Conitec

Recomendation report

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Dabigatran for prevention of stroke in patients over 60 years with non-valvular atrial fibrillation who are unable to remain in the therapeutic range of international normalized ratio with warfarin and idarucizumab for reversing the anticoagulant effect of dabigatran

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Technologies: Dabigatran etexilate (Pradaxa®) and idarucizumab (Praxbind®).

Indications: Dabigatran etexilate is indicated for the prevention of stroke, systemic embolism and reduction of risk of death in patients with Non-Valvular Atrial Fibrillation (NVAF). Idarucizumab is a specific reversal agent for dabigatran and it is indicated for patients treated with dabigatran etexilate when rapid reversal of its anticoagulant effects is required (emergency surgery/urgent procedures; and in life-threatening or uncontrolled bleeding).

Applicant: Boehringer-Ingelheim.

Background: Atrial Fibrillation (AF), a chronic condition, is a disorder of the electrical conduction system of the atria (upper heart chambers) that leads to a fast and irregular heart rhythm and a poor contraction. Symptoms include palpitations, dyspnoea and dizziness. It has an important impact on the quality of life of patients due to the clinical consequences, mainly related to thromboembolic events, especially stroke. Management of AF is based on improving symptoms, through heart rate or rhythm control, and preventing thromboembolic events (stroke). Treatment may include drugs such as antiplatelet agents, acetylsalicylic acid, vitamin K antagonists, especially the coumarin derivative warfarin, and new oral anticoagulants (e.g., dabigatran), as well as cardioversion procedures, catheter ablation, cardiac monitoring, among others.

Research questions: I) Is dabigatran effective, safe and cost-effective in patients with NVAF, including those over 60 years and who are unable to remain in the therapeutic range of international normalized ratio (INR) with warfarin? **II)** Is idarucizumab safe and cost-effective for the reversal of the anticoagulant effect of dabigatran?

Scientific evidence: The systematic review retrieved ten reports (three reports on dabigatran and seven on idarucizumab). For dabigatran it was included one Randomized Controlled Trial (RCT) with two reports, and one retrospective cohort study; and for idarucizumab, four retrospective cohort studies, and two prospective cohort studies. The studies on dabigatran evaluated the following outcomes: stroke or systemic embolism, stroke (haemorrhagic, ischemic, without disability and with disability), myocardial infarction, pulmonary embolism, hospitalization, mortality from vascular or other causes, bleeding, and adverse events. The RCT, which compared dabigatran 110 mg and 150 mg versus warfarin, was assessed using the Cochrane risk of bias tool (RoB 1.0), and most domains were judged to be at low risk of bias, but a high risk of bias was detected in the selective outcome reporting domain. The cohort study on dabigatran, Chan et al. (2016), was considered as high quality by the Newcastle-Ottawa Scale (NOS). For the RCT primary outcome of stroke or systemic embolism, treatment with dabigatran 110 mg and 150 mg was not inferior to warfarin, and dabigatran 150 mg was superior to warfarin (it reduced by 34% the risk of stroke/systemic embolism versus warfarin). Evidence was classified as low by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for this critical outcome. The studies on idarucizumab evaluated the following outcomes: dabigatran reversal, dabigatran and idarucizumab concentrations, bleeding, mortality, thrombotic events, appropriateness of idarucizumab usage, and adverse events. About six studies evaluated idarucizumab; most of them were considered as low quality by NOS, but one study was considered high quality (Singh et al., 2019). Pollack et al. (2017), evaluating dabigatran reversal as an intermediate outcome, showed a percentage of 100% of the patients achieving anticoagulant reversal; however, the set of studies showed a variation between 67% and 100% for the dabigatran reversal outcome. It is noteworthy to mention that this outcome was considered not important, and the quality of evidence was very low by the GRADE system. For mortality, the most relevant outcome, rates ranged from 6.3% to 31% among studies. Moreover, Singh et al. (2019) demonstrated that patients with intracerebral haemorrhage treated with idarucizumab compared with those not treated with idarucizumab had a higher rate of mortality ($p = 0.0011$), but only the unadjusted analysis was presented. However, the results regarding gastrointestinal bleeding were not statistically significant among patients treated with idarucizumab compared with those not treated with idarucizumab (adjusted odds ratio [OR]: 1.33; 95% confidence interval [CI]: 0.51-3.45). This outcome was considered critical, but the quality of evidence was rated as very low by the GRADE

system. Overall, the evidence for dabigatran was moderate and the outcomes were classified as critical by the GRADE system, and the evidence for idarucizumab was very low with two critical outcomes and one not important.

Economic evaluation: A cost-effectiveness analysis was conducted for the use of sequential dose dabigatran (150 mg in patients aged < 80 years and 110 mg in patients aged ≥ 80 years) with idarucizumab versus warfarin 5 mg with blood products for control of bleeding, over a lifetime horizon. The estimated incremental Cost-Effectiveness Ratio (ICER) was BRL 12,670.34 per QALY (Quality Adjusted Life Years) gained and BRL 11,256.17 per life-year gained. In the deterministic sensitivity analysis, the variable that most affected the model was to consider that patients aged 80 years would enter the cohort (ICER of BRL 30,215.26/QALY), and the one that reduced the ICER was to increase the INR monitoring cost (BRL 3,456.95/QALY).

Budget impact analysis: In the base case, the budget impact analysis showed incremental costs of approximately BRL 692 million after five years. Sensitivity analyses, considering alternative scenarios and deterministic analysis, ranged from savings of BRL 151 thousand to an incremental cost of approximately BRL 892 million.

International recommendations: The National Institute for Health and Care Excellence (NICE), Scottish Medicines Consortium (SMC), All Wales Medicines Strategy Group (AWMSG), Canadian Agency for Drugs and Technologies in Health (CADTH), National Medicines and Products Authority of Health, IP (INFARMED), Pharmaceutical Management Agency (PHARMAC), and Pharmaceutical Benefits Advisory Committee (PBAC) recommended the treatment with dabigatran in patients with NVAF. NICE, AWMSG, and CADTH have not evaluated idarucizumab in their country's context, but SMC, PHARMAC, PBAC, and INFARMED recommended its incorporation.

Technology horizon scanning: The following drugs were identified: apixaban and edoxaban for patients with NVAF, and a reversal agent for apixaban and rivaroxaban (andexanet alfa).

Considerations: Based on the RCT, for the outcome of stroke/systemic embolism, non-inferiority of both doses of dabigatran was established and dabigatran 150 mg was shown to be superior compared with warfarin. Most RoB 1.0 domains were judged to be at low risk of bias, but a high risk of bias was detected in the selective outcome reporting domain. This outcome was rated as low and critical by the GRADE system. Therefore, the results should be viewed with caution. In relation to the results of idarucizumab, most studies did not have a comparator group and were of low quality, and there was large heterogeneity in the intermediate outcomes assessed by the studies. Dabigatran reversal, an outcome considered not important in GRADE, showed an important variation. However, two studies compared patients treated and untreated with idarucizumab. For the mortality outcome, Barbe et al. (2020), with low methodological quality, demonstrated that there was no difference between the treatment groups. Singh et al. (2019), with high methodological quality, demonstrated that patients with intracerebral haemorrhage treated with idarucizumab compared with those not treated had a higher rate of mortality ($p<0.0011$), but there was no statistically significant difference in the results regarding gastrointestinal bleeding (adjusted OR: 1.33; 95% CI: 0.51-3.45). For the thrombotic event outcome, there was also no statistically significant difference in the study by Barber et al. (2020), but in Singh et al. (2019) there were fewer thrombotic events among the patients with intracerebral haemorrhage treated with idarucizumab compared with those not treated, but there were no differences regarding gastrointestinal bleeding between the groups. Consequently, data are conflicting and of low quality (NOS). Regarding the economic modelling, cost data was confusing and did not clearly explain the references used for cost composition of stroke events. Moreover, the use of alteplase in the model for patients with ischemic stroke was inadequate, and the applicant's analysis showed that its withdrawal worsened the ICER. In the probabilistic sensitivity analysis, the lack of variables and the type of probability distribution used resulted in uncertainties in the Monte Carlo Method (MCM). In the budget impact analysis, the deterministic analysis did not mitigate the uncertainties, because many variables were important to change the budget impact in the fifth year of incorporation, even with different scenarios. Therefore, the probabilistic analysis by MCM could have shown where most scenarios would be concentrated, as well as a tornado diagram for deterministic analysis would have been more appropriate than descriptive texts. Furthermore, alteplase should not have been considered in the budget

impact analysis. Finally, the unit costs of dabigatran 110 mg or 150 mg were 20-fold higher than the current costs of warfarin (BRL 2.01 and BRL 0.10, respectively).

Initial Recommendation: Conitec, at its 88th Ordinary Meeting, on July 7, 2020, decided that the subject matter should be made available in a public consultation with a preliminary recommendation against the incorporation of dabigatran for prevention of stroke in patients over 60 years with non-valvular atrial fibrillation who are unable to remain in the therapeutic range of international normalized ratio with warfarin, and idarucizumab for reversing the anticoagulant effect of dabigatran, in the scope of the Brazilian Public Health System - SUS. Among other factors, it was considered that, in relation to the last assessment of dabigatran conducted by Conitec in 2018, there was no reduction in the price of dabigatran, resulting in a high budget impact, and it is associated with a higher risk of bleeding.

Public consultation: The Public Consultation No. 29/2020 was held from July 27 to August 17, 2020. A total of 2,339 contributions were received, of which 1,534 (66%) were technical-scientific contributions, and 805 (34%) were experience or opinion contributions of patients, relatives, friends or caregivers of patients, health professionals or people interested in the subject. Regarding the 1,534 technical-scientific contributions, 1,490 (97%) were excluded because forms were addressing another issue, experience or opinion, or were not filled out properly, or lacked scientific evidence. Regarding the 805 experience or opinion contributions, 295 (37%) were excluded because forms were not filled out properly or completely, or were addressing another issue. After analysing the contributions received in the Public Consultation No. 29/2020, the members of Conitec's plenary session considered the following information: I) Boehringer-Ingelheim did not present a new price in the public consultation, so dabigatran continued to be 20-fold more expensive than warfarin, and a high incremental cost was indicated in the budget impact analysis; II) Changes were made in the risk of bias in the RE-LY study and in the quality of evidence in the GRADE system, but there were no changes in the results; III) New scientific evidence for idarucizumab was not presented; IV) Although some limitations in the economic model and budget impact analysis were partially mitigated, others remained, such as: use of alteplase, utilities not specific to the target population, no reference was presented regarding the rate of patients unable to remain in the therapeutic range of INR with warfarin, among others; V) The managed entry agreement presented by Boehringer-Ingelheim had many uncertainties associated with its implementation since not all centres would receive the donations of drugs or treat stroke episodes (Ordinance/GM [Minister's Office] No. 665, from April 12, 2012 - Brazilian Ministry of Health).

Final Recommendation: The Conitec's members present at the 90th Ordinary Meeting, on September 3, 2020, unanimously decided not to recommend the incorporation of dabigatran for prevention of stroke in patients over 60 years with non-valvular atrial fibrillation who are unable to remain in the therapeutic range of international normalized ratio with warfarin, and idarucizumab for reversing the anticoagulant effect of dabigatran. The Deliberation Record No. 554/2020 was signed.

Decision: Not to incorporate dabigatran for prevention of stroke in patients over 60 years with non-valvular atrial fibrillation who are unable to remain in the therapeutic range of international normalized ratio with warfarin, and idarucizumab for reversing the anticoagulant effect of dabigatran, in the scope of SUS, according to Ordinance No. 47, published in the Official Gazette of the Federal Executive No. 189, Section 1, page 861, on October 1, 2020.