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

HEALTH TECHNOLOGY ASSESSMENT

Praxbind

2,5 g/50 ml solution for injection/infusion x 2 vials

Idarucizumab

Therapeutic indication(s)	Praxbind is a specific reversal agent for dabigatran and is indicated in adult patients treated with Pradaxa (dabigatran etexilate) when rapid reversal of its anticoagulant effects is required: • For emergency surgery/urgent procedures; • In life-threatening or uncontrolled bleeding.
Start/end date of procedure	13.04.2020 – 20.11.2020
Final decision	Inclusion in Annex 2 of the Positive Drug List (PDL) for purchase by medical establishments with state and/or municipal participation and under Art. 5 of the Medical Establishments. Rejects inclusion in Annex 1 of the PDL for home treatment of diseases, paid by the NHIF.

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

Health problem

In various clinical situations, anticoagulation is crucial in the treatment and prevention of thrombosis and thromboembolic complications. The rate of occurrence of the common conditions, indicated for anticoagulant treatment, such as atrial fibrillation (AF), is steadily increasing due to an aging population, an increase in the burden of chronic diseases, and the introduction of new, more accurate diagnostic methods. At the same time, the number of patients at risk of bleeding with a significant increase in mortality and morbidity is increasing, including due to the rapid entry into clinical practice of NOACs (non-vitamin K-antagonists oral anticoagulants). NOACs have proven to be a very successful alternative to conventional anticoagulants, including vitamin K antagonists. NOACs are being notably rapidly introduced in the treatment of patients with deep vein thrombosis (DVT) with/without pulmonary embolism (PE) and especially in patients with atrial fibrillation, for active treatment and prevention of relapses and new thromboembolic complications. The favorable benefit/risk ratio profile of NOACs compared to vitamin K antagonists is associated with a lower incidence of any type of bleeding and in particular intracranial hemorrhage. Despite their confirmed more beneficial effect on bleeding, in some patients they can also cause bleeding complications of varying severity. The occurrence of heavy bleeding or its prevention requires the use of specific anticoagulant-neutralizing drugs that have the ability to effectively, quickly and safely restore hemostasis. Praxbind (idarucizumab) represents an important development in terms of the management of a delayed initiation of treatment in cases of bleeding or emergency surgery in patients treated with Pradaxa (dabigatran). Clinical trials with Praxbind (idarucizumab) have shown that fatalities (including systemic embolic complications) can be successfully overcome by using existing anticoagulant options (using frozen plasma or prothrombin concentrate or recombinant coagulation factors).

Epidemiological data

In clinical trials with this group of medicinal products, an average bleeding rate of 2% (at both doses of Pradaxa used) per year was observed.

Efficacy data

The clinical program to evaluate the efficacy and safety of Praxbind (idarucizumab) focuses on the evidence for the pharmacological elimination of the anticoagulant effect of Pradaxa (dabigatran), a member of the NOACs group. The program is based on several clinical trials in patients treated with Pradaxa, in line with generally accepted indications.

The main clinical study to evaluate the effectiveness/safety of Praxbind (idarucizumab) was RE-VERSE AD - *Idarucizumab for Dabigatran Reversal*, which included 2 groups of patients treated with pradaxa (dabigatran). The conclusion of the study is that Praxbind (idarucizumab) rapidly and completely reversibly influenced the anticoagulant effect of Pradaxa (dabigatran) in 88% to 98% of patients. No serious safety events were reported.

The ongoing REVERSE AD study is *Idarucizumab for Dabigatran Reversal - full Cohort Analysis.* 100% elimination of the anticoagulant effect of Pradaxa has been reported. In group A, 45% of patients had gastrointestinal bleeding and 32.6% had intracranial hemorrhage. The median time to cessation of bleeding after administration of idarucizumab was 2.5 hours. In group B, the average time to start a specified procedure is 1.6 hours. Peripheral hemostasis was assessed as normalized in 93.4% of patients, slightly abnormal hemostasis in 5.1% and moderately abnormal in 1.5%. On day 90, thrombotic complications were reported in 6.3% of patients in group A and 7.4% in group B.

A study with data from the global patients cohort of REVERSE AD, included in the study due to gastrointestinal bleeding - *Idarucizumab for Dabigatran Reversal in the Management of Patients With Gastrointestinal Bleeding, Circulation*, evaluated the efficacy and safety of Praxbind (idarucizumab) and its benefit/risk profile during the administration of Pradaxa (dabigatran) used to treat DVT and non-valvular AF. The investigators concluded that Praxbind achieved a rapid and complete reversibility of the anticoagulant effect of Pradaxa (dabigatran) in virtually all observed patients who presented with gastrointestinal bleeding.

The *Dabigatran Reversal With Idarucizumab in Patients With Renal Impairment* study aimed to determine the degree of reversibility of the anticoagulant effect of Pradaxa (dabigatran) and to monitor the clinical outcomes in non-dialysis patients with impaired renal function. 503 patients from RE-VERSE AD were evaluated in whom a change in the effect of the drug with respect to renal function was monitored. The results showed that Praxbind (idarucizumab) fully restored haemostasis in 98% of patients, regardless of renal function. The authors conclude that, regardless of renal function, Praxbind is sufficiently effective in terms of the inducible level of reversibility of anticoagulation.

The disease morbidity, evaluated in clinical trials with Praxbind (idarucizumab) was generally related to data on the incidence of bleeding complications and residual medical problems. The administration of an anticoagulation neutralizing agent results in significant reduction of bleeding-related morbidity. In this regard, it was important to evaluate the effect of Praxbind (idarucizumab) on the frequency of complete elimination of the anticoagulant effect of Pradaxa (dabigatran). The complete reversibility of the effect of Pradaxa was 100% for a period of 4 hours for all dose groups, complete reversibility assessed by dilution thrombin time (dTT) was found in 100% of patients, and in all but one monitored patient (97,1%), when

using ethacrine clotting time (ECT). The mean time to reversibility of anticoagulation after administration of Praxbind (idarucizumab) is 5-6 minutes, with a mean duration of reversibility of 72 hours.

Safety data

The most common side effects are headache - 8.4%, skin inflammation - 2.8%, nasopharyngitis - 1.9%, fatigue - 1%, migraine - 1.9%, abdominal pain - 0.9%.

Data on comparators

Praxbind (idarucizumab) is the only neutralizing agent of the anticoagulant effect of Pradaxa (dabigatran). The introduction of the health technology is essential for the safe use of Pradaxa as a representative of the NOACs group.

Pharmacoeconomic indicators

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

The health technology has been evaluated by the following agencies: NICE (UK), HAS (France), SCM (Scotland), AETS (Spain), Norway, Portugal, CADTH (Canada), with all of them recommending reimbursement of the medicinal product.

Applied analysis

Idarucizumab is a medicine without an existing alternative. To evaluate idarucizumab, a comparative analysis of the cost of treatment with idarucizumab and alternative approaches is presented. Cost-effectiveness analysis was also performed with independent alternatives, the measure of outcome being the percentage of patients who survived after taking idarucizumab and the prothrombin complex as an antidote to dabigatran. The perspective of the analysis is that of the medical establishments. The single costs of controlling life-threatening or uncontrolled bleeding in emergency surgery/emergency procedures have been compared. As comparator, the clinical practice of life-threatening or uncontrolled bleeding management and emergency surgery/emergency procedures has been selected. The following therapeutic approaches have been used:

- Administration of prothrombin complex concentrate
- Administration of fresh frozen plasma
- Transfusion of human fibrinogen concentrate

The evaluated health technology idarucizumab is a specific antidote to dabigatran with proven efficacy that provides complete neutralization of the anticoagulant effect of dabigatran (dTT: 98.7%; ECT: 82.2%; aPTT: 92.5%) within 4 hours after the application. None of the other

therapeutic approaches is specific to patients treated with dabigatran. Discounting is not applied, as only single administration costs are estimated. Modelling is also not applied.

The additional cost-effectiveness analysis shows that ICER was below the break-even point, making idarucizumab cost-effective.

Costs of the assessed health technology

Included are costs of Praxbind and of the comparators, frozen plasma, average cost of prothrombin complex, average cost of fibrinogen concentrate.

Budget impact analysis

The budget impact analysis has been prepared from the point of view of the medical establishments. The time horizon is 5 years. The estimated number of patients is 30 in the first year, reaching 40 in the fifth year. The results of the analysis show that the introduction of the new technology has a positive impact on the medical institutions' budget.

Conclusion

Praxbind (idarucizumab) is an alternative-free medicine, a specific antidote to dabigatran. It is characterized by very good clinical outcomes and low mortality. Rapid neutralization of the anticoagulant effect is needed in many situations, including emergency operations/procedures, required in acute conditions or injuries. Idarucizumab is cost-effective with respect to the healthcare system in Bulgaria and its payment with public resources is associated with a positive budget impact.