HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
OPINION
22 JULY 2020

dabigatran
PRADAXA 75 mg hard capsules
PRADAXA 110 mg hard capsules
PRADAXA 150 mg hard capsules

Reevaluation

Key points

Favourable opinion for reimbursement in:

- Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery;
- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF), with one or more risk factors (for more details, see MA).

Clinical benefit now substantial (previously it was moderate) in the prevention of stroke and systemic embolism in patients with NVAF in view of the new data available, in particular the findings of observational studies, and maintenance of the clinical benefit in the prevention of venous thromboembolic events (VTE) in elective surgery in the absence of new data.

Role in the care pathway?

Prevention of stroke and systemic embolism in NVAF

The management of patients with AF includes two types of interventions, along with control of contributing factors (hypovolaemia, hypokalaemia, hypoxia, etc.) and comorbidities (hypertension, diabetes, heart failure, valve disease, etc.): control of heart rate and arrhythmia and prevention of thromboembolic events.

The prescription of oral anticoagulant therapy in patients with non-valvular atrial fibrillation (NVAF) for the prevention of thromboembolic events depends on the patient's thromboembolic risk, assessed by the CHA2DS2-VASc score**.**

When initiating anticoagulant therapy, the Committee considers that either a VKA or a DOAC may be prescribed as first-line treatment. The choice between these two anticoagulant classes should be made on a per case basis, taking into consideration a large number of criteria, in particular age, weight, renal function, predicted compliance and patient preference following appropriate information. All these anticoagulants can cause serious bleeding, in particular gastrointestinal bleeding. In contrast with DOACs, there is greater clinical experience with the use VKAs and it is possible to monitor the degree of anticoagulation obtained with the latter, particularly in the most vulnerable patients.

When a DOAC is envisaged (apixaban, dabigatran, edoxaban or rivaroxaban), the choice must take into account the characteristics of the patient concerned, along with the pharmacological profiles and prescription conditions specific to each medicinal product.

Role in the care pathway:

Considering:

- the availability of reassuring new clinical data concerning the safety profile of dabigatran in specific populations (in the event of catheter ablation or percutaneous coronary intervention (PCI) with stenting),
- the findings of observational studies, in particular the French ENGEL 2 study conducted based on health insurance scheme reimbursement data (SNIIRAM data) over the year 2013, now with a follow-up period of 3 years, which:
    - support the efficacy and bleeding safety profile of dabigatran 110 mg and 150 mg compared to VKAs,
    - did not reveal any new signal or additional risk of ACS between dabigatran and VKAs, thereby providing reassurance with respect to the doubts identified by the Committee following the results of the RE-LY pivotal study compared to warfarin, with a risk of ACS after a median follow-up of 2 years,
- that it is the only DOAC with a specific neutralising agent,
- and although the risk of myocardial infarction is still an important potential risk in the latest version of the RMP,

the Committee considers that PRADAXA (dabigatran) is now a first-line medicinal product in the same way as other DOACs for patients with NVAF.

Prevention of thromboembolic events in elective THR and TKR surgery

Following major orthopaedic surgery on the lower limb for total hip or total knee replacement, the thromboembolic risk is high and systematically requires pharmacological thromboprophylaxis, combined or otherwise with mechanical measures.

The anticoagulants recommended as first-line drugs for short-term thromboprophylaxis are low molecular weight heparins (non-inferiority of LMWH compared to UFH), fondaparinux 2.5 mg (ARIXTRA 2.5 mg) and DOACs. The treatment duration is a maximum of 9 to 14 days depending on the medicinal product (see SPC). An unfractionated heparin (UFH; morbidity and mortality data available for UFHs) is recommended in the event of severe renal impairment.
The continuation of thromboprophylaxis is recommended in the event of total hip replacement. Only certain UFHs, DOACs and two LMWHs (enoxaparin and dalteparin) are recommended for up to 35 to 38 days depending on the medicinal product (see SPC).

The prescription of enoxaparin or a direct-acting oral anticoagulant should be envisaged as a first-line approach. When a DOAC is envisaged, the choice must take into account the characteristics of the patient concerned, along with the pharmacological profiles and prescription conditions specific to each medicinal product.

Role in the care pathway:
In the absence of new clinical data and in view of the initial data already analysed by the Committee, the role of PRADAXA (dabigatran) is unchanged in this indication.
When the therapeutic strategy envisages the use of a DOAC, the decision to prescribe PRADAXA (dabigatran) should take into account the fact that:

- in the pivotal studies apixaban and rivaroxaban were more effective than enoxaparin for the endpoint VTE + death, with no increase in bleeding risk, and dabigatran was non-inferior to enoxaparin and without an advantage in terms of major bleeding,
- it is the DOAC most eliminated by the renal route and the only one to be contraindicated in severe renal impairment (creatinine clearance between 15 and 29 ml/min);
- that it is the only DOAC with a specific neutralising agent.

Special recommendations

Best practice recommendations

In line with its previous opinion, the Committee reiterates that non-compliance with the SPCs for oral anticoagulants exposes patients to an increased risk of thrombosis or bleeding. Observational studies had identified the existence of DOAC misuse in the population treated for non-valvular atrial fibrillation, in particular under-dosing and use in populations for whom this treatment is neither indicated nor recommended (CHA2DS2-VASC=0).

COMMITTEE'S CONCLUSIONS

Clinical benefit

Prevention of stroke and systemic embolism in NVAF

◗ Non-valvular atrial fibrillation is life-threatening for patients, either immediately or following complications (such as stroke) and significantly impairs quality of life.

◗ This is a preventive treatment, for which a specific neutralising agent exists.

◗ The efficacy/adverse effects ratio of dabigatran remains moderate: the RE-LY pivotal study versus warfarin was performed using an open-label design, making the expected assessment of the effect size uncertain (with a possible over-estimation of the effect in its favour). The advantages in terms of intracranial haemorrhage need to be examined in the light of the effects of dabigatran on gastrointestinal bleeding and the additional risk of acute coronary syndrome observed in the RE-LY pivotal study but not found in observational studies, in particular the French ENGEL 2 study, with follow-up of 3 years, as requested by the Committee. The other clinical data submitted are also reassuring in terms of the safety profile of dabigatran.

◗ There are therapeutic alternatives, including VKAs and the other three DOACs.

◗ Considering:
- the availability of reassuring new clinical data concerning the safety profile of dabigatran in specific populations (in the event of catheter ablation or percutaneous coronary intervention (PCI) with stenting),
- the findings of observational studies, in particular the French ENGEL 2 study conducted using health insurance scheme reimbursement data (SNIIRAM data) for the year 2013, with a follow-up period of 3 years now, which:
    - support the efficacy and bleeding safety profile of dabigatran 110 mg and 150 mg compared to VKAs,
    - did not reveal any new signal or additional risk of ACS between dabigatran and VKAs, thereby providing reassurance with respect to the doubts identified by the Committee following the results of the RE-LY pivotal study compared to warfarin with a risk of ACS after a median follow-up of 2 years,
- that it is the only DOAC with a specific neutralising agent,
- and although the risk of myocardial infarction is still an important potential risk in the latest version of the RMP,

the Committee considers that PRADAXA (dabigatran) is now a first-line medicinal product in the same way as other DOACs for patients with NVAF.

◗ Public health impact:
On the basis of currently available data, the previous assessment of the PHI is not modified: PRADAXA (dabigatran) is unlikely to have an additional impact on public health compared to other oral anticoagulants.

Given all these elements, the Committee deems that the clinical benefit of PRADAXA (dabigatran) is now substantial for the prevention of stroke and systemic embolism in patients with NVAF, with one or more risk factors.

The Committee issues a favourable opinion for maintenance of inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the marketing authorisation indication and dosages.

Prevention of thromboembolic events in elective THR/TKR surgery

◗ Venous thromboembolic disease is a serious disease that can be life-threatening to patients (potentially fatal pulmonary embolism) or have serious sequelae (post-thrombotic syndrome).

◗ This is a preventive treatment, for which a specific neutralising agent exists.

◗ The efficacy/adverse effects ratio of dabigatran remains moderate in this indication, given that the loss of efficacy accepted compared to enoxaparin (non-inferiority) is not clearly counterbalanced by a benefit, particularly in terms of a reduction in bleeding risk. In addition, two other direct-acting anticoagulants (apixaban, rivaroxaban) are now available, with a preventive efficacy (VTE + death) greater than that of enoxaparin and with no increase in bleeding risk.

◗ There are several medicinal alternatives, administered orally or by injection.

◗ In the absence of new clinical data and in view of the initial data already analysed by the Committee, the role of PRADAXA (dabigatran) is unchanged in this indication.
When the therapeutic strategy envisages the use of a DOAC, the decision to prescribe PRADAXA (dabigatran) should take into account the fact that:
- in the pivotal studies apixaban and rivaroxaban were more effective than enoxaparin for the endpoint VTE + death, with no increase in bleeding risk, and dabigatran was non-inferior to enoxaparin and without an advantage in terms of major bleeding,
- it is the DOAC most eliminated by the renal route and the only one to be contraindicated in severe renal impairment (creatinine clearance between 15 and 29 ml/min);
- that it is the only DOAC with a specific neutralising agent.

◗ Public health impact:
On the basis of currently available data, the previous assessment of the PHI is not modified: PRADAXA (dabigatran) is unlikely to have an additional impact on public health compared to other oral anticoagulants.

Given all these elements, the Committee deems that the clinical benefit of PRADAXA (dabigatran) remains moderate in the primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.

The Committee issues a favourable opinion for maintenance of inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the marketing authorisation indication and dosages.