TRANSPARENCY COMMITTEE

OPINION

16 July 2008

PRADAXA 75 mg, hard capsules
B/10, aluminium/polyvinylchloride-polyvinylacetate copolymer acrylate/PVC blister pack(s) (CIP: 385 255-4)
B/30, aluminium/polyvinylchloride-polyvinylacetate copolymer acrylate/PVC blister pack(s) (CIP: 385 256-0)
B/60, aluminium/polyvinylchloride-polyvinylacetate copolymer acrylate/PVC blister pack(s) (CIP: 385 257-7)

PRADAXA 110 mg, hard capsules
B/10, aluminium/polyvinylchloride-polyvinylacetate copolymer acrylate/PVC blister pack(s) (CIP: 385 260-8)
B/30, aluminium/polyvinylchloride-polyvinylacetate copolymer acrylate/PVC blister pack(s) (CIP: 385 261-4)
B/60, aluminium/polyvinylchloride-polyvinylacetate copolymer acrylate/PVC blister pack(s) (CIP: 385 262-0)

Applicant: BOEHRINGER INGELHEIM FRANCE

Dabigatran etexilate (as mesilate)

List I

ATC class: B01AE07

Date of Marketing Authorization (by centralized European procedure): 18 March 2008

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance and approved for use by hospitals.
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Dabigatran etexilate (as mesilate)

1.2. Originality
Dabigatran etexilate (PRADAXA) is a prodrug which is rapidly converted to its active substance, dabigatran, after oral administration. Dabigatran is a direct, competitive, reversible inhibitor of free or fibrin-bound thrombin.

1.3. Indication
“Primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery.”

1.4. Dosage
“Primary prevention of venous thromboembolic events (VTE) in patients who have undergone total knee replacement surgery:
The recommended dose is 220 mg once daily taken as 2 capsules of 110 mg.

Treatment should be initiated orally within 1-4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 10 days.

Prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip replacement surgery:
The recommended dose is 220 mg once daily taken as 2 capsules of 110 mg.

Treatment should be initiated orally within 1-4 hours of completed surgery with a single capsule and continuing with 2 capsules once daily thereafter for a total of 28-35 days.

For both surgeries, if haemostasis is not secured, initiation of treatment should be delayed. If treatment is not started on the day of surgery then treatment should be initiated with 2 capsules once daily.

Special patient populations

Hepatic impairment
Patients with elevated liver enzymes > 2 upper limit of normal (ULN) were excluded in clinical trials. Therefore the use of Pradaxa is not recommended in this population. ALT should be measured as part of the standard pre-operative evaluation.

Renal impairment:
In patients with moderate renal impairment (creatinine clearance 30-50 ml/min), there is limited clinical experience. These patients should be treated with caution. The recommended dose is 150 mg taken once daily as 2 capsules of 75 mg. Treatment with Pradaxa in patients with severe renal impairment (creatinine clearance < 30 ml/min) is contraindicated.

Elderly patients (> 75 years):
There is limited clinical experience. These patients should be treated with caution. The recommended dose is 150 mg taken once daily as 2 capsules of 75 mg.

Patients with a body weight < 50 kg (or > 110 kg):
There is very limited clinical experience in these patients at the recommended posology.
Post-surgical patients with an increased risk for bleeding: patients at risk for bleeding or patients at risk of overexposure should be treated with caution.

Switching from PRADAXA treatment to parenteral anticoagulant:
It is recommended to wait 24 hours after the last dose before switching from Pradaxa to a parenteral anticoagulant.

Switching from parenteral anticoagulants treatment to PRADAXA:
No data are available, therefore it is not recommended to start the administration of Pradaxa before the next scheduled dose of the parenteral anticoagulant should be injected.

Spinal anaesthesia/epidural anaesthesia/lumbar puncture:
In patients undergoing major orthopaedic surgery, epidural or spinal haematomas that may result in longterm or permanent paralysis cannot be excluded with the concurrent use of dabigatran and spinal/epidural anaesthesia or spinal puncture. The risk of these rare events may be increased by the postoperative use of indwelling epidural catheters or by concomitant administration of other medicinal products that affect haemostasis. Therefore the use of Pradaxa is not recommended in patients undergoing anaesthesia with post-operative indwelling epidural catheters. Administration of the first dose of Pradaxa should occur a minimum of two hours after the catheter is removed. These patients require frequent observation for neurological signs and symptoms.
2.1. ATC Classification

B Blood and blood-forming organs
B01 Antithrombotic agents
B01A Antithrombotic agents
B01AE Direct thrombin inhibitors
B01AE07 Dabigatran etexilale

2.2. Medicines in the same therapeutic category

(Other direct thrombin and factor Xa inhibitors):

- per os : none.
- administered parenterally: desirudin: REVASC

2.3. Medicines with a similar therapeutic aim

2.3.1 Direct thrombin and factor Xa inhibitors administered parenterally:
- lepirudin: REFCLUDAN
  Indication. “Anticoagulation in adult patients with heparin-induced thrombocytopenia (HIT) type II and thromboembolic disease mandating parenteral antithrombotic therapy. The diagnosis should be confirmed by the HIPAA (heparin induced platelet activation assay) or an equivalent test”.

2.3.2 Indirect thrombin and factor Xa inhibitors:

- For initial thromboprophylaxis in major orthopaedic surgery of the lower limbs:
  - Unfractionated heparins: CALCIPARINE
    Ind. “This is a classic, unfractionated heparin. Prevention of venous thromboembolism:
    - in surgery;
    - in bedridden patients presenting an acute medical condition (especially after stroke, heart failure, or ischaemic cerebrovascular accident with paralysis of the lower limbs). In this case its use is reserved for severe renal impairment (creatinine clearance estimated at around 30 ml/min according to the Cockcroft formula) as a possible alternative to the prescription of a low molecular weight heparin”.

  - low molecular weight heparins (LMWH):
    - dalteparin: FRAGMINE 0.2 ml
    - enoxaparin: LOVENOX 0.4ml
    - nadroparin: FRAXIPARINE
    - reviparin: CLIVARINE 0.6 ml
    - tinzaparin: INNOHEP 10,000 IU anti-Xa/1 ml

  - Fondaparinux: ARIXTRA 2.5 mg.
For long-term thromboprophylaxis in major orthopaedic surgery of the lower limbs: the benefit of prophylactic treatment after orthopaedic hip surgery has been established for enoxaparin for 4-5 weeks (LOVENOX) and for dalteparin (FRAGMINE) up to 35 days. For other LMWHs, the recommended duration of treatment is 10 days in the majority of cases; a vitamin K antagonist (VKA) should then be considered as a relay treatment.

- Danaparoid: ORGARAN
  Ind.: “Prevention of thromboembolic events in patients undergoing oncological and orthopaedic surgery.
  Prophylactic treatment of thromboembolic events in patients:
  - suffering from acute type II heparin-induced thrombocytopenia (HIT) without thromboembolic complications;
  - or with a prior history of type II HIT requiring preventive parenteral antithrombotic treatment”.

- Oral anticoagulants (vitamin K antagonists)
  Ind.: “Prevention of venous thrombosis and pulmonary embolism in hip surgery”.

3.1. Efficacy

The clinical benefit assessment of PRADAXA in the prevention of venous thromboembolic events (VTE) after orthopaedic surgery for total hip replacement (THR) or total knee replacement (TKR) is based on the results of five clinical trials: two dose-finding studies: 1160.11 (BISTRO-I) and 1160.19 (BISTRO-II) and three phase III clinical trials which compared the efficacy and adverse events of dabigatran etexilate with those of enoxaparin: the European trials RE-NOVATE (1160.48) and RE-MODEL (1160.25) and the American trial RE-MOBILIZE (1160.24).

The efficacy results of the American trial are not discussed in this opinion, as the dosage regimen for enoxaparin differs from that recommended by the Marketing Authorization (MA).

3.1.1 Results of dose-finding studies (phase II)
- The BISTRO-I open-label trial evaluated the safety of dabigatran etexilate at oral doses of between 25 mg and 600 mg a day in patients who had undergone hip replacement surgery. A dose-dependent increase in bleeding was observed; it was considered clinically unacceptable from 300 mg of dabigatran etexilate twice daily.
- The BISTRO-II double-blind trial tested 4 oral doses of dabigatran etexilate (50 mg twice daily, 150 mg twice daily, 300 mg once daily and 225 mg twice daily, beginning 1-4 hours after surgery) vs. enoxaparin 40 mg once daily (beginning 12 hours before surgery) in parallel groups on patients who had undergone THR or TKR surgery. The primary endpoint was symptomatic DVT/PE or DVT detected by phlebography. 1,464 (75%) of the 1,973 patients included in the trial were assessable. A dose-dependent reduction in VTE (p < 0.001) was observed as the dose of dabigatran etexilate increased: 28.5% (50 mg x 2), 17.4% (150 mg x 2), 16.6% (300 mg x 1), 13.1% (225 mg x 2) and 24% with enoxaparin. These events were mainly asymptomatic distal DVT. Major bleeding was less frequent with 50 mg x 2 (0.3%) than with enoxaparin (2%), but higher with the other doses (4.1% with 150 mg x 2; 4.7% with 300 mg x 1; 3.8% with 225 mg x 2).

3.1.2 Results of the two European trials
These were non-inferiority trials. It should be noted that the non-inferiority threshold set to evaluate non-inferiority corresponds to the greatest loss of efficacy allowed with the medicine evaluated (dabigatran etexilate) compared with the reference treatment used in the trial (enoxaparin).

These two double-blind randomized trials in three parallel groups compared the effect on VTE prevention and the adverse events of dabigatran etexilate at the doses of 220 mg and 150 mg compared with those of enoxaparin 40 mg:
- for 28-35 days after elective total hip replacement surgery: RE-NOVATE trial
- for 6-10 days after elective total knee replacement surgery: RE-MODEL trial

NB: In the RE-NOVATE trial, the duration of treatment (28-35 days) complied with current EMEA guidelines³ for the primary prevention of VTE after THR surgery. In the RE-MODEL trial, the duration of treatment (6-10 days), which complied with the 2000 EMEA guidelines⁴, may sometimes be slightly shorter than that currently recommended in knee surgery (10-14 days’ treatment, or even up to 35 days according to the American College of Chest Physicians guidelines published in 2008).

The doses tested are not those evaluated in the phase II dose-finding studies.

The primary endpoint was the same in both trials: a composite endpoint combining asymptomatic venous thromboembolic events detected by phlebography and the clinical events: incidence of total VTEs (including pulmonary embolism [PE], proximal and distal symptomatic or asymptomatic DVT detected by routine phlebography) and all-causes mortality.

The composite endpoint that combines the incidence of major VTEs (including proximal symptomatic or asymptomatic PE and DVT detected by routine phlebography) and VTE-related deaths constituted a secondary endpoint, although it is considered more clinically relevant.

The incidence of major bleeding\(^5\) or bleeding “considered clinically significant”\(^6\) was also taken into account (secondary safety endpoint).

3.1.2.1 Results of RE-NOVATE trial (after THR):

Choice of non-inferiority margin

After THR, the incidence of total VTEs and deaths in the patients treated with enoxaparin was between 14 and 20%.

The non-inferiority margin, set at 7.7%, represents 1/3rd of the lower estimate of the difference in incidence of total VTEs and deaths between the placebo and enoxaparin, calculated on the basis of three trials, on the 11th day (D11).

Trial population data

- Inclusion criteria: age: >18 years, weight > 40 kg.

- Non-inclusion criteria: recent (< 3 months) history of bleeding, major surgery or trauma (hip fracture), recent uncontrolled cardiovascular disease (uncontrolled hypertension, recent myocardial infarction < 3 months, etc.) or venous thromboembolic events, severe renal impairment (creatinine clearance < 30 mL/min), illness requiring anticoagulant treatment, active malignant illness, severe liver disease (aminotransferase > 2ULN).

- Number of assessable patients: 3,494 patients were randomized (ITT population), 3,463 of whom received at least one dose of the treatment under study (“population safety set”); 2,651 were treated, operated on and generated data which enabled us to confirm or rule out the existence of a VTE (FAS population), and 2,452 according to the per-protocol population criteria. The proportion of patients who completed the treatment period in accordance with the protocol was between 87% and 88.5% in the three groups.

- Patient characteristics: mean age of randomized patients: 63.9± 10.8 years; 32.7% were over 70 and 13.5 % over 75 years old
  Over a quarter (27.5 %) of these patients were obese.
  Over half (57.2%) had an unimpaired kidney function (creatinine clearance > 80 mL/min).

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\(^5\) Major bleeding events have been defined as any fatal haemorrhage, any manifest bleeding greater than would be expected when associated with a haemoglobin loss > 2 g/dL or requiring a transfusion of more than 2 blood units, any symptomatic retroperitoneal, intracranial, intraocular or intrathecal haemorrhage, or any bleeding requiring discontinuation of the treatment under study or further surgery.

\(^6\) The clinically significant bleeding events were spontaneous hematoma > 25 cm\(^2\), wound hematoma > 100 cm\(^2\), spontaneous epistaxis or gingivorrhagia lasting over 5 minutes, spontaneous macroscopic haematuria or macroscopic haematuria lasting over 24 hours after the procedure, spontaneous rectal bleeding, or any other bleeding which was clinically significant in the investigator’s opinion.
- Other treatments: during the treatment period 56.5% of the patients received NSAIDs, and 4.6% received platelet aggregation inhibitors.

Results:

Dabigatran etexilate (220 mg and 150 mg) proved non-inferior to enoxaparin 40 mg as regards the incidence of total VTEs and deaths (composite primary endpoint). For a non-inferiority margin set at 7.7%, the difference in risk versus enoxaparin 40 mg was -0.9% (CI 95% [-3.3; 1.4]) for dabigatran etexilate 220 mg and + 1.3% (CI 95% [-1.2; 3.9]) for dabigatran etexilate 150 mg (2,452 patients: per-protocol population).

The non-inferiority conditions were also fulfilled as regards the secondary endpoint (which is more clinically relevant).

Comments

This is a non-inferiority study. It should be noted that the most clinically relevant endpoint was chosen as secondary endpoint. The incidence of events of the composite endpoint used as primary endpoint was lower than that used to calculate the number of subjects to be included in order to test for non-inferiority. The risk that the allowed loss of efficacy was under-estimated therefore cannot be ruled out. Moreover, the non-inferiority is mainly based on a comparison of the incidence of asymptomatic events detected by phlebography (85%) and the distal location of half of them.

3.1.2.2 Results of RE-MODEL trial (after TKR):

Choice of non-inferiority margin

The non-inferiority margin, set at 9.2%, represents 1/3rd of the lower limit of the 95% confidence interval (95% CI) of the difference in incidence of DVT reported in a trial comparing enoxaparin with a placebo (45.3%; 95% CI [27.7; 62.9]) [Leclerc et al. 1992]. In this trial, enoxaparin was used at the dose of 30 mg x 2 (asymptomatic distal or proximal DVT, 35/54 vs. 8/41).

After TKR, the incidence of the composite primary endpoint in the patients treated with enoxaparin was between 30 and 48% [Geerts et al. 2001; Leclerc et al. 1992; Levine et al. 1996].

Trial population data

- Inclusion and non-inclusion criteria: identical to those of RE NOVATE.

- Number of assessable patients: 2,101 patients were randomized (ITT population), 2,076 of whom were treated with at least one dose of the treatment under study (population safety set); 1,541 were treated, operated on and generated data which enabled us to confirm the existence of VTE for the composite primary endpoint. The FAS population therefore represents 75% of all patients treated and operated on (ie. 25% of non-assessable phlebographies); the per-protocol population consisted of 1,439 patients. The proportion of patients who completed the treatment period in accordance with the protocol was between 91.1% and 92.8% in the three groups.

- Patient characteristics: mean age of randomized patients: 67.7± 8.9 years, 46.2% of whom were over 70 and 20% over 75 years old. Nearly half the patients were obese. Over half (55.3%) had an unimpaired kidney function (creatinine clearance > 80 mL/min).

- Other treatments: during the treatment period over 60% of the patients received NSAIDs, and approximately 3% received platelet aggregation inhibitors.
Results:

In the per-protocol population (1,439 patients), the non-inferiority of dabigatran etexilate (220 mg and 150 mg) vs. enoxaparin 40 mg was demonstrated as regards the incidence of total VTEs and deaths. For a non-inferiority margin set at 9.2%, the difference in risk versus enoxaparin 40 mg was -0.8% (CI95% [-7.0; 5.3]) for dabigatran etexilate 220 mg and 2.9% (CI95% [-3.3; 9.0]) for dabigatran etexilate 150 mg.

No significant difference was observed between dabigatran etexilate (220 mg and 150 mg) and enoxaparin 40 mg for the secondary endpoint “major VTEs and VTE-related deaths”.

Comments

This is a non-inferiority study. It should be noted that the most clinically relevant endpoint was chosen as secondary endpoint. Non-inferiority is mainly based on comparison of the incidence of asymptomatic events detected by phlebography and distal location.

Table 1: Summary of European clinical trials vs. enoxaparin (ITT results)

<table>
<thead>
<tr>
<th>Trial no.</th>
<th>Methodological design</th>
<th>Patients randomized</th>
<th>Surgery</th>
<th>Treatment groups</th>
<th>Duration of treatment</th>
<th>Primary efficacy endpoint/results</th>
<th>Secondary efficacy endpoint/results</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-NOVATE (1160.48)</td>
<td>Multicentre Randomized Controlled Double-blind Double-placebo 3 parallel groups</td>
<td>3 494</td>
<td>Total hip replacement</td>
<td>D 220 mg/day PO D 150 mg/day PO (1-4 h post-surgery on the 1st day, half dose) E 40 mg/day SC (12 h pre-surgery on the 1st day)</td>
<td>28-35 days</td>
<td>Incidence of total VTEs*/all-causes mortality: D 220: 53 (6.0 %) 95% CI [4.5; 7.6] D 150: 75 (8.6 %) 95% CI [6.7; 10.4] E 40: 60 (6.7 %) 95% CI [5.1; 8.3]</td>
<td>Incidence of major VTEs**/VTE-related deaths: D 220: 28 (3.1%) 95% CI [2.0; 4.2] D 150: 38 (4.3 %) 95% CI [2.9; 5.6] E 40: 36 (3.9 %) 95% CI [2.7; 5.2]</td>
</tr>
<tr>
<td>RE-MODEL (1160.25)</td>
<td>Multicentre Randomized Controlled Double-blind Double-placebo 3 parallel groups</td>
<td>2 101</td>
<td>Total knee replacement</td>
<td>D 220 mg/day PO D 150 mg/day PO (1-4 h post-surgery on the 1st day, half dose) E 40 mg/day SC (12 h pre-surgery on the 1st day)</td>
<td>8 ± 2 days</td>
<td>Incidence of total VTEs*/all-causes mortality: D 220: 183 (36.4%) 95% CI [32.2; 40.6] D 150: 213 (40.5%) 95% CI [36.3; 44.7] E 40: 193 (37.7%) 95% CI [33.5; 41.9]</td>
<td>Incidence of major VTEs**/VTE-related deaths: D 220: 13 (2.6%) 95% CI [1.2; 3.9] D 150: 20 (3.8%) 95% CI [2.2; 5.4] E 40: 18 (3.5 %) 95% CI [1.9; 5.1]</td>
</tr>
</tbody>
</table>

D 220/D 150: dabigatran etexilate 220/150 mg; E 40: enoxaparin 40 mg; PO: per os; SC: subcutaneous

VTE: Venous Thromboembolic Events

* total VTEs: proximal and distal DVT detected by an assessable phlebogram, confirmed symptomatic DVT, confirmed PE

** major VTEs: proximal DVT/PE
3.2. Adverse effects

According to the SPC, 10,084 patients received at least one dose of the medicines under study in four controlled trials relating to prevention of VTEs. 5,419 of these patients received 150 mg or 220 mg/day of Pradaxa, 389 under 150 mg/day, and 1,168 over 220 mg/day.

Hepatic toxicity

In the 3 clinical trials which compared dabigatran etexilate with enoxaparin, evaluation of the liver function parameters did not indicate any particular hepatotoxic risk with dabigatran etexilate for an exposure period of up to 35 days. Patients with a liver enzyme count exceeding twice the upper limit of the normal range (ULN) were not included in the clinical trials. The administration of PRADAXA to these patients is not recommended by the marketing authorization.

Bleeding risk

The adverse event most frequently reported was bleeding, which occurred in some 14% of patients, with the same frequency as in patients treated with enoxaparin 40 mg. The frequency of major bleeding (including bleeding from the wound) was under 2%.

Table 2: Major bleeding events and bleeding of all types in pivotal trials conducted in relation to prevention of VTE after total hip or knee replacement.

<table>
<thead>
<tr>
<th></th>
<th>Dabigatran etexilate 150 mg no. (%)</th>
<th>Dabigatran etexilate 220 mg no. (%)</th>
<th>Enoxaparin no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated</td>
<td>1 866 (100,0)</td>
<td>1 825 (100,0)</td>
<td>1 848 (100,0)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>24 (1,3)</td>
<td>33 (1,8)</td>
<td>27 (1,5)</td>
</tr>
<tr>
<td>All types of bleeding</td>
<td>258 (13,8)</td>
<td>251 (13,8)</td>
<td>247 (13,4)</td>
</tr>
</tbody>
</table>

N.B. There is no antidote to dabigatran. In the event of haemorrhagic complications, the treatment must be terminated and the cause of bleeding investigated. As dabigatran is mainly excreted renally, sufficient diuresis must be maintained. Dabigatran can be dialysed, but there are no clinical data to demonstrate the usefulness of this approach.

Data in the event of moderate renal impairment (Cl Cr between 30 and 50 mL/min)

The clinical data are limited in this situation. As dabigatran etexilate is mainly eliminated renally, the risk of bleeding may be increased in the event of impaired kidney function. In the sub-groups of patients aged over 75 years, the incidence of major bleeding was 1.4% in the patients treated with dabigatran etexilate 150 mg, 3.7% in those treated with dabigatran etexilate 220 mg, and 2.9% in those treated with enoxaparin 40 mg. In patients with moderate renal impairment, the incidence of major bleeding was 0.8% in those treated with dabigatran etexilate 150 mg, 3.4% in those treated with dabigatran etexilate 220 mg, and 3.4% in those treated with enoxaparin 40 mg.

3.3. Conclusion

On the basis of the results of two European double-blind, parallel-group non-inferiority trials, patients who had undergone major elective orthopaedic surgery involving total knee replacement (RE MODEL) or hip replacement (RE NOVATE) received 75 or 110 mg of dabigatran etexilate (PRADAXA) 1-4 hours after the end of the operation, followed by 150 or 220 mg/day for the next few days, or enoxaparin 40 mg the day before the operation and for

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7 It should be noted that ximelagatran, which is similar to dabigatran etexilate, has proved hepatotoxic, and has consequently been withdrawn from the market.
the next few days. The duration of the treatment was 6-10 days in the RE-MODEL trial (total knee replacement) and 28-35 days in the RE-NOVATE trial (total hip replacement).

In total, 2,076 patients (knee) and 3,463 patients (hip) were treated (population safety set).

The primary endpoint (efficacy) was a composite endpoint combining the incidence of total VTEs (including PE, symptomatic or asymptomatic proximal and DVT detected by routine phlebography) and all-causes mortality. The composite endpoint that combines the incidence of major VTEs (including symptomatic or asymptomatic proximal PE and DVT detected by routine phlebography) with VTE-related deaths constituted a secondary endpoint, although it is considered more clinically relevant.

The results of the two trials demonstrated that the antithrombotic effect of Pradaxa 220 mg and 150 mg was statistically not inferior to that of enoxaparin on total VTEs and all-causes mortality, taking account of the non-inferiority thresholds used.

The non-inferiority decision is mainly based on a comparison of the incidence of asymptomatic events detected by phlebography and distal location (knee replacement). According to the SPC, “the point estimate for incidence of major VTE and VTE related mortality for the 150 mg dose was slightly worse than enoxaparin. Better results were seen with the 220mg dose where the point estimate of major VTE/VTE-related mortality was slightly better than enoxaparin”.

The clinical studies have been conducted in a patient population with a mean age > 65 years.

The bleeding risk of these two medicinal products does not seem to differ at the doses and treatment durations tested.

The clinical data in patients suffering from renal impairment are limited (263 patients); the lowest dosage is recommended for these patients.

N.B.: the question of whether the results of the two trials are transposable to the oldest patient population arises.

According to the PMSI data (2006):
- THR: mean age 69.5 ± 11.9 years, 37% of whom were aged 70-80 years and 20% aged 80 years and over for the 104,207 patients registered.
- TKR: mean age 71.6 ± 8.8 years, 49% of whom were aged 70-80 years and 17% aged 80 years and over for the 54,557 patients registered.

However, in the RE-NOVATE and RE-MODEL trials, the patients are younger.

After the age of 80, some patients will certainly have severe impairment of the kidney function, and may not benefit from dabigatran etexilate. For those with moderate renal impairment, the recommended dosage is 150 mg/day, but the clinical data in this sub-population are limited.

Moreover, the first dose of dabigatran etexilate (PRADAXA) must be administered 1-4 hours after the end of the operation. The possible risk of vomiting (5% in the first 6 hours in the clinical trials) after general anaesthesia may prejudice this dosage regimen.

8 According to the SPC, if the treatment does not begin on the day of surgery, the dosage must be 2 capsules once daily from the start of the treatment.
4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Venous thromboembolic events are a serious disorder which may be life-threatening (potentially fatal pulmonary embolism) or involve major sequelae (post-thrombotic syndrome).

Patients who undergo major orthopaedic surgery involving a total hip or knee replacement are a population at high thromboembolic risk.

PRADAXA is a first-line treatment indicated for primary prevention of venous thromboembolic events in adult patients who have undergone elective surgery involving total hip or knee replacement.

Public health benefit:
The public health burden represented by VTE is high. In the prophylaxis of venous thromboembolic events, the availability of effective treatments which are well tolerated in terms of bleeding, especially in at-risk patients, constitutes a public health need.
The available data do not suggest that dabigatran etexilate (PRADAXA) will have an additional impact, compared with present treatment, in terms of reducing morbidity and mortality associated with the complications of VTE or major bleeding caused by antithrombotic treatments in patients who have undergone elective orthopaedic surgery involving total hip or knee replacement.
Whether the clinical trial data are transposable to real life will depend mainly on the occurrence of vomiting after general anaesthesia, which can prejudice compliance with the dosage regimen (first dose of dabigatran etexilate 1-4 hours after the end of surgery). In the absence of evidence, it cannot be assumed that PRADAXA will have any impact on the organization of healthcare which could be expected in view of the lack of need for specific biochemical monitoring and oral administration of this product.
All things considered, PRADAXA is not expected to have any public health benefit.

Dabigatran etexilate has a high efficacy/adverse effects ratio. There are alternative drugs available.

Conclusion: the actual benefit (AB) of the medicinal products PRADAXA 75 mg and 110 mg is substantial.

4.2. Improvement in actual benefit

PRADAXA (dabigatran etexilate) provides no improvement in actual benefit (IAB V) compared with LOVENOX (enoxaparin) in “primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery”. The Committee notes the availability of a useful oral form in this indication.
4.3. Therapeutic use

The purpose of preventing VTEs is to prevent their two complications: pulmonary embolism and post-thrombotic syndrome; it is usually performed until the patient begins walking actively.

After major orthopaedic surgery of the lower limbs involving total hip or knee replacement, the thromboembolic risk is high, requiring systematic prescription of prophylactic measures. In this case, short-term thromboprophylaxis (in the 10 days after surgery) is therefore recommended: the first-line anticoagulant prescribed could be a low molecular weight heparin (not inferior to non fractionated heparins) or fondaparinux 2.5 mg (ARIXTRA 2.5 mg). A UFH (morbidity and mortality data available for UFHs) is recommended in case of severe renal impairment.

Continued thromboprophylaxis is also recommended in the event of total hip (or even knee) replacement. Only UFHs and two LMWHs, enoxaparin (LOVENOX) and dalteparin (FRAGMINE), are indicated for prevention up to 35 days. A relay treatment after short-term thromboprophylaxis by VKA could also be considered.

PRADAXA (dabigatran etexilate) is a novel antithrombotic which could be prescribed as first-line treatment. It is administered orally. Its efficacy and safety have been compared in short-term and long-term thromboprophylaxis (after hip replacement) with those of enoxaparin (LOVENOX). It has proved non-inferior to enoxaparin (LOVENOX) for a composite endpoint with a similar bleeding risk.

In some patients (those suffering from renal impairment, and patients aged over 80 years), the dosage of 150 mg/day is recommended for thromboprophylaxis. Clinical data for these patients are limited.

As for fondaparinux (ARIXTRA 2.5 mg), it is not known whether dabigatran etexilate reduces VTE-related clinical complications as much as, more than, or even less than UFH (or LMWH).

Like fondaparinux (ARIXTRA 2.5 mg), dabigatran etexilate does not require specific laboratory investigations. The dosage of 150 mg/day is recommended for thromboprophylaxis in some patients (those suffering from renal impairment, and patients aged over 75 years). The efficacy evidence level is lower with this dosage (few clinical data). PRADAXA therefore represents a useful alternative treatment for primary prevention of venous thromboembolic events in patients who have undergone elective surgery involving total hip replacement or total knee replacement.

In patients for whom the administration of an oral anticoagulant is continued after discharge from hospital (especially after a hip replacement), PRADAXA represents an alternative to the prescription of a VKA.

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4.4. Target population

The target population of PRADAXA is defined as adult patients who have undergone elective surgery for total hip or knee replacement.

Quantitative estimate: according to the PMSI 2006 data:
- 104,207 patients have undergone hip arthroplasty (not including joint replacement in the event of hip fracture or removal of prosthesis when a new one is fitted);
- 54,557 patients have undergone knee arthroplasty (not including single-compartment prostheses or removal of prosthesis when a new one is fitted)

ie. a total of 158,764 patients (in 2006).

The target population of PRADAXA can therefore be estimated at approximately 160,000 patients.

N.B.: This calculation tends to over-estimate the target population liable to benefit from thromboprophylaxis with dabigatran etexilate in view of the prevalence of severe renal impairment among the elderly population.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services for the indications and at the doses specified in the Marketing Authorization.

Request for trial: The Commission would like a follow-up cohort study to be set up for patients treated in France with PRADAXA to establish:
- the characteristics of the patients treated (age, type of surgery, type of anaesthesia, comorbidities, etc.),
- the real conditions of use of PRADAXA (dosage, duration of treatment, compliance with administration regimen, etc.),
- the frequency of clinical venous thromboembolic events,
- safety in terms of major bleeding,
- the impact on the organization of healthcare (level of prescription of platelet monitoring, level of use of nursing procedures and call-outs, etc.).

The duration of the study must be justified by an independent scientific committee.

If scheduled or ongoing studies, in particular within the scope of the European Risk Management Plan, would not be able to answer all the questions raised by the Transparency Committee, a specific study must be carried out.

The protocol will be analysed in liaison with AFSSAPS in the case of the objectives which concern it.

Packaging: appropriate for the prescription conditions specified in the Marketing Authorization.

Reimbursement rate: 65%