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

HEALTH TECHNOLOGY ASSESSMENT

Roteas
15 mg film-coated tablet x 10
30 mg film-coated tablet x 30
60 mg film-coated tablet x 30
edoxaban

Therapeutic indication(s)	Indicated in prevention of stroke and systemic embolism in adult patients with nonvalvular atrial fibrillation (NVAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack (TIA).
Start/end date of procedure	31.03.2020 – 30.09.2020
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 Roteas

Health problem

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias and hence one of the most common causes of stroke, heart failure (HF), sudden cardiac death (SCD) and cardiovascular morbidity in the world. Atrial fibrillation is characterized by disorganized atrial depolarization without concomitant effective atrial contraction. The therapeutic strategy in patients with AF includes the use of treatment regimens with prognostic significance (anticoagulation and treatment of various cardiovascular clinical conditions), as well as methods directed at the benefit in terms of symptoms (ventricular rate control, rhythm control, quality of life optimization). Anticoagulation (unfractionated heparin, low molecular weight heparin, vit. K antagonists, novel oral anticoagulants [NOAC]) plays a major role in terms of the prognostic benefit in patients with AF, since the main complication of arrhythmia - stroke, is a major cause of deterioration of quality and duration of life.

AF is a common arrhythmia, reported in about 1% of subjects over 60 years of age and in 5% of subjects over 69 years. History of congestive heart failure (CHF), presence of valvular heart disease, stroke, increased volume of the left atrium (LA), abnormal mitral or aortic valve function, long-term systemic hypertension, old age are the main independent factors for the occurrence of AF. AF can be intermittent or permanent (chronic), but regardless of its manifestation, this arrhythmia predisposes to stroke.

AF symptoms are determined by multiple factors. Patients with AF may be completely asymptomatic (12% -25%) or have symptoms of pulmonary congestion. Patients complain of palpitations (42% -55%), asthenia (15% -20%), dyspnea (24% -49%). In addition to hemodynamic abnormalities, the other most common and most disabling complication is the occurrence of systemic embolization. The highest frequency of embolization is seen in patients with the so-called nonvalvular AF. The risk of cerebral embolization is 5 to 7 times higher in patients with non-valvular AF compared to individuals without AF. Over 20 - 25% of ischemic strokes are due to cardiogenic emboli.

Risk factors that predict the occurrence of embolism in patients with non-valvular AF are: history of previous stroke or transient ischemic attack, diabetes mellitus, history of hypertension and older age.

The annual incidence of stroke in patients without anticoagulant treatment in five large clinical trials was about 4.5%, but decreased to 1.4% in patients treated with a vit. K

antagonist. The use of aspirin 325 mg/day also reduces the risk of occurrence of stroke by 44%.

The main goal in the treatment of AF remains reduction of the risk of thromboembolism and symptom control.

Roteas with INN edoxaban, is a medicinal product for oral use, administered once daily in patients with AF for the prevention of stroke and systemic embolism. It is an anticoagulant that directly inhibits factor Xa, a key component in the formation of blood clots, and belongs to the group of NOAC, which are preferred in a large proportion of patients for the prevention of ischemic stroke in patients with AF. NOAC have an advantage over vit. K antagonists due to confirmed lower frequency of bleeding and especially of intracranial hemorrhage.

Epidemiological data

The incidence of the disease in the general population is estimated between 0.5% and 1%. Over the last decade the number of patients with AF has increased significantly, which affects the number of hospitalizations, emergency calls, the burden of outpatient physician visits. The average increase in the incidence of AF-related complications in Europe has doubled in the last 5-6 years.

Efficacy data

The efficacy and safety of Roteas (edoxaban) health technology has been evaluated in several clinical trials, the main one being the **ENGAGE-AF-TIMI 48** trial. The study was randomized, double-blind, comparing two models of anticoagulation - with warfarin and edoxaban in 21,105 patients with AF of moderate/high risk and mean duration of 2.8 years. The primary efficacy endpoint was stroke or systemic embolism. The study population was randomized to treatment with high (60 mg) and low dose (30 mg) edoxaban or warfarin. During the treatment period each of the two edoxaban dosing regimens were tested for non-inferiority. The main safety endpoint is assessment of the frequency of bleeding. The conclusion of the investigators is that a single daily dose of edoxaban (30 mg and 60 mg) demonstrated non-inferiority with regard to the prevention of stroke or systemic embolism in comparison with the vit. K antagonist warfarin. At the same time, the use of edoxaban demonstrates a lower rate of bleeding and cardiovascular-related mortality.

ENSURE-AF clinical trial evaluated the safety and efficacy of edoxaban vs. warfarin in patients with nonvalvular AF treated with electrocardioversion and anticoagulation. The study is one of the largest clinical trials in the field of anticoagulation in patients eligible for electrocardioversion, which cinfirms the benefit and safety of using NOAC in such a clinical situation.

ENTRUST-AF-PCI study evaluated edoxaban/clopidogrel compared to vit. K antagonist/dual antiplatelet therapy for patients with AF, undergoing coronary artery stenting. The main primary outcomes - major or clinically manifested minor bleeding at 12 months of follow-up occurred in 17% of patients on treatment with edoxaban and in 20% of patients in the vitamin K antagonist group. Secondary endpoint follow-up (CVD, myocardial infarction, stroke, systemic embolism, definite stent thrombosis) shows 7% event rate in Roteas (edoxaban) group vs. 6% for vitamin K antagonist group.

ESC-FA study evaluated the efficacy and safety of antithrombotic agents for stroke prevention in patients with nonvalvular AF in the real world practice. The study is population-based, retrospective and observational. The results show a greater benefit of vitamin K antagonists for prevention of stroke and mortality compared to patients without such treatment, without an increase in the frequency of bleeding complications. The application of NOAC shows the greatest benefit in terms of the lower incidence of hemorrhagic events (equal results between the individual NOAC).

ELIMINATE - AF study tracks the results of continuous treatment with edoxaban vs. vitamin K antagonists in patients who are to undergo ablation treatment for AF. The study was multicenter, randomized, open with parallel groups. The objective is to evaluate the safety and efficacy of edoxaban administered once daily in doses of 60 and 30 mg vs. vitamin K antagonists. The primary endpoint (major bleeding) was observed in 0.3% of edoxaban group and in 2% of vitamin K antagonists group. In the group of patients with AF ablation, the primary endpoint was reported in 2.7% (edoxaban treatment group) and in 1.7% of patients treated with vit. K antagonists. Cerebral microembolism was detected in 13.8% of patients on edoxaban treatment and in 9.6% of patients in the vitamin K antagonists group.

ETNA-AF-EUROPE was a multicenter and observational study, conducted in 10 European countries. Data on edoxaban treatment in routine clinical practice were evaluated in patients with AF. A history of bleeding has been documented more frequently in patients receiving the low dose of edoxaban compared to those treated with the higher dose. The study confirms the tendency of the real practice the lower dose of the medicinal product to be used much more frequently.

A meta-analysis of randomized trials to evaluate and compare efficacy and safety of NOAC compared with warfarin in patients with AF uses data from 71,683 participants in four clinical trials. The assessed outcomes were stroke, systemic embolism, ischemic stroke, hemorrhagic stroke, all-cause mortality, myocardial infarction, major bleeding, intracranial haemorrhage and gastrointestinal bleeding. NOAC were used in 42,411 participants and 29,272 received

warfarin. NOAC significantly reduced the incidence of stroke and systemic embolism by 19% compared with warfarin, the main component being the reduction of hemorrhagic stroke. NOAC also significantly reduced all-cause mortality, as well as the frequency of intracranial hemorrhage, while on the other hand the frequency of gastrointestinal bleeding increased. A greater relative decrease of major bleeding was also observed in patients treated with NOAC, especially when the time in the therapeutic range for warfarin is below 66% compared to the group in which this time is above 66%. Low-dose NOAC have a much more favorable profile in terms of bleeding, but at the same time lead to a significantly higher incidence of strokes.

A meta-analysis assesses the importance of NOAC in adult patients with AF. Compared are populations of large phase 3 clinical trials with the four major NOAC. Compared are NOAC with vit. K antagonists used in a group over 75 years of age with AF. NOAC have been found to lead to a significant 30% reduction in risk in adults over 75 years compared to adults on warfarin treatment without heterogeneity in studies. No similar trend as well as difference between NOAC and vit. K antagonists was observed in younger patients under 75 years of age. Regarding the risk of major bleeding in adults, the overall comparative risk of NOAC does not differ significantly from the risk of vit. K antagonists.

Safety data

The major indicator of safety is the appearance of a bleeding complication of varying severity (intracranial haemorrhage, haemorrhagic stroke, major bleeding, life-threatening bleeding, clinically manifested minor bleeding). The annual frequency of major bleeding was 3.43% in patients treated with warfarin, 2.75% in patients on high-dose endoxaban and 1.61% in patients treated with the 30 mg dose. The review of side effects, as well as the assessment of bleeding and other adverse events during edoxaban treatment indicates that the health technology has fewer adverse effects compared to warfarin.

Data on comparators

Edoxaban health technology, as a representative of the NOAC, has warfarin and other non-vitamin K oral anticoagulants as alternatives. The alternatives of Roteas (edoxaban), which belong to the NOAC group, are dabigatran, rivaroxaban and apixaban.

Pharmacoeconomic indicators

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

Edoxaban health technology assessments have been completed for the healthcare systems of the UK, France, Germany, Sweden and Canada, with these institutions recommending its reimbursement.

Applied analysis

Cost-utility analysis (CUA) has been applied, with health benefit outcome measure quality adjusted life years (QALY). The perspective of the analysis is that of the payer – the National Health Insurance Fund (NHIF). The selected time horizon is 30 years. Health benefits and costs are discounted with an annual discount factor of 3.5%.

Comparators are vit. K antagonists (warfarin, sintrom), being the first anticoagulants used in patients with AF. Warfarin, as the main alternative to edoxaban, was excluded as a therapeutic alternative from the analysis because it is not listed in the PDL. Comparators are also NOAC, including a direct thrombin inhibitor - dabigatran, and factor Xa inhibitors - apixaban, rivaroxaban.

A Markov cohort model consisting of 18 health conditions was applied. Health conditions are related to the clinical outcomes considered to have constant impact on patients and assumed to have both initial and long - term impact on costs, quality of life and mortality. The health conditions associated with these events are further divided in:

- An initial health condition, which takes into account costs and quality of life associated with the acute event, with mortality rate applied to the case;

- A long-term health condition, in which costs of events, values for quality of life and mortality are applied at each cycle.

The applied modeling with included data for QALY and individual health conditions, uses the ENGAGE AF-TIMI 48 clinical trial and network metaanalysis as sources.

The results of the cost-benefit analysis indicate that apixaban therapy is broadly dominated by other therapeutic alternatives. Edoxaban is a dominated therapy by dabigatran 110 mg and dabigatran 150 mg. Compared with rivaroxaban therapy, edoxaban is the dominant therapy, demonstrating higher health benefits and lower cost of therapy.

Probabilistic and one-way sensitivity analysis was performed. The results of the sensitivity analysis confirm the results of the main analysis, except for dabigatran 110 mg therapy.
Subgroup analysis has not been applied.

Costs of the assessed health technology

The following groups of costs are included in the analysis:
- Edoxaban medication.
- Comparator medication.

Budget impact analysis

The budget impact analysis was conducted from the point of view of the payer - NHIF, the time horizon is 5 years. The estimated number of patients eligible for treatment with Roteas in the first year is 1,661, increasing to 7,606 in the fifth year. Sensitivity analysis using a tornado diagram is attached. The biggest influence on the budget pertains to change in the cost of edoxaban therapy and the cost of therapy with alternatives. The reimbursement of the new health technology by the NHIF will lead to an increase in costs for the paying institution, not taking into account risk-sharing agreements and patient access schemes.

Conclusion

Edoxaban has no demonstrated clinical benefits compared to other NOAC, with degree of added benefit being negligible in terms of results for disabling stroke, clinically significant bleeding, serious adverse events and composite endpoint for stroke, systemic embolism, major bleeding or all-cause mortality. The cost-benefit analysis shows that the therapy with edoxaban is cost-effective compared to rivaroxaban therapy, demonstrating higher health benefits and lower treatment costs. After reimbursement of health Roteas technology for the prevention of stroke and systemic embolism in adults patients with nonvalvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, previous stroke or transient ischemic attack (TIA), it is expected that there will be added expenditure for the paying institution NHIF, which gradually increases through the fifth year without taking into account risk - sharing agreements and patient access schemes.