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)	Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and for the prevention of recurrent DVT and PE in adults.
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

Venous thromboembolism (VTE) is the third most common cardiovascular disease after myocardial infarction and stroke. VTE denotes both deep vein thrombosis (DVT), pulmonary embolism (PE) and the combination of the two conditions. The disease is associated with high morbidity and mortality. Predisposing factors for disease occurrence are fracture of the lower limbs, hospitalization for heart failure symptoms (HF), atrial fibrillation/flutter (AF/F), hip or knee joint replacement, major trauma, myocardial infarction (within 3 months), prior VTE, spinal cord damage.

In 50% of the cases the disease is asymptomatic, and in another 20-30% - oligosymptomatic. The modern diagnostic strategy integrates clinical findings with various diagnostic techniques. Despite advances in technology, quite frequently (over 50% of patients) a limited PE remains undetected ante-mortem.

A key element of the treatment of acute PE is anticoagulant therapy to prevent early death and recurrent symptomatic or fatal relapses of the disease. Classical first step regimens depending on the severity of PE include the use of parenteral anticoagulation - thrombolytics, unfractionated heparin and/or low molecular weight heparins, vitamin K-antagonists.

Efficacy data

Hokusai -VTE study is an international, randomized, double-blind, non-inferiority study that evaluated the effectiveness and safety of edoxaban as alternative to warfarin (a vitamin K antagonist). An initial treatment with heparin, followed by edoxaban or warfarin for acute symptomatic VTE or for prevention of symptomatic recurrent VTE were compared. The results show that in patients with PE and right ventricular dysfunction, the incidence of recurrent VTE is 3.3% in the Roteas/edoxaban treatment group and 6.2% of patients on warfarin therapy. Treatment with Roteas (edoxaban) or warfarin lasts at least 3 months and is extended to a maximum of 12 months. The treatment duration is determined by the risk of recurrence of VTE, the risk of bleeding and patient preferences. For both groups the average treatment duration was 8.5 months. Non-inferiority of edoxaban as compared to warfarin was demonstrated in terms of efficacy and safety. It was noted that there is a lower incidence of intracranial hemorrhage in patients in edoxaban group, which brings potential benefits. Edoxaban has a convenient once daily dosing and requires a single annual examination of the renal function.

eTRIS study (a rindomized, open-label, multicenter study of the efficacy and safety of edoxaban monotherapy vs. LMWH/warfarin in patients with symptomatic deep vein thrombosis - Edoxaban Thrombus Reduction Imaging Study) is an open multicenter study with a primary endpoint - the relative changes derived from nuclear magnetic resonance venogram used to quantify thrombus volume from the time of inclusion in the study through 14-21 days of treatment. The primary safety outcome is defined as large or clinically manifested minor bleeding. The results show that the average relative change in thrombus volume from onset to day 14-21 is identical for the two groups of patients treated with Roteas (edoxaban) or with LMWH/warfarin. Also, the proportion of patients with positive dynamics in thrombus volume and with an improvement in the thrombosis load is the same for both groups. Regarding the incidence of recurrent thromboembolism as well as the incidence of clinically manifested minor bleeding, there is no statistically significant difference between the two groups of patients. There were no cases of major bleeding during the study period.

A network meta-analysis includes 17 randomized acute (26,860 studies patients) or prolonged (9 328 patients) treatment studies, with the majority of patients (a total of 36,188) having DVT and index event - PE. The network analysis has the following outcome objectives: recurrent VTE, recurrent DVT, recurrent PE, major bleeding, intracranial hemorrhage, stroke, all - cause mortality and cardiovascular death. The results show no statistical difference between repeated VTE and repeated DVT with respect to new oral anticoagulants (NOAC) vs. standard anticoagulant therapy. Also, no significant difference was found between the NOAC and standard therapy regarding the incidence of major bleeding, intracranial hemorrhage, all-cause mortality and cardiovascular mortality.

Hokusai VTE Cancer Investigators is an open, designed as non-inferiority, randomized study with a primary endpoint repeated VTE or major bleeding within 12 months after randomization, regardless of individual duration of treatment. The results show that the primary endpoint for complications occurred in 67 patients in the edoxaban group (12.8%) and in 71 patients (13.5%) in the dalteparin group. Data show non-inferiority of Roteas (edoxaban) versus dalteparin. Recurrent VTE occurred in 41 patients treated with edoxaban (7.9%) and in 59 patients from the deltaparin (11.3%). Major bleeding occured in 6.9% of patients in the Roteas (edoxaban) group compared to 4.1% in the dalteparin group.

New clinical trials with various NOAC provide additional data on the treatment options with NOAC in patients with cancer and DVT. Although NOAC treatment is associated with a lower recurrence rate than VTE and with a comparable incidence of major bleeding versus LMWH/warfarin treatment, some practical considerations may limit the use of the NOAC. In conclusion, the presented results of the treatment with NOAC in patients with cancer show that edoxaban, rivaroxaban, apixaban and dabigatran are equally or even more effective than

deltaparin/LMWH/warfarin for the prevention of VTE in cancer patients. At the same time, edoxaban and rivaroxaban carry a higher risk of major bleeding in the same patients, especially in patients with gastrointestinal cancer. The association of gastrointestinal carcinoma and bleeding from the upper gastrointestinal tract in patients treated with edoxaban may be due to high concentrations of edoxaban in the gastrointestinal lumen.

Safety data

The primary complication and a measure of safety is the appearance of bleeding of varying severity (major or clinically manifested minor bleeding). The most common adverse drug reactions associated with bleeding are (skin) soft tissue haemorrhage, epistaxis, vaginal hemorrhages.

Other treatment-related adverse events are infections, gastrointestinal disorders, neurological disorders, disorders of the skin and subcutaneous tissues.

Data on comparators

The available therapeutic alternatives in Bulgaria for the treatment of acute VTE and prevention of recurrent VTE are vitamin K antagonists and medicinal products from the NOAC group (rivaroxaban, dabigatran, apixaban).

Pharmacoeconomic indicators

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

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

Applied analysis

Economic analyses of the cost-utility type were used (cost-utility analysis [CUA]), where health benefits for patients are measured as years of life with good quality gained (quality adjusted life years, QALY), and cost-minimization analysis (CMA) for comparative assessment of edoxaban health technology with equally efficacious comparators. The applied cost-minimization analysis is based on the described lack of significant differences in efficacy or safety between NOAC and edoxaban and the confirmed lack of difference in the occurrence of recurrent VTE between the four NOAC when the groups are stratified by age - over/under 75 years. The perspective of the analysis is that of the payer - National Health Insurance Fund (NHIF). The health benefits and costs are discounted with an annual discount

factor of 3.5%. Warfarin, as the main alternative to edoxaban is excluded as a comparator because it is not included in PDL.

A cost-minimization analysis was performed, according to which the inclusion of a therapeutic regimen with edoxaban in the national therapeutic practice will result in added cost as compared to dabigatran therapy and will lead to cost reduction compared to rivaroxaban and apixaban therapies.

According to the national strategy, it is agreed that anticoagulant treatment should continue for 3 months. Subgroup analysis is not applied.

Costs of the assessed health technology

The following groups of costs are included in the analysis:

- Edoxaban medication.
- Comparator medication.

During a hospital stay, a parenteral anticoagulant is to be administered first before switching to oral anticoagulant. The cost of treatment during hospital stay is included in the relevant clinical pathways (CP).

Budget impact analysis

The budget impact analysis was conducted from the point of view of the paying institution – the NHIF, for a time horizon of 5 years. The number of patients who will be treated with edoxaban in the first year is expected to be 201, rising to 1283 in the fifth year. The reimbursement of the new health technology will lead to a reduction of the costs for the payer NHIF with the total cost saved increasing with each year, without taking into account risk-sharing agreements and patient access schemes. A sensitivity analysis using a tornado diagram has been applied, which shows that the cost of the comparator treatment exerts the largest impact on the budget.

Conclusion

The administration of the health technology Roteas (edoxaban) in patients with VTE (DVT and PE) is non-inferior as compared to warfarin, and the efficacy and safety of Roteas (edoxaban) are comparable to other NOAC, indicated for the treatment/prevention of DVT/PE. The cost-minimization analysis indicates that edoxaban therapy will result in added cost compared to dabigatran therapy and will save costs compared to rivaroxaban and apixaban. On reimbursement of Roteas health technology for the treatment of DVT, PE and prevention of recurrent DVT and PE in adults, it is expected that savings will be realized for the payer compared to other therapeutic alternatives.