a non-inferior mean change from baseline BCVA at week 40/44/48 compared to aflibercept-treated patients, as the lower limit of the 95% CI for the adjusted mean difference between the faricimab and aflibercept arms was greater than 4 letters. At week 40/44/48, the adjusted mean change from baseline in BCVA was 6.6 and 6.6 letters in the faricimab and aflibercept arms, respectively. The difference in adjusted mean change from baseline in BCVA between the faricimab arm compared with the aflibercept arm at weeks 40/44/48 was 0.0 letters (95% CI -1.7 to 1.8).

Safety data

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

Data on comparators

In order to reflect the real clinical practice in the affected group of patients and taking into account the possibilities of comparison of efficacy, the comparative alternative of the candidate health technology faricimab includes the humanized antibodies with anti-VEGF action 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 assessments from OH&S agencies of other countries are presented - NICE (Great Britain), HAS (France), G-BA and IQWiG (Germany), SMC (Scotland) and CADTH (Canada).

Applied analysis
The following pharmacoeconomic analyses were applied:

• Cost-Minimization Analysis (CMA) applied for basic analysis for inclusion in Annex 1 of the PDS at 75% reimbursement;

• Incomplete pharmacoeconomic analysis of the costs of the hospitalization period applied for additional scenario No. 1 for the inclusion of faricimab in Annex 2 of the PDL;

• Cost-minimization analysis applied for additional scenario No. 2 with the payer-society perspective included.

• Cost-minimization analysis applied for additional scenario No. 3 for inclusion in Annex 1 of the PDL at 100% reimbursement.

The cost-minimization analysis looked at the cost differences between faricimab and its comparator alternatives. In the main scenario, as well as in the developed additional scenarios No. 1 and No. 3, the model uses a health perspective and the point of view of the paying institution -

the National Health Insurance Fund (NHIF). An additional scenario No. 2 is also presented in which the perspective and perspective of society is included. The chosen time horizon in the model is 24 years. All costs and results in the model are discounted at 3.5% on an annual basis. In view of the real clinical practice in Bulgaria, the choice of comparative alternatives includes the humanized antibodies with anti-VEGF action aflibercept and brolucizumab.

The demonstrated similar therapeutic efficacy and safety profile of faricimab compared to aflibercept and brolucizumab allows for a cost-minimum economic analysis. Scenario No. 1 and Scenario No. 3 compared the cumulative costs of treating one patient with the health technology being evaluated and with the comparative alternatives. The results show that treatment with faricimab results in cost savings for the paying institution. In addition, faricimab therapy reduces the frequency of intravitreal injections, which predisposes to lower administration costs.

Subgroup analyses
No subgroup analyzes were performed.

Costs for the assessed health technology
The following cost components are considered: costs of drug therapy with the evaluated health technology and comparative alternatives, costs of administration, costs of medical services and medical services related to visual impairment, costs of monitoring the disease, costs of controlling adverse events, costs from a societal perspective - loss of productivity, costs of informal care and transport to the hospital and additional costs to the patient.

Budget impact analysis
The analysis of the budget impact was conducted from the point of view of the paying institution - NHIF. The time horizon of the analysis is 5 years. The estimated number of patients to be treated with faricimab in the first year is 154, and in the fifth year – 407. Three analyzes were developed: Main analysis - when the health technology is included in Annex 1 of the PDL and 75% reimbursement; Additional scenario 1 - when the health technology is included in Annex 1 of the PDL and 100% reimbursement; Additional scenario 2 - when the health technology is included in Annex 2 of the PDL and 100% reimbursement by the NHIF.

The results of the budget impact analysis show that, in all three developed scenarios, the inclusion of Vabysmo in the Positive Drug List will result in savings over the entire analysis period, not taking into account risk-sharing agreements and patient access schemes.

Conclusion

The demonstrated similar therapeutic efficacy and safety profile of faricimab compared to aflibercept and brolucizumab, as well as the improved duration of treatment effect of faricimab, has the potential to significantly reduce treatment burden for patients and their caregivers, as well as allow more efficient use of health resources and a long-term decrease in costs to the health

system due to fewer injections and examinations. The results of the budget impact analysis show that under all three health technology reimbursement scenarios, the inclusion of Vabysmo on the Positive Drug List will result in savings to the paying institution over the 5-year analysis period.