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

HEALTH TECHNOLOGY ASSESSMENT

Xarelto

2.5 mg film-coated tablets x 56

Rivaroxaban

Therapeutic indication(s)	Co-administered with acetylsalicylic acid (ASA), indicated for the prevention of atherothrombotic events in adult patients with coronary artery disease (CAD) or symptomatic peripheral artery disease (PAD) at high risk of ischaemic events.
Start/end date of procedure	23.03.2020 - 07.01.2021
Final decision	Rejects inclusion in Annex 1 of the Positive Drug List (PDL) for home treatment of diseases, paid for by the NHIF and in Annex 2 of the PDL for purchase from medical institutions with state and/or municipal participation and under Art. 5 of the Medical Establishments Act and payment by the NHIF beyond the cost of the rendered medical services.

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

Health problem

Atherosclerosis is a polyarterial disease with clinical manifestation depending on the vascular area where the critical narrowing occurs. The development of the atherosclerotic process is continuous and progressive, characterized by the occurence of inflammation, plaque formation in the intima of the vascular wall and as a consequence of all of these, activation of thrombotic processes. Atherothrombosis, defined as rupture of atherosclerotic plaque or plaque erosion with thrombosis, is a leading cause of death worldwide. Atherosclerosis is directly related to cardiovascular risk factors. The appearance of atherosclerotic changes and complications in the arteries of the lower extremities is associated mainly with smoking and diabetes. Atherosclerotic disease passes through several stages: asymptomatic period, subclinical atherosclerosis, plaque progression and acute vascular complications.

Frequently, the atherosclerotic arterial disease has no clinical manifestation for a long period of its development. This progressive condition during its asymptomatic period is characterized by endothelial dysfunction, low degree of inflammation, accumulation of lipids plaque formation in the intimate area of the vascular wall.

The therapeutic strategy in patients with high and very high cardiovascular risk provides for a treatment to normalize the lipid profile, control blood sugar in cases of diabetes mellitus, control blood pressure and in certain indications - antithrombotic treatment.

Epidemiological data

Atherosclerosis forms the underlying pathophysiology for the development of coronary artery disease, peripheral arterial disease and cerebrovascular carotid arterial disease.

The REACH registry (patients from Canada, France, Germany) shows that on average about 1/4 to 1/3 of the monitored patients (mean age 68 years) have atherosclerotic arterial disease affecting more than one vascular bed. The data indicate that 18%-35% have CAD and PAD and/or cerebrovascular disease, and 46%-68% of patients with PAD also have CAD and/or cerebrovascular disease.

According to data from the National Epidemiological Register on the prevalence of PAD, it is detected in 35.2%. Data on coronary heart disease indicate its presence in 16.6% of patients with PAD.

Efficacy data

Efficacy/safety assessment is based on the results of the following clinical trials:

ATLAS ACS 2-TIMI 51/Rivaroxaban in Patients with Recent Acute Coronary Syndrome, is a double-blind, placebo-controlled study of 15,526 patients with a new acute coronary artery disease syndrome (ACS) receiving Xarelto (rivaroxaban) 2.5 or 5 mg twice daily or placebo. The results show that rivaroxaban reduces the incidence of primary endpoint of efficacy compared with placebo, reduces mortality due to cardiovascular causes, as well as all-cause mortality. Compared to placebo, rivaroxaban significantly increased the incidence of major bleeding, unrelated to coronary bypass surgery and the incidence of intracranial hemorrhage. Stent thrombosis is more common in the rivaroxaban treatment group. The 2.5 mg dose of rivaroxaban in combination with acetylsalicylic acid and thienopyridines reduces the frequency of the primary efficacy endpoint compared to placebo, as well as the risk of cardiovascular death. Rivaroxaban 2.5 mg shows insignificant but permanent benefit in reducing the incidence of myocardial infarction (MI). At the same time the incidence of major bleeding unrelated to bypass surgery and bleeding that requires medical attention is significantly greater.

A comparison was made for the efficacy/safety of two doses of Xarelto (rivaroxaban) in patients with acute coronary syndrome whose results are based on data from ATLAS ACS 2-TIMI 51. The design of this analysis is aimed at two low doses rivaroxaban to be compared with placebo in terms of efficacy/safety. The data show greater benefit for cardiovascular mortality for patients with rivaroxaban 2.5 mg compared to those treated with 5 mg twice daily. There is no statistically significant difference between the two groups in terms of stroke and stent thrombosis.

COMPASS is a double-blind randomized study of 27,395 participants with stable atherosclerotic vascular disease who met the criteria for coronary artery disease, peripheral arterial disease, or a combination of both clinical conditions. In patients with stable atherosclerotic disease the combination rivaroxaban 2.5 mg twice daily and aspirin, the statistical risk of the combined endpoint (cardiovascular death, stroke, MI) is significantly lower compared to aspirin monotherapy.

A summary of results obtained from clinical trials in patients treated with xarelto (rivaroxaban) 2.5 mg twice daily and 100 mg aspirin or xarelto (rivaroxaban) alone or aspirin alone in high-risk groups with coronary heart disease and PAD, or both in terms of efficacy show that the efficacy of the combination is of greater benefit to the composite primary endpoint formulated as cardiovascular death, stroke or MI. The efficacy is also accompanied by a significantly increased risk of bleeding, assessed according to various international

criteria, and mainly a risk of major bleeding. The results of the studies show almost identical percentage for intracranial haemorrhage rate, with a 70% increased risk in the group of patients treated with xarelto (rivaroxaban) 2.5 mg twice daily and aspirin 100 mg, compared to the aspirin-only group. Cardiovascular mortality rate does not achieve a significant reduction when comparing the two main therapeutic groups.

Safety data

The mechanism of action of xarelto (rivaroxaban) and aspirin determines the nature of the most common treatment-associated complication, namely the occurrence of bleeding. The other components of rivaroxaban profile in terms of cardiovascular safety are based on data from several phase III clinical trials, namely hypotension, renal impairment, peripheral edema and others.

The COMPASS study identifies several parameters that are monitored for safety assessment (primary safety outcome) and are classified in the following way: fatal bleeding, symptomatic bleeding in a critical area or organ (intracranial bleeding, retroperitoneal bleeding, pericardial or intramuscular bleeding), bleeding in the area of surgical intervention that requires reoperation, bleeding that leads to hospitalization. The results of the study indicate that major bleeding occurs in the majority of patients enrolled in the study, treated with xarelto combined with aspirin versus aspirin alone. Most of the bleedings are localized in the gastrointestinal tract. The frequency of bleeding complications defined by ISTH criteria also show statistically greater reliability of the incidence in patients treated with the combination xarelto (rivaroxaban) with aspirin.

Data on comparators

The main alternatives to the health technology are anticoagulant and antiplatelet drugs.

Platelet inhibitors (as mono- or combination therapy) are the classic basic choice for the prevention of arterial thrombosis in patients with cardiovascular disease. Aspirin irreversibly inhibits cyclooxygenase 1 and prevents platelet-dependent thromboxane A2 formation. ADP inhibitors ($P2Y_{12}$ receptor blockers) include thienopyridines (clopidogrel and prasugrel) and cyclopentyltriazolopyramidine-type inhibitors (ticagrelor).

Pharmacoeconomic indicators

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

NICE, UK recommend the use of RIV + ASA in certain cases. TLV, Sweden gives a positive decision.

Applied analysis

Cost-benefit analysis and additional cost-effectiveness analysis are attached with outcome measure the number of years of life gained (LYG). The perspective of the analysis is of the paying institution - NHIF. The time horizon is lifelong. All costs and results in the model are discounted by 3.5% on an annual basis. The presented economic analysis is based on Markov's model with 5 states - "no events", first main event, first follow-up event, second main event, second follow-up event and death. Acetylsalicylic acid was used as the main comparator (ASA). Ticagrelor and clopidogrel were also included in the analysis for the purpose of a maximum reflection of the clinical practice due to the wide variety of manifestations of the consequences of CAD and PAD. The results of the analysis show that the combination of rivaroxaban + ASA is associated with greater benefit, expressed as quality adjusted life years (QALY) and higher efficiency, expressed as years of life gained (LYG) for all alternatives in the analysis. Rivaroxaban + ASA is a cost-effective alternative in terms of QALY and LYG compared to clopidogrel. Ticagrelor is an alternative with a high ICER value. A deterministic analysis of the sensitivity in which 15 parameters are varied was conducted.

Analysis of subgroups

Not applicable.

Cost of the assessed health technology

Cost for drug therapy with alternatives and cost of treatment of the consequences of CAD and PAD are attached.

Budget impact analysis

The analysis of the budget impact was conducted from the perspective of the payer institution – the NHIF, the time horizon is 5 years. The estimated number of patients eligible for treatment with the assessed technology is 1500 in the first year, reaching 1950 in the fifth year. The results of the analysis show that the introduction of the new technology for CAD and PAD will have a positive impact on the budget, not taking into account risk - sharing agreements and access schemes for patients.

Conclusion

The results of the pharmacoeconomic analysis show that the combination of rivaroxaban + ASA is associated with a likely greater benefit, expressed as quality-adjusted life years

(QALY) and higher efficacy, expressed as years of life gained (LYG), as compared to acetylsalicylic acid. The expected budget impact of the reimbursement of rivaroxaban for the treatment of CAD and PAD leads to an increase in the NHIF expenditure for the entire period of the analysis.