HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

21 January 2009

XARELTO 10 mg, film-coated tablets
Package of 5 tablets, blister (PP/Alu) - CIP Code: 388 381-0
Package of 10 tablets, blister (PP/Alu) - CIP Code: 388 382-7
Package of 30 tablets, blister (PP/Alu) - CIP Code: 388 383-3
Package of 100 tablets, blister (PP/Alu) - CIP Code: 573 628-9

Applicant : BAYER SANTE

Rivaroxaban

List I

ATC code: B01AX06

Date of the MA (centralised procedure): 30 September 2008

Reason for request: Inclusion on the list of medicines reimbursed by National Insurance (packages of 5, 10 and 30 tablets) and approved for use by hospitals (packages of 5, 10, 30 and 100 tablets).

Medical, Economic and Public Health Assessment Division.

1 PROPERTIES OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Rivaroxaban

1.2. Background

A new anticoagulant, rivaroxaban is a direct (not acting through antithrombin), competitive, reversible and specific factor Xa inhibitor. It is active after oral administration (once a day fixed dose).

1.3. Indication

'Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.'

1.4. Dosage

'The recommended dose is 10 mg rivaroxaban taken orally once daily. The initial dose should be taken 6 to 10 hours after surgery, provided that haemostasis has been established. The duration of treatment depends on the individual risk of the patient for venous thromboembolism which is determined by the type of orthopaedic surgery.

For patients undergoing major hip surgery, a treatment duration of 5 weeks is recommended.

For patients undergoing major knee surgery, a treatment duration of 2 weeks is recommended.'

Special patient populations and situations

Renal impairment

No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50-80 ml/min) or moderate renal impairment (creatinine clearance 30-49 ml/min).

Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased in this patient population, therefore, Xarelto is to be used with caution in these patients.

Use is not recommended in patients with creatinine clearance < 15 ml/min.

Patients above 65 years No dose adjustment is necessary.

Extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25%). No dose adjustment for weight is necessary.

Spinal/epidural anaesthesia or puncture

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic agents for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the post-operative use of indwelling epidural catheters or the concomitant use of medicinal products affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture.

Prior to neuraxial intervention the physician should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis.

An epidural catheter is not to be removed earlier than 18 hours after the last administration of rivaroxaban. The next rivaroxaban dose is to be administered not earlier than 6 hours after the removal of the catheter. If traumatic puncture occurs the administration of rivaroxaban is to be delayed for 24 hours.

Hepatic impairment
Xarelto is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. Xarelto may be used with caution in cirrhotic patients with moderate hepatic impairment. No dose adjustment is necessary in patients with other hepatic diseases.

XARELTO is contraindicated (due to lack of data) in pregnant and breast-feeding women (see SPC), as are fondaparinux (ARIXTRA) and dabigatran (PRADAXA).

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

B	Blood and blood-forming organs
B01	Antithrombotic agents
B01A	Antithrombotic agents
B01AX	Other antithrombotic agents
B01AX06	Rivaroxaban

2.2. Medicines in the same therapeutic category

Other oral direct factor Xa inhibitors: none.

2.3. Medicines with a similar therapeutic aim

2.3.1. Direct thrombin inhibitors

- oral: dabigatran etexilate: PRADAXA 75 mg and 110 mg, capsules.

- intravenous:
  - desirudin: REVASC
  - lepirudin: REFLUDAN
    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
  Indications: *'This is a standard or unfractionated heparin.*
  Prevention of venous thromboembolic accidents:
  - in a surgical context
  -in bed-ridden patients with acute medical conditions (particularly following myocardial infarction, in cases of heart failure, and following ischaemic stroke with paralysis of the lower limbs). Use in this case is reserved for severe renal impairment (creatinine clearance < 30 ml/min by Cockcroft's formula) as a possible alternative to prescribing low-molecular-weight heparin.'

  - Low-molecular-weight heparins (LMWHs):
    - dalteparin: FRAGMIN 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 extended thromboprophylaxis in major orthopaedic surgery of the lower limbs:
Prophylactic treatment following orthopaedic hip surgery with enoxaparin (LOVENOX) for 4-5 weeks and with dalteparin (FRAGMIN) for up to 35 days has been found to be beneficial. The recommended treatment duration for the other LMWHs is 10 days in most cases, after which a switch to anti-vitamin K (AVK) treatment should be considered.

- Danaparoid: ORGARAN
  Indications: *'Thromboprophylaxis in oncological and orthopaedic surgery.*
  Thromboprophylaxis in patients with:
  - *acute heparin-induced thrombocytopenia (HIT) type II without thromboembolic complications;*

  - or a documented history of HIT type II disease mandating preventative parenteral antithrombotic therapy.'

2.3.3. Vitamin K antagonists (oral anticoagulants)

Indication: *'Prevention of venous thrombosis and pulmonary embolism in hip surgery.'*

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

Evaluation of the clinical benefit of XARELTO in preventing venous thromboembolic disease (VTED) after total hip replacement (THR) or total knee replacement (TKR) surgery is based on the results of eight clinical studies: four phase II dose-finding studies: 10942, 10944, 11527 and 10945 ; and four phase III clinical studies comparing the efficacy and undesirable effects of rivaroxaban with those of enoxaparine: RECORD 1 (study 11354) and RECORD 2 (study 11357) after elective hip replacement, and RECORD 3 (study 11356) and RECORD 4 after knee replacement.

The RECORD 2 and RECORD 4 efficacy results will not be commented on in this opinion since:
- the objective of RECORD 2 was to demonstrate the superiority of 5 weeks of rivaroxaban thromboprophylaxis over 2 weeks of enoxaparin thromboprophylaxis. The two arms in this study differed in both the antithrombotic agent administered and the duration of thromboprophylaxis. It is not possible, therefore, to determine whether the results are due to the drug and/or to the duration of thromboprophylaxis. In addition, the enoxaparin dosing regimen was different from that recommended in the marketing authorisation.
- in RECORD 4, the enoxaparin dosing regimen (30 mg twice daily) was different from that recommended in the marketing authorisation.

RECORD 1[1] and RECORD 3 protocols:

Study No & name/Type of surgery	Surgical event	Total number of patients in study	No of patients in rivaroxaban arm	No of patients in enoxaparin arm	Rivaroxaban dose and treatment duration	Enoxaparin dose and treatment duration
11354 **RECORD 1** (**THR**) (pivotal study)	Total hip replacement	4 541	Randomised: 2 266 Safety: 2209 mITT: 1595 PP: 1537	Randomised: 2 275 Safety: 2 224 mITT: 1 558 PP: 1 492	10 mg (1 tablet daily) 35 ± 4 days	40 mg (1 inj. daily) 36 ± 4 days
11356 **RECORD 3** (**TKR**) (pivotal study)	Total knee replacement	2 531	Randomised: 1 254 Safety: 1 220 mITT: 824 PP: 793	Randomised: 1 277 Safety: 1 239 mITT: 878 PP: 838	10 mg (1 tablet daily) 12 ± 2 days	40 mg (1 inj. daily) 13± 2 days

mITT: patients who had undergone surgery and had at least one venographic assessment for VTE.
PP: mITT patients who had an 'adequate' assessment for VTE between 36 hours (in the event of a positive outcome) and 72 hours (for a negative outcome) after the last treatment dose, without deviating substantially from the protocol.

[1] - In RECORD 1, the treatment duration of 31-39 days was in accordance with current EMEA guidelines for primary prevention of VTE after total hip replacement. In RECORD 3, the treatment duration of 10-14 days followed the 2001 EMEA guidelines (or up to 35 days, according to the American College of Chest Physicians guidelines published in 2008).
- Day 1 = day of surgery.
- There was a 30 ± 5 day follow-up period after the last dose of antithrombotic treatment. The last visit was on Day 65 ± 5 days (RECORD 1) and Day 42 ± 5 days (RECORD 3).

3.1.1 The RECORD 1 and RECORD 3 studies

The results of the two pivotal (approximately 7,000 patients) clinical studies, RECORD 1 (THR) and RECORD 3 (TKR), are presented to show the clinical benefit of XARELTO (size of effect and clinical relevance, and transposability of results).

Design

These two studies followed the same design: randomised, double-blind, double placebo-controlled, parallel-group studies. The efficacy and safety of rivaroxaban 10 mg daily were compared with those of enoxaparin 40 mg daily for VTE prophylaxis in patients aged 18 and above undergoing elective hip (RECORD 1) or knee (RECORD 3) replacement surgery.
The objective was to demonstrate the non-inferiority of rivaroxaban compared with enoxaparin and, if this hypothesis of non-inferiority was shown to be correct, to establish the superiority of rivaroxaban over enoxaparin.

The primary endpoint was a composite one: the incidence of all venous thromboembolism (VTE) events, defined as a combination of pulmonary embolisms (PE), proximal and distal deep vein thromboses (DVT) (symptomatic or asymptomatic detected by routine venography), and death from any cause.

The secondary endpoints were:

- a composite endpoint, regarded as more clinically relevant than the primary endpoint: the incidence of major VTE,[2] defined as a combination of PE, proximal DVT (symptomatic or asymptomatic detected by routine venography), and VTE-related death
- the incidence of symptomatic VTE (combining proximal and distal VTE and PE).

- The hypothesis of inferiority was rejected in favour of non-inferiority if the upper limit of the 95% CI for the difference between the two treatments was less than:
- 3.5% (absolute value) in RECORD 1 (THR)
- 4% (absolute value) in RECORD 3 (TKR). The 4% limit was chosen on the basis of the recommendations of the 6th ACCP Conference. [3]

- The hypothesis of equality was rejected in favour of superiority if the upper limit of the 95% CI for the difference in treatments was less than 0, which is equivalent to the usual superiority test.

Three populations were defined for analysis:
- Safety population: randomised patients who had received at least one dose of study treatment (placebo or active substance).
- mITT (modified ITT) population: only patients who had undergone surgery and had at least one adequate assessment for VTE (i.e. documented symptomatic VTED or venography performed between days 29 and 42).
- Per-protocol population: mITT patients who had an adequate assessment for VTE between 36 hours (in the event of a positive outcome) and 72 hours (for a negative outcome) after the last treatment dose, without deviating substantially from the protocol.

2 In the analysis of the main secondary endpoint (major VTE), the test for superiority was preceded by a test for non-inferiority with the non-inferiority limit set by the protocol at 1.5% (of the absolute value).
[3] WH Geerts, JA Heit, GP Clagett et al. Prevention of venous thromboembolism: The Sixth ACCP Conference on antíthrombotic therapy. Chest 2001;119 (Suppl.):132S-175S.

Results

3.1.1.1 RECORD 1 results (following THR, 5 weeks)[4]

Study population characteristics

- The 4,433 patients in the safety population had an average age of 63 years (13% above 75), with 55% women; average weight 78 kg; average BMI 28 kg/m^2 (29.7% with BMI > 30); few with a history of VTE (2.6%); first THR (95.7%) for osteoarthritis (87%), performed under locoregional anaesthetic (59.5%).
- High-risk populations treated with rivaroxaban:
    - 282 (12.8%) patients were aged above 75 years
    - 123 (5.6%) patients had moderate renal impairment (creatinine clearance from 30 to < 50 ml/min)
    - 11 (0.5%) patients had severe renal impairment (creatinine clearance < 30 ml/min)
    - 370 (16.7%) patients had at least one of the following factors: age > 75 years, weight ≤ 50 kg or creatinine clearance < 50 ml/min.

Efficacy results:

As the conditions for non-inferiority were met, only the results of the superiority test (performed on the modified ITT population) are presented and discussed here, particularly as they provide a measure of the clinical contribution made by rivaroxaban (especially the size of the effect): total VTE incidence was 1.1% (18/1,595) on rivaroxaban against 3.7% (58/1,558) on enoxaparin (p<0.001), or an absolute benefit of -2.62%, 95% CI [-3.69%; -1.54%], and a reduction in relative risk of 69.7%, 95% CI [48.8%; 82.1%], in favour of rivaroxaban.

Incidence of major VTE (most relevant secondary endpoint) was 0.2% (4/1,686) on rivaroxaban against 2% (33/1,678) on enoxaparin (p<0.001), or an absolute benefit of -1.74%, 95% CI [-2.45%; -1.03%], and a reduction in relative risk of 87.9%, 95% CI [66.0%; 95.7%], in favour of rivaroxaban.

In the high-risk populations, the total VTE incidence was comparable in the two arms in patients aged above 75 (4.2% versus 5.2%), in patients with moderate renal impairment (2.5% versus 3.3%) and in 'frail' patients (3.5% versus 3.9%). These incidences were lower with rivaroxaban than with enoxaparin in patients with VTE risk factors (0% versus 5.3%) and a history of VTE (0% versus 12.1%).

Conclusion and remarks

Thromboprophylaxis following a total hip replacement was more effective with rivaroxaban 10 mg/day orally than with enoxaparin 40 mg subcutaneously after 35 days of treatment in terms of preventing both total VTE and major VTE. The size of the effect was small (< 2% for total VTE) after 35 days. This benefit arises essentially from a difference in frequency of proximal DVT (1 (<0.1%) versus 31 (2%) in the enoxaparin arm), only 5 of which were symptomatic. The frequency of symptomatic VTE (proximal and distal DVT, fatal and non-fatal PE) was 0.3% (6/2,209) in patients treated with rivaroxaban and 0.5% (11/2,224) in patients treated with enoxaparin: a difference of -0.23%, 95% CI [-0.59%; 0.14%].

This analysis does not include the whole randomised population (modified ITT analysis).

[4] Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, Bandel TJ, Beckmann H, Muehlhofer E, Misselwitz F, Geerts W; RECORD 1 Study Group. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Eng J Med 2008;358 (26):2765-75.

3.1.1.2 RECORD 3 results (following TKR, 2 weeks)[5]

Study population characteristics

- The 2,459 patients in the safety population had an average age of 68 years (20.7% above 75), with 68% women; average weight 80 kg; average BMI 29.7 kg/m^2 (42.3% with BMI > 30); few with a history of VTE (4%); first TKR (96%), unilateral (97%), performed under regional anaesthetic (63.5%).
- High-risk populations treated with rivaroxaban:
    - 262 (21.5%) patients were aged above 75 years
    - 92 (7.5%) patients had moderate renal impairment (creatinine clearance from 30 to < 50 ml/min)
    - 9 (0.7%) patients had severe renal impairment (creatinine clearance < 30 ml/min)
    - 309 (25.3%) patients had at least one of the following factors: age > 75 years, weight ≤ 50 kg or creatinine clearance < 50 ml/min.

Efficacy results:

As the conditions for non-inferiority were met, only the results of the superiority test (performed on the modified ITT population) are presented and discussed here, particularly as they provide a measure of the clinical contribution made by rivaroxaban (especially the size of the effect):

- Total VTE incidence was 9.6% (79/824) on rivaroxaban against 18.9% (166/878) on enoxaparin (p<0.001), or an absolute benefit of -9.15%, 95% CI [-12.40%; -5.89%], and a reduction in relative risk of 49.3%, 95% CI [34.9%; 60.5%]. This result is essentially due to a difference in the frequency of distal DVT: 70 (8.5%) versus 140 (15.9) on enoxaparin, only 26 of which were symptomatic.

Incidence of major VTE (a secondary endpoint considered clinically more relevant) was 1.1% (9/908) on rivaroxaban against 2.6% (24/925) on enoxaparin, or an absolute benefit of -1.59%, 95% CI [-2.80%; -0.38%] (p=0.010), and a reduction in relative risk of the incidence of major VTE of 62%, 95% CI [18%; 82%], in favour of rivaroxaban.

The frequency of symptomatic VTE (secondary endpoint) during the treatment period was 0.7% (8/1,220) for rivaroxaban versus 2.0% (24/1,239) for enoxaparin, or a difference of -1.3%, 95% CI [-2.2%; 0.4%] (p=0.005) in favour of rivaroxaban. The result is essentially due to a difference in the frequency of distal DVT: 6 (0.5%) versus 20 (1.6) in the enoxaparin arm.

Conclusion

Thromboprophylaxis for 13 days following a total knee replacement was more effective with rivaroxaban 10 mg/day orally than with enoxaparin 40 mg subcutaneously in terms of preventing both total VTE and major VTE. The size of the effect was small (< 1.6% after 13 days). This benefit arises essentially from a difference in frequency of distal DVT (8.5% versus 15.9%), most of which were asymptomatic. The frequency of symptomatic events was less than 1% for rivaroxaban.

This analysis does not include the whole randomised population (modified ITT analysis).

The data obtained during the various studies in terms of the reduction of total VTE, major VTE and symptomatic VTE were confirmed by a pooled analysis of the results of the phase III studies (RECORD 1, RECORD 3 and RECORD 2).

[5] Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, Misselwitz F, Turpie AG; RECORD3 Investigators. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Eng J Med 2008;358(26):2776-86.

3.2. Adverse effects

Exposure to rivaroxaban (XARELTO)
The safety of rivaroxaban 10 mg was assessed within the three phase III studies (RECORD 1, 2 and 3, SPC data), involving 4,571 patients who had undergone major surgery for a total hip or knee replacement and were treated with rivaroxaban for up to 39 days. In total, approximately 14% of the patients treated experienced undesirable effects. Bleeding was observed in approximately 3.3% of patients and anaemia in approximately 1% of patients. The other common undesirable effects were nausea, raised gamma glutamyl transferase (GGT) and raised transaminase levels.

Bleeding risk
- The table below shows the incidence of major bleeding in the three clinical studies in patients treated with rivaroxaban or enoxaparin.

	RECORD 1		RECORD 2		RECORD 3	
Major haemorrhagic events	rivaroxaban: 6/2209 (0.3 %)	enoxaparin: 2/2224 (0.1 %)	rivaroxaban: 1/1228 (0.1 %)	enoxaparin: 1/1229 (0.1 %)	rivaroxaban: 7/1220 (0.6 %)	enoxaparin: 6/1239 (0.5 %)

The risk of major haemorrhage with oral rivaroxaban 10 mg daily was similar to that observed with subcutaneous enoxaparin 40 mg daily across the three clinical studies. Rivaroxaban, like other antithrombotic agents, is to be used with caution in patients with an increased bleeding risk.[6]

Antidote to rivaroxaban
- No specific antidote to rivaroxaban is available in the event of bleeding complications.[7] Due to high plasma protein binding, rivaroxaban is not expected to be dialysable.

Coagulation monitoring
There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine.

Renal impairment
- There are no available data for patients with creatinine clearance < 15 ml/min. XARELTO is not recommended for these patients.
- Xarelto is to be used with caution in patients with creatinine clearance 15-29 ml/min and in patients with moderate renal impairment (creatinine clearance 30-49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations.

Hepatic toxicity
- No data are available in patients with severe hepatic impairment.
-XARELTO is contraindicated in cases of 'hepatic disease associated with coagulopathy and clinically relevant bleeding risk'.

[6] Patients at risk of haemorrhagic complications: congenital or acquired bleeding disorders, uncontrolled severe arterial hypertension, active ulcerative gastrointestinal disease, recent gastrointestinal ulcerations, vascular retinopathy, recent intracranial or intracerebral haemorrhage, intraspinal or intracerebral vascular abnormalities, recent brain, spinal or ophthalmological surgery, other haemostasis-modifying medicinal products. These patients are to be carefully monitored for signs of bleeding complications after initiation of treatment, by means of regular physical examination of the patients, close observation of the surgical wound drainage and periodic measurements of haemoglobin. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site. Haemorrhagic complications may present as weakness, asthenia, paleness, dizziness, headache or unexplained swelling.

[7] According to the SPC, the procedure to be adopted in the event of bleeding complications comprises the following measures: use of activated charcoal to reduce absorption in case of rivaroxaban overdose; delay of next rivaroxaban administration or discontinuation of treatment as appropriate, since rivaroxaban has mean terminal half-lives of between 7 and 11 hours; appropriate symptomatic treatment, e.g. mechanical compression, surgical interventions, fluid replacement and haemodynamic support, blood product or component transfusion.
If these measures are insufficient and the patient's life is threatened, administration of recombinant factor VIIa may be considered, although this recommendation is based on limited non-clinical data and there is currently no experience with the use of recombinant factor VIIa in individuals receiving rivaroxaban.

In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban plasma levels may be significantly increased, which may lead to an increased bleeding risk. XARELTO may be used with caution in cirrhotic patients with moderate hepatic impairment

3.3. Conclusion

The results of two randomised, double-blind, parallel-group clinical studies testing non-inferiority and then superiority in patients undergoing elective major orthopaedic surgery for total hip replacement (RECORD 1) or total knee replacement (RECORD 3) are available for assessment of the benefit of thromboprophylaxis with rivaroxaban:
The results of the two studies showed that the antithrombotic effect of oral rivaroxaban 10 mg daily was greater than that of subcutaneous enoxaparin 40 mg daily on total VTE and major VTE. The composite endpoint combining the incidence of major VTE (including PE and proximal DVT, whether symptomatic or venographically detected) and VTE-related death was a secondary endpoint, although considered more clinically relevant.

The increased clinical benefit due to rivaroxaban (XARELTO) derives essentially from a comparison of the incidences of venographically detected asymptomatic events, proximal in the case of hip replacements and distal in the case of knee replacements. The effect size is small. The modified intention-to-treat population was used for the superiority test.

The bleeding risks of rivaroxaban (XARELTO) and enoxaparin (LOVENOX) do not appear to differ at the dosages and treatment durations tested. XARELTO 10 mg daily does not seem to expose patients to a greater risk of vomiting (452/2,957 or 9.7% for rivaroxaban versus 482/4,692 or 10.3% for enoxaparin) compared with enoxaparin s.c. 40 mg daily.
The marketing authorisation (SPC) does not recommend any dose adjustment for patients aged above 65 years, obese (or underweight) patients and/or those with mild or moderate renal impairment. The bleeding risk does not seem to increase in patients aged above 65 years, obese (or underweight) patients and/or those with mild or moderate renal impairment; no dose adjustment is recommended for these patients. However, only limited clinical data are available for these groups at risk of VTED. Only limited clinical data are available for patients with severe renal impairment; therefore, rivaroxaban is to be used with caution, and its use is contraindicated where creatinine clearance is < 15 ml/min.

N.B.: There is some doubt as to whether the results of the two studies can be transposed to the very elderly patient population.
The clinical studies were performed on patient populations with an average age of 63 years following THR and 68 years following TKR. Patients aged above 75 accounted for only 13% (THR) and 21% (TKR) of the patients included. Some patients above the age of 80 have severely impaired renal function and may not be able to receive rivaroxaban treatment. Clinical data for patients in this sub-population who have moderate renal impairment are limited. According to PMSI (2006) data, 20% of THR patients and 17% of TKR patients were aged above 80 years.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Venous thromboembolism is a serious disease which may be life-threatening (potentially fatal pulmonary embolism) or cause major sequelae (post-thrombotic syndrome).

Patients undergoing major orthopaedic surgery for a total hip or knee replacement form a population at high risk of thromboembolism.

XARELTO is a first-line treatment indicated for the primary prevention of venous thromboembolism in adult patients who have undergone elective total hip or knee replacement surgery.

Public health benefit

The public health burden of venous thromboembolic disease (VTED) is considerable.

Having effective thromboprophylactic treatments that are well tolerated in terms of bleeding, particularly for high-risk patients, is a public health need.

From the available data, the medicinal product XARELTO may be expected to have little additional impact compared with current therapeutic management in terms of reducing the morbidity and mortality associated with complications of VTED or major bleeding induced by antithrombotic treatments in patients who have undergone elective total hip or knee replacement surgery.

The transposability of the experimental data to real life situations will depend particularly on the profile of the patients treated, which may well differ in real life from that of the study patients.

Since it has not been demonstrated, one cannot surmise what impact XARELTO might be expected to have on the healthcare system, because no specific laboratory monitoring is required and this medicinal product is taken orally.

All in all, XARELTO should help in responding to this identified public health need. Consequently, XARELTO is expected to provide some public health benefit. This benefit is small.

The efficacy/adverse effects ratio of rivaroxaban is high. There are alternative medicinal products, both oral (dabigatran etexilate; oral anticoagulants) and for injection (LMWH, UFH and fondaparinux sodium in particular).

Conclusion: the actual benefit of XARELTO 10 mg tablets is substantial.

4.2. Improvement in actual benefit

XARELTO 10 mg tablets provides a minor improvement in actual benefit (IAB IV) in terms of efficacy compared with LOVENOX (enoxaparin) for the prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery.

4.3. Therapeutic use

The objective of thromboprophylaxis is to prevent two main complications: pulmonary embolism and post-thrombotic syndrome. Treatment is usually given until the patient is actively walking. The risk of thromboembolism is high after major orthopaedic surgery of the lower limbs (total hip or knee replacement) and routinely requires prophylactic measures to be prescribed.[8]
In such cases, short-term thromboprophylaxis (in the 10 days following surgery) is therefore recommended: the first-line anticoagulant prescribed may be a low molecular weight heparin (LMWH non-inferiority compared with UFH) or fondaparinux 2.5 mg (ARIXTRA 2.5 mg).
An unfractionated heparin (UFH; morbidity/mortality data available for UFHs) is recommended for patients with severe renal impairment.
In addition, more prolonged thromboprophylaxis is recommended[9] for total hip (and knee[10]) replacements. UFHs, two LMWHs, enoxaparin (LOVENOX) and dalteparin (FRAGMIN) are the only products indicated for up to 35 days of prevention. Switching to short-term thromboprophylaxis with an oral anticoagulant (VKA) may also be considered.

PRADAXA (dabigatran etexilate) is an orally active antithrombotic agent that can be prescribed as first-line treatment. Its efficacy and safety were compared with those of enoxaparin (LOVENOX) for both short-term and prolonged (after hip replacement) thromboprophylaxis. It was shown to be non-inferior to enoxaparin (LOVENOX) in a composite endpoint (combining total VTE incidence and death from any cause), with a similar bleeding risk.

Therapeutic use of XARELTO
XARELTO (rivaroxaban) is a new antithrombotic agent that is also orally active and can be prescribed as first-line treatment. Its efficacy and safety were compared with those of enoxaparin (LOVENOX) for both short-term (after knee replacement) and prolonged (after hip replacement) thromboprophylaxis. XARELTO at a daily dose of 10 mg in adults showed slightly greater efficacy than enoxaparin (LOVENOX) for a composite endpoint, without increasing the bleeding risk. This clinical benefit was properly demonstrated. The extent to which this additional benefit leads to a reduction in the clinical events to be prevented (death, pulmonary embolism, and symptomatic DVT and its complications) is unknown.
The reference treatment for patients with moderate or severe renal impairment is UFH; the use of LMWH is not recommended (and contraindicated if creatinine clearance (CrCl) is < 20 ml/min). For some patients (those with renal impairment, and patients aged above 80 years) PRADAXA 150 mg daily is recommended for thromboprophylaxis, but clinical data are limited for these patients. Subcutaneous administration of 2.5 mg of fondaparinux sodium (ARIXTRA) seems to expose these patients to an increased risk of haemorrhage. Fondaparinux sodium is contraindicated if CrCl < 30 ml/min; data are limited for 20 < CrCl < 30 ml/min. Rivaroxaban (XARELTO) may be prescribed without requiring a dose adjustment in the event of severe renal impairment when CrCl > 15 ml/min. It is to be prescribed with caution when 15 < CrCl < 30 ml/min. Clinical data are, however, limited for these patients.
XARELTO may be prescribed according to the SPC, without requiring a dose adjustment, for patients aged above 65 years or who are overweight (> 120 kg) or underweight (< 50 kg). These data, however, are limited (few patients have been assessed) and an increase in bleeding risk cannot be ruled out (a tendency towards an increased bleeding risk was observed in the RECORD studies).

[8] Société Française d'Anesthésie et de Réanimation (SFAR). Prévention de la maladie thromboembolique veineuse périopératoire et obstrétricale – Recommandations pour la pratique clinique, 2005.
[9] ACCP. Prevention of venous thromboembolism – The seventh ACCP conference on antithrombotic and thrombolytic therapy. Chest 2004; 126(3):338S-400S.
[10] Jack Hirsh, Gordon Guyatt, Gregory W. Albers, Robert Harrington, and Holger J. Schünemann. Antithrombotic and thrombolytic therapy, 8th ed: ACCP Guidelines: Executive Summary: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133: 71S - 109S.

As with fondaparinux (ARIXTRA 2.5 mg) and dabigatran etexilate (PRADAXA), rivaroxaban (XARELTO) does not require routine monitoring of blood parameters.

4.4. Target Population

The target population for XARELTO comprises adult patients who have undergone elective total hip or knee replacement surgery.

Quantitative estimate: according to data from the PMSI Medicine Surgery Obstetrics database in 2007 (complete public and private database), the number of hospital stays was 117,400 (GHM 08C23V and 08C23W) for total hip replacement (with or without comorbidities) and 63,894 (GHM 08C24Z) for knee replacement, making a total of 181,294 procedures. The target population may be estimated at approximately 200,000 patients for the year 2009 (assuming that one procedure corresponds to one patient).
This figure tends to overestimate the target population likely to benefit from rivaroxaban thromboprophylaxis, given the prevalence of severe renal impairment in the very elderly.

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 in the indications and at the posology in the marketing authorisation.

The Transparency Committee would like to see a monitoring programme set up for a cohort of patients treated in France with XARELTO, in order to determine:

- the characteristics of the patients treated (age, type of surgery, type of anaesthesia, comorbidities, etc.)
- the actual conditions under which XARELTO is used (posology, treatment duration, compliance with administration regimen, etc.)
- the frequency of venous thromboembolic events
- safety in terms of major bleeding
- the impact on the healthcare system (extent to which platelet monitoring is requested, extent to which nursing procedures and call-outs are required, 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, cannot answer all the questions raised by the Transparency Committee, a specific study must be conducted.

AFSSAPS will also examine the study protocol in relation to the objectives that concern it, particularly the safety aspects.

Packaging: appropriate for the prescription conditions laid down in the marketing authorisation.

Reimbursement rate: 65%.