HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
12 June 2013

XARELTO 15 mg, film-coated tablet
B/10 (CIP: 34009 219 228 0 6)
B/14 (CIP: 34009 219 225 1 6)
B/28 (CIP: 34009 219 226 8 4)
B/42 (CIP: 34009 219 227 4 5)
B/100 (CIP: 34009 581 416 7 6)

XARELTO 20 mg, film-coated tablet
B/10 (CIP: 34009 219 231 1 7)
B/14 (CIP: 34009 219 229 7 4)
B/28 (CIP: 34009 219 230 5 6)
B/100 (CIP: 34009 581 419 6 6)

Applicant: BAYER SANTE

INN	rivaroxaban
ATC Code (2012)	B01AF01 (Antithrombotic agent)
Reason for the review	**Inclusion for an extension of the indication**
Lists concerned	**Social Security** (French Social Security Code L.162-17): for boxes of 10, 14, 28 and 42 **Hospital use** (French Public Health Code L.5123-2): only for box of 100.
Indication concerned	**"Treatment […] of pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (see Special warnings and precautions for use section for haemodynamically unstable PE patients)."**

Actual Benefit	**Substantial.** **The Committee emphasises that available data (EINSTEIN-EP study) are based on patients who mainly received an LMWH, an UFH or fondaparinux in the acute phase (24-36th hour) of pulmonary embolism.**
Improvement in Actual Benefit	**The Committee considers that XARELTO does not provide an improvement in actual benefit (IAB V, non-existent) in the treatment of pulmonary embolism (PE) and the prevention of recurrent DVT and PE in adults.**
Therapeutic use	**This product is a 1st line treatment.**
Recommendations	

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Initial Marketing Authorisation (European centralised procedure, rapporteur country: Sweden): 9 December 2011 (in the prevention of stroke and systemic embolism in cases of non-valvular AF, and in the treatment of deep-vein thrombosis and the prevention of the recurrence of DVT and pulmonary embolism (PE)) Extension of the indication: 15 November 2012 (treatment of PE and the prevention of recurrent DVT and PE)
Prescribing and dispensing conditions / special status	List I

ATC Classification	2013	
	B	Blood and blood forming organs
	B01	Antithrombotic agents
	B01AF	Direct factor Xa inhibitors
	B01AF01	Rivaroxaban

02 BACKGROUND

XARELTO (rivaroxaban) is an active anticoagulant when administered orally that directly inhibits factor Xa. The 15 and 20 mg doses have Marketing Authorisation in the treatment of deep-vein thrombosis (substantial AB, IAB V) and the prevention of systemic embolism -stroke and PE - in patients with non-valvular atrial fibrillation (Substantial AB, IAB V). In 2012, XARELTO obtained an extension of the indication in the treatment of pulmonary embolism and in the prevention of recurrent pulmonary embolism or deep-vein thrombosis.

The 10 mg dose only has Marketing Authorisation in the prevention of venous thromboembolic events in adult patients undergoing elective hip or knee replacement surgery.

03 THERAPEUTIC INDICATIONS

"• Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.
• **Treatment** of deep-vein thrombosis (DVT) and **pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (see Special warnings and precautions for use section for haemodynamically unstable PE patients[1]).**"

[1] *"Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy: XARELTO is not recommended as an alternative to unfractionated heparin in patients with pulmonary embolism who are haemodynamically unstable or may receive* thrombolysis or pulmonary embolectomy since the safety and efficacy of XARELTO have not been established in these clinical situations."

04 DOSAGE

"The recommended dose for the initial treatment of acute DVT or PE is 15 mg twice daily for the first three weeks, followed by 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE:

	Dosage	Maximum daily dose
Days 1-21	15 mg twice daily	30 mg
Day 22 and onwards	20 mg once daily	20 mg

The duration of therapy should be individualised after careful assessment of the treatment benefit against the risk for bleeding. Short duration of therapy (at least 3 months) should be based on transient risk factors (e.g. recent surgery, trauma, immobilisation) and longer durations should be based on permanent risk factors or idiopathic DVT or PE.

Special populations:

Renal impairment:
- In patients with mild renal impairment (creatinine clearance 50 - 80 ml/min): no dose adjustment is necessary.
- In patients with moderate (creatinine clearance 30 to 49 ml/min) or severe (creatinine clearance 15 to 29 ml/min) renal impairment:
    - patients should be treated with 15 mg twice daily for the first 3 weeks.
    - Thereafter, the recommended dose is 20 mg once daily. A reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on pharmacokinetic modelling and has not been studied in this clinical setting.
- Limited clinical data for patients with severe renal impairment (creatinine clearance 15 to 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, XARELTO is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min."

Hepatic impairment: XARELTO is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C.

Elderly population: no dose adjustment.

Body weight / Gender: no dose adjustment.

Dose recommendations before and after invasive procedures and surgical procedures: "If an invasive procedure or surgical intervention is required, XARELTO should be stopped at least 24 hours before the intervention, if possible and based on the clinical judgement of the physician. If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention. XARELTO should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established."

NB. The extension of the indication in pulmonary embolism has led to the following warning being removed from the SPC: "experience of the use of XARELTO in this indication for longer than 12 months is limited" and in moderate to severe renal impairment to stating that a reduction in dose is considered "if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE."

05 THERAPEUTIC NEED

In France, despite there being progress in diagnosis and awareness of thromboprophylaxis, thromboembolic disease (DVT and PE) remains a major cause of morbidity and death through pulmonary embolism, with approximately 10,000 deaths attributable each year (3rd cause of vascular deaths). Without treatment, patients are exposed to a significant risk of recurrence, estimated at around 20% at three months, often down to a chronic post-embolic pulmonary cardiac presentation.

The aim of treatment is to reduce immediate morbidity and mortality then the risk of recurrence (DVT, PE). Excluding haemodynamically unstable embolisms or those requiring thrombolysis or pulmonary embolectomy, the treatment involves anticoagulant therapy, prescribed quickly. Initial treatment, in the absence of renal impairment, involves an unfractionated heparin (UFH, via SC injection or IV), a low molecular weight heparin (LMWH via SC injection) or fondaparinux (ARIXTRA via SC injection). Continued treatment with LMWHs or a Vitamin K antagonist anticoagulant (VKA) is to be considered with a minimum treatment duration of 3 months. Beyond this timeframe, the clinical likelihood of the occurrence of PE is the parameter that determines the risk of thromboembolic relapse and the duration of anticoagulant treatment. In cases of renal impairment, the standard treatment remains a UFH.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

NAME (INN) *Company*	Identical TC* yes/no	Indication	Date of opinion	AB	IAB (Wording)
INNOHEP (tinzaparin) *Léo*	no LMWH	Curative treatment of pulmonary embolism with no clinical signs of seriousness, in the absence of pre-existing cardiac or pulmonary disease and excluding emboli that are likely to have resulted from thrombolytic or surgical treatment. If there are signs of haemodynamic instability, unfractionated heparin and, in some cases, thrombolysis or surgical embolectomy should be used in preference. This treatment is not indicated for patients who have undergone recent surgery.	28 /03/ 2001	Substantial	Confirms the level of IAB agreed in 1996 (IAB IV in terms of ease of use in comparison with CLIVARIN, FRAGMIN, FRAXIPARIN and LOVENOX)
LOVENOX (enoxaparin) *Sanofi*	no LMWH	Curative treatment of established deep-vein thrombosis **with or without pulmonary embolism with no signs of clinical seriousness**, except for pulmonary embolisms that are likely to have resulted from thrombolytic or surgical treatment.	6 /07/ 2005	Substantial	IAB V
CALCIPARIN (heparin calcium) *Sanofi*	no UFH	Curative treatment of established deep-vein thrombosis and pulmonary embolism, in the acute phase.	ND	Substantial	ND
HEPARIN CHOAY (heparin sodium) *Sanofi*	no UFH	Curative treatment of established deep-vein thrombosis and pulmonary embolism, in the acute phase.	ND	Substantial	ND
ARIXTRA (fondaparinux) *GSK*	no	Treatment of acute deep vein thrombosis (DVT) and acute pulmonary embolism (PE), except in patients who are haemodynamically unstable and those who require thrombolysis or pulmonary embolectomy.	21 /09/ 2005	Substantial	IAB IV in terms of safety in comparison with standard treatment

SINTROM MINI-SINTROM (acenocoumarol) *Novartis* Pharma	no VKA	Treatment of DVT and PE, and prevention of recurrence of these conditions, as a follow-on treatment from heparin.	ND	Substantial	ND
PREVISCAN (Fluindione) *Merck Santé*				Substantial	
COUMADIN (Warfarin) *Bristol-Myers Squibb*				Substantial	

*therapeutic category; ND: no data

All of these medicinal products are reimbursed.

◗ Conclusion

The comparators stated are all clinically relevant; oral vitamin K antagonist anticoagulants (VKA) only being prescribed after a heparin (UFH or LMWH).

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Data regarding the reimbursement or not of the medicinal product in Europe and in North America:

Country	REIMBURSED	
	YES/NO If no, why not	Population(s) That of the Marketing Authorisation or restricted
Denmark	yes	Marketing Authorisation

The FDA granted XARELTO Marketing Authorisation in this indication.

08 ANALYSIS OF AVAILABLE DATA

The assessment of rivaroxaban (XARELTO) for adults in the treatment of pulmonary embolism (PE) and the prevention of recurrence of deep-vein thrombosis (DVT) or PE is based on:

- a non-inferiority study (EINSTEIN-PE) that compared rivaroxaban with enoxaparin followed by a VKA over 3, 6 or 12 months in patients with PE;
- a study that compared rivaroxaban with placebo in the maintenance treatment of PE (patients from the EINSTEIN-PE study[2]) or DVT (patients from the EINSTEIN-TVP study), previously treated for 6 to 12 months. Efficacy results for this study are presented for information only, since the duration of prolonged treatment with rivaroxaban has not been validated through a Marketing Authorisation.

08.1 Efficacy

EINSTEIN-PE study

Aims:

The aim of this randomised, open-label study was to demonstrate the non-inferiority (then secondly superiority) of rivaroxaban compared with treatment with enoxaparin followed by a vitamin K antagonist (warfarin or acenocoumarol) in the treatment of pulmonary embolism (PE) with or without concomitant deep-vein thrombosis (DVT) and in the secondary prevention of recurrent venous thromboembolic events (VTE).

Another aim of this study was to compare the risk of haemorrhage for the two treatments with the incidence of major haemorrhages or non-major clinically significant haemorrhages (primary safety endpoint).

Study design (figure 1):

Trial method:
This multi-centred study took place in 263 centres across 38 countries between March 2007 and December 2011. In France, 34 centres included 1,169 patients, which is 24% of the total population size.
The protocol authorised the administration of a treatment with LMWH, UFH or fondaparinux (for a maximum duration of 48 hours) prior to randomisation. During the study, use of acetylsalicylic acid (<100 mg/day) or clopidogrel (75 mg/day) was permitted.

[2] EINSTEIN–PE Investigators, Büller HR, Prins MH, Lensin AW et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366:1287-97.

Inclusion criteria:
Adults with a confirmed acute symptomatic PE with or without DVT.

Non-inclusion criteria included:

- severe renal impairment with creatinine clearance (Cr Cl) <30 ml/min.
- active haemorrhaging or high risk of haemorrhaging, which contraindicates treatment with enoxaparin or VKA.
- Serious liver disease (acute hepatitis, active chronic hepatitis or cirrhosis) or ALT >3 times the upper limit of normal (ULN).
- Concomitant use of inhibitors or strong inducers of CYP3A4.

Dosage of the medicines evaluated:

- Rivaroxaban: 15 mg x2/day for 3 weeks, then 20 mg/day in one daily dose;
- Enoxaparin: 1 mg/kg x2/day for at least 5 days combined with a VKA (warfarin or acenocoumarol) (overlap of 4 to 5 days), then treatment with VKA alone until two consecutive INR spaced at an interval of 24 hours were ≥2. The target INR was 2.5 (range: 2.0-3.0).

Three treatment durations were possible: 3, 6 and 12 months, depending on the risk factors for the patient and local recommendations. The treatment duration was decided by the investigator at the time of randomisation. For the analysis of results, stratification into sub-groups according to treatment duration was carried out. The planned follow-up period after the end of treatment was 30 days.

Primary efficacy endpoint:

The primary efficacy endpoint combined recurrence of DVT or PE (whether fatal[3] or not). The occurrence of the first of these events was taken into account when evaluating this endpoint.

Secondary efficacy endpoints:

- Each of the component events of the primary efficacy endpoint (recurrence, whether fatal or not, of DVT or PE)
- Death from any cause
- Recurrence of PE (DVT, PE) or death from any cause
- The net clinical benefit was estimated on the basis of the composite endpoint, which combined recurrence of DVT or PE (whether fatal or not) and major haemorrhages.
- An endpoint combining major haemorrhages[4] and non-major but clinically significant haemorrhages[5] was the primary safety endpoint.
- The incidence of vascular events.

Method and strategy for the analysis of the results:

Three populations were defined for the analysis of the results:

- The ITT Population: all randomised patients.
- The Per-protocol Population (PP): patients from the ITT population, excluding those with at least one major protocol violation.

[3] Fatal pulmonary embolism was defined as either pulmonary embolism, which had been confirmed by diagnostic tests or by autopsy, or death of unknown cause and/or where DVT/PE could not be excluded.
[4] Major haemorrhages were defined as all fatal haemorrhages, any obvious bleeding associated with a loss of haemoglobin ≥2 g/dl or requiring transfusion of 2 units of blood or more, any haemorrhage involving a critical organ (intracranial, intraspinal, intraocular, pericardial, intramuscular with compartment syndrome and retroperitoneal haemorrhage).
[5] Bleeding that is not major but is clinically significant is defined as any excessive bleeding, which does not fit the definition of a major haemorrhagic event, but which is associated with medical intervention or with non-scheduled contact with a doctor or with a (temporary) interruption of treatment, or with problems for the patient (such as pain) or with changes in the activities of daily life.

- Safety population (population treated): randomised patients, who received at least one dose of anticoagulant (enoxaparin, warfarin, acenocoumarol or rivaroxaban).

The mean incidence of the occurrence of DVT or PE was expected to be 3% for the two treatment groups. The null hypothesis was that rivaroxaban was equivalent to the reference treatment. In order to refute this with a statistical power of 90%, an α risk of 5% and a hazard ratio non-inferiority margin of 2, a sample size of at least 1,465 patients per group was judged to be needed in order to have the number of events reach 88. The protocol anticipated that recruitment could be interrupted if the steering committee estimated that the total number of at least 88 recurrent thromboembolic events could be achieved. In such a case, the patients had to complete the scheduled duration of treatment, with the exception of patients in the 12-month cohort, who had completed at least 6 months of treatment.

The time elapsed between randomisation and the occurrence of the first event for the primary efficacy endpoint was analysed using the Cox proportional risk model, stratified by the planned duration of treatment (3, 6 or 12 months) and adjusted for the presence of cancer at the time of enrolment. The hazard ratio for rivaroxaban/comparator was calculated with a two-sided confidence interval of 95%.

On the basis of this model, rivaroxaban was considered to be at least as effective as the comparator if the upper limit of the hazard ratio confidence interval was below 2.0. Similar limit values were obtained in recent clinical trials (limit = 2 in the Van Gogh[6] (2007) and Thrive 2[7] (2005) studies; limit = 1.7 in the Matisse[8] (2004) study.

If non-inferiority for the primary efficacy endpoint was demonstrated, the superiority was investigated (in the ITT and PP populations). Furthermore, if non-inferiority was established with respect to the primary efficacy endpoint, the safety population was subjected to a procedure of sequential tests as follows:

a) test of superiority for the primary safety endpoint (major haemorrhages and non-major but clinically significant haemorrhages),

b) test of superiority for the major haemorrhages alone.

Sub-group analyses:

Previously planned analyses for the primary efficacy endpoint and for the primary safety endpoint in the various sub-groups were carried out; these analyses measured the influence of the following co-variants: active cancer, idiopathic DVT, history of DVT or PE, known thrombophilia, gender (male vs. female), age (<60 years vs. >60 years and <65 years vs. 65-75 years vs. >75 years), weight (<90 kg vs. >90 kg), renal function (creatinine clearance <50 ml/min, between 50 and 80 ml/min or >80 ml/min), presence or absence of lung disease, heart disease, presence or absence of immobilisation at the time of randomisation, location of the DVT (femoral or proximal vs. popliteal or distal). Results according to treatment duration (3, 6 or 12 months) and, in the enoxaparin/VKA arm, as a function of INR, were also analysed. Results for the population of "vulnerable patients," defined as those with at least one of the following characteristics: age >75 years, body weight <50 kg or creatinine clearance <50 ml/min, were subjected to post-hoc analysis.

[6] Van Gogh investigators. Idraparinux versus standard therapy for venous thromboembolic disease. N Engl J Med 2007;357 :1094-1104.
[7] Fiessinger JN. Ximelagatran versus low-molecular-weight heparin and warfarin for treatment of deep vein thrombosis. JAMA 2005;293 :681-89.
[8] Matisse investigators. Fondaparinux or enoxaparin for initial treatment of symptomatic deep venous thrombosis. Ann Intern Med 2004;140 :867-73.

Results:

Populations analysed

Table 1: Number of patients by analysis population

	Rivaroxaban	Enoxaparin/VKA	Total
Randomised	2,420	2,413	4,833
ITT population	2,419	2,413	4,832
Safety population	2,412	2,405	4,817
Per-protocol population (PP)	2,224	2,238	4,462

Characteristics of the population evaluated

The demographic characteristics of the patients at baseline were similar in the two treatment groups, with a mean age of 58 years (nearly 31% were aged between 60 and 75 years and nearly 20% were older than 75 years), a mean weight of 83 kg (BMI 28 kg/m^2), with the majority being male (51-54%) and Caucasian (66%). Of the patients with an impaired renal function (approximately 1/3 of the overall population), nearly 26% had mild renal impairment (Cr Cl between 50 and 80 ml/min), 8-9% had moderate renal impairment (Cr Cl between 30 and 50 ml/min), and less than 0.5% had severe renal impairment (Cr Cl <30 ml/min).

The distribution of patients as a function of the treatment duration predetermined by the investigator is presented in Table 2.

Table 2. Distribution of patients according to treatment duration

N (%)	Rivaroxaban N = 2,420	Enoxaparin/VKA N = 2,413	Total N = 4,833
3 months	127 (5.2)	122 (5.1)	249 (5.2)
6 months	1,388 (57.4)	1,387 (57.5)	2,775 (57.4)
12 months	905 (37.4)	904 (37.5)	1,809 (37.4)

The patients' demographic characteristics were comparable between the two treatment arms for the same treatment period.

At inclusion, the diagnosis of PE was confirmed for 99% of patients (ITT population). PE was considered as secondary[9] in approximately 35% of patients. DVT was associated with PE in one quarter of patients, with the DVT being proximal in 9 cases out of 10. Twenty percent (20%) of patients had a history of VTED. The median period between the onset of PE symptoms and randomisation was 4 days in both groups. The two groups were comparable both with respect to the spontaneous nature or otherwise of the PE and with respect to the trigger factor (Table 3).

Table 3. PE aetiology (ITT population)

N (%)	Rivaroxaban N = 2,419	Enoxaparin/VKA N = 2,413
Spontaneous PE	1,566 (64.7)	1,551 (64.3)
Secondary PE	853 (35.3)	862 (35.7)
Recent surgery or injury	415 (17.2)	398 (16.5)
Immobilisation	384 (15.9)	380 (15.7)
Use of medicines containing oestrogens	207 (8.6)	223 (9.2)
Active cancer	114 (4.7)	109 (4.5)
post-partum	6 (0.2)	5 (0.2)

Table 4. Thromboembolic risk factors (ITT Population)

N (%)	Rivaroxaban (N = 2,419)	Enoxaparin/VKA (N = 2,413)
Idiopathic DVT/PE	1,196 (49.4)	1,186 (49.2)
History of DVT/PE	455 (18.8)	489 (20.3)
Recent surgery or injury	415 (17.2)	398 (16.5)
Immobilisation	384 (15.9)	380 (15.7)
Use of medicines containing oestrogens	207 (8.6)	223 (9.2)

[9] DVT is considered as being secondary if at least one of the following factors is present at the time of diagnosis: recent surgery or injury, immobilisation, oestrogen treatment, post-partum period and active cancer.

Known constitutional thrombophilic status	138 (5.7)	121 (5.0)
Active cancer	114 (4.7)	109 (4.5)
Obesity	95 (3.9)	97 (4.0)

Table 5. Thromboembolic risk factors according to treatment duration – ITT population

	Rivaroxaban N (%)	Enoxaparin/VKA N (%)
Planned treatment duration = 3 months	(N = 127)	(N = 122)
Recent surgery or injury	55 (43.3)	58 (47.5)
Idiopathic DVT/PE	43 (33.9)	33 (27.0)
Immobilisation	30 (23.6)	37 (30.3)
Use of medicines containing oestrogens	12 (9.4)	14 (11.5)
Active cancer	7 (5.5)	6 (4.9)
History of DVT/PE	8 (6.3)	3 (2.5)
Planned treatment duration = 6 months	(N = 1,387)	(N = 1,387)
Idiopathic DVT/PE	684 (49.3)	699 (50.4)
Recent surgery or injury	272 (19.6)	259 (18.7)
Immobilisation	254 (18.3)	266 (19.2)
Use of medicines containing oestrogens	151 (10.9)	152 (11.0)
History of DVT/PE	142 (10.2)	147 (10.6)
Active cancer	68 (4.9)	62 (4.5)
Known thrombophilic status	65 (4.7)	47 (3.4)
Planned treatment duration = 12 months	(N = 905)	(N = 904)
Idiopathic DVT/PE	469 (51.8)	454 (50.2)
History of DVT/PE	305 (33.7)	339 (37.5)
Immobilisation	100 (11.0)	77 (8.5)
Recent surgery or injury	88 (9.7)	81 (9.0)
Known thrombophilic status	72 (8.0)	71 (7.9)
Use of medicines containing oestrogens	44 (4.9)	57 (6.3)
Obesity	42 (4.6)	46 (5.1)
Active cancer	39 (4.3)	41 (4.5)

Treatment duration: nearly half of patients (44% in the rivaroxaban group and 41% in the enoxaparin/VKA group) were treated for between 6 and 9 months. The median treatment duration in the ITT analysis population was 183 days (179-352) in the rivaroxaban group and 182 days (178-351) in the enoxaparin/VKA group.

Other medicines received

In the ITT population, 92% of patients randomised in the two treatment groups had already received an LMWH, a UFH or fondaparinux before being randomised for treatment of their PE. After randomisation, 30% of patients in the rivaroxaban group and 36% of patients in the enoxaparin/VKA group received other antithrombotic agents (among others at the time of their surgical procedure). The most commonly used agents were enoxaparin (rivaroxaban group: 8%; enoxaparin/VKA group: 14%) and warfarin (rivaroxaban group: 4.5%; enoxaparin/VKA group: 3.6%). An anti-platelet aggregation agent was administered to 15.7% of patients in the rivaroxaban group and 14.4% in the enoxaparin/VKA group (14.3% and 13.3% of patients received acetylsalicylic acid respectively).

The median initial treatment duration with LMWH for PE for patients randomised in the enoxaparin/VKA group was 8 days.

Monitoring of INR

The mean percentage of adjusted time spent within the target therapeutic period was 62.7% of the total study duration. Under real life usage conditions, following a transversal study carried out in France by the Limousin-Poitou-Charentes region Health Insurance medical department (Service Médical de l'Assurance Maladie) in 2002,[10] this percentage was actually 54%.

[10] Chastagner M, Gault M, Aboyans V, Lacroix P. A long-term follow-up quality evaluation of patients taking oral anticoagulant therapy. Arch Mal Coeur Vaiss 2005;98:199-204.

Efficacy results:

Primary efficacy endpoint

In the PP population, the incidence of recurrence of DVT or PE, whether fatal or not, was 1.7% in the rivaroxaban group and 1.6% in the enoxaparin/VKA group, HR = 1.045 (95% CI: [0.662-1.648]), p=0.0026. The limit of non-inferiority was calculated to ensure that a 66% efficacy of the standard treatment was conserved (enoxaparin+VKA). The upper limit of the confidence interval observed was 1.648 (PP population) which corresponds to a conservation of at least 78.4% of the efficacy of the comparator (1 + (1 – 0.784)*(1/0.25 - 1) = 1.648).

Results were similar in the ITT population, with an incidence for the primary efficacy endpoint of 2.1% in the rivaroxaban group and 1.8% in the enoxaparin/VKA group, HR = 1.123 (95% CI: [0.749-1.684]) in the ITT population. The upper limit of the confidence interval was below the margin of non-inferiority and the non-inferiority of rivaroxaban compared with enoxaparin/VKA was demonstrated.

Table 6: Results for the primary efficacy endpoint

Population	ITT[a]	PP[b]
Rivaroxaban	50/2 419 (2.1%)	38/2 224 (1.7%)
Enoxaparin/VKA	44/2 413 (1.8%)	36/ 2238 (1.6%)
Cox proportional risk model for rivaroxaban versus enoxaparin/VKA		
Hazard ratio	1.123	1.045
Confidence Interval	0.749-1.684	0.662-1.648
$p_{non\text{-}inferiority}$	0.0026	0.0026
$p_{superiority}$	0.5737	0.8504

[a]: events until the end of the planned treatment period, regardless of whether the medicine was taken (for the ITT population)

[b]: events during treatment, until the last documented dose of the medicine + 2 days (for the PP population)

Between the 1st and 21st day of treatment, the period during which the risk of recurrence is high and rivaroxaban was administered at a dosage of 15 mg twice daily, the cumulative rate of primary efficacy endpoint events (Kaplan Meier method) was similar in the rivaroxaban group (18 events (0.7%) and in the enoxaparin/VKA group (21 events (0.9%)).

Superiority of rivaroxaban over treatment with enoxaparin/VKA has not been demonstrated (p = 0.5737 in the ITT population).

Sub-group analysis (ITT population)

The results for the primary efficacy endpoint were uniform in the various pre-specified sub-groups, particularly in terms of treatment duration (3, 6 or 12 months, see Table 7), in vulnerable patients (see Table 8), and as a function of age, previous treatment with LMWH or fondaparinux before randomisation, the presence or absence of a history of DVT or PE and the presence of cancer or renal impairment.

Table 7: incidence of the primary efficacy endpoint according to treatment duration (ITT population)

Duration of treatment	Rivaroxaban n/N	(%)	Enoxaparin/VKA n/N	(%)	Hazard ratio (95% CI)	Value of p for the interaction test
3 months	6/127	(4.7%)	2/122	(1.6%)	2.909 (0.587-14.414)	0.440
6 months	27/1,387	(1.9%)	24/1,387	(1.7%)	1.116 (0.644-1.933)	
12 months	17/905	(1.9%)	18/904	(2.0%)	0.939 (0.484-1.822)	

Table 8: incidence of the primary efficacy endpoint in the sub-group of vulnerable patients (ITT population)

	Rivaroxaban n/N (%)	Enoxaparin/VKA n/N (%)	Hazard Ratio	95% CI
Vulnerable patients	14/510 (2.7%)	17/477 (3.6%)	0.748	0.369-1.519
Non-vulnerable patients	36/1,909 (1.9%)	27/1,936 (1.4%)	1.345	0.816-2.215

Secondary efficacy endpoints

Primary efficacy endpoint events:

Table 9: incidence of primary efficacy endpoint events (ITT and PP populations)

	ITT population		PP Population	
N (%)	Rivaroxaban N = 2,419	Enox./VKA N = 2,413	Rivaroxaban N = 2,224	Enox./VKA N = 2,238
Primary efficacy endpoint	50 (2.1)	44 (1.8)	38 (1.7)	36 (1.6)
Death (PE)	3 (0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Death (PE cannot be ruled out)	8 (0.3)	6 (0.2)	7 (0.3)	5 (0.2)
Symptomatic PE and DVT	0	2 (<0.1)	0	2 (<0.1)
Symptomatic, recurrent PE alone	23 (1.0)	20 (0.8)	16 (0.7)	16 (0.7)
Symptomatic, recurrent DVT alone	18 (0.7)	17 (0.7)	15 (0.7)	14 (0.6)

Death from any cause: see adverse effects section.

Endpoint combining recurrence of DVT, fatal or non-fatal PE and death from any cause:

The incidence of these events was 4.0% (97/2,419) in the rivaroxaban group and 3.4% (82/2,413) in the enoxaparin/VKA group for the ITT population, HR = 1.156 (95% CI: [0.862-1.552]) according to the Cox proportional risks model. The results for the PP population are comparable, HR = 1.022 (95% CI: [0.691-1.513]).

Table 10: incidence of secondary endpoint events

N (%)	ITT population		PP Population	
	Rivaroxaban N = 2,419	Enox./VKA N = 2,413	Rivaroxaban N = 2,224	Enox./VKA N = 2,238
Secondary efficacy endpoint (predefined)	97 (4.0)	82 (3.4)	51 (2.3)	49 (2.2)
Death (PE)	3 (0.1)	1 (<0.1)	1 (<0.1)	1 (<0.1)
Death (PE cannot be ruled out)	8 (0.3)	6 (0.2)	7 (0.3)	5 (0.2)
Death (haemorrhaging)	5 (0.2)	4 (0.2)	1 (<0.1)	2 (<0.1)
Death (cardiovascular)	10 (0.4)	3 (0.1)	3 (0.1)	1 (<0.1)
Death (other)	32 (1.3)	36 (1.5)	9 (0.4)	10 (0.4)
Symptomatic PE and DVT	0	2 (<0.1)	0	2 (<0.1)
Symptomatic, recurrent PE alone	23 (1.0)	20 (0.8)	16 (0.7)	16 (0.7)
Symptomatic, recurrent DVT alone	18 (0.7)	17 (0.7)	15 (0.7)	14 (0.6)

Estimation of the net clinical benefit: the incidence of recurrent DVT or PE and of major haemorrhages up to the end of treatment was 3.4% (83/2,419) in the rivaroxaban group and 4.0% (96/2,413) in the enoxaparin/VKA group for the ITT population, HR = 0.849 (95% CI: [0.633 - 1.139]) according to the Cox proportional risks model. In the PP population, this incidence was 2.3% (62/2,224) in the rivaroxaban group and 3.5% (79/2,238) in the enoxaparin/VKA group.

08.2 Adverse effects

08.2.1 Adverse effects in the EINSTEIN-PE study

In the EINSTEIN-PE study, 2,412 patients were treated with rivaroxaban (median duration: 182 days) and 2,405 patients with enoxaparin/VKA (median duration: 181 days). The frequency of treatment discontinuation due to an adverse event was of the same order in both groups: 123 (5.1%) in the rivaroxaban group and 99 (4.1%) in the enoxaparin/VKA group. The incidence of adverse effects occurring during treatment was similar for both groups (32% of patients) and the incidence of serious adverse effects was also comparable (nearly 19%).

Risk of haemorrhage

The occurrence of the primary safety endpoint, defined as major and clinically significant but non-major haemorrhages, was similar between the groups: 10.3% (249/2,412) with rivaroxaban versus 11.4% (274/2 405) with enoxaparin/VKA, with a HR of 0.900 (95% CI [0.758-1.069]), p=0.2305.

Results for the sub-group analysis:

Primary safety endpoint events:

Non-inferiority with respect to the primary endpoint having been established, in accordance with the protocol, tests for superiority with respect to safety endpoints were performed.
Incidence of major haemorrhages[11] was less for patients in the rivaroxaban group (26 patients, 1.1%) than those in the enoxaparin/VKA group (52 patients, 2.2%), HR = 0.493 95% CI: [0.308-0.789], p=0.0032. This result is only exploratory due to the discontinuation of the hierarchical analysis.

There were seven non-fatal major haemorrhages involving a vital organ in the rivaroxaban group versus 26 in the enoxaparin/VKA group.
There were two major fatal haemorrhages in the rivaroxaban group, and three in the reference group.

[11] The result is exploratory, given the discontinuation of the hierarchical analysis.

Table 11: major haemorrhages that occurred during treatment (Safety population)

n (%)	Rivaroxaban N=2,412	Enoxaparin/VKA N=2,405
Major haemorrhagic events	26 (1.1)	52 (2.2)
Fatal haemorrhage	2 (<0.1)	3 (0.1)
Intracranial	*2 (<0.1)*	*2 (<0.1)*
Retroperitoneal	*0*	*1 (<0.1)*
Haemorrhage involving a vital organ	7 (0.3)	26 (1.1)
Not coded	*0*	*1 (<0.1)*
Intracranial	*1 (<0.1)*	*10 (0.4)*
Retroperitoneal	*1 (<0.1)*	*7 (0.3)*
Intraocular	*2 (<0.1)*	*2 (<0.1)*
Pericardial	*0*	*2 (<0.1)*
Intra-articular	*0*	*3 (0.1)*
Adrenal	*1 (<0.1)*	*0*
Pulmonary	*1 (<0.1)*	*0*
Abdominal	*1 (<0.1)*	*2 (<0.1)*
Non-fatal haemorrhage not involving a vital organ (reduction in Hb level ≥2 g/dl and/or transfusion ≥2 units of blood)	17 (0.7)	25 (1.0)
Surgical site	*0*	*3 (0.1)*
Cutaneous (not at injection site)	*1 (<0.1)*	*2*
Genitourinary	*1 (<0.1)*	*1*
Gastrointestinal	*9 (0.4)*	*16 (0.7)*
Nasal	*1*	*0*
Rectal	*1*	*0*
At injection site/where blood was taken	*0*	*1 (<0.1)*
Uterine	*3 (0.1)*	*0*
Pulmonary	*1 (<0.1)*	*0*
Intramuscular	*0*	*2 (<0.1)*
Abdominal	*0*	*1 (<0.1)*
Other: rectal*	*0*	*1 (<0.1)*

* : one patient had a gastrointestinal bleed associated with a reduction in Hb levels ≥2 g/dl and transfusions ≥2 units of blood, however the reduction in Hb level and the transfusion were not documented in the database and the site coding was not corrected as gastrointestinal.

The incidence of non-major but clinically significant haemorrhages was similar in the two treatment groups: 9.5% (228/2,412) with rivaroxaban versus 9.8% (235/2,405) with enoxaparin/VKA.

Analysis of the primary safety endpoint according to the predetermined treatment duration:
In the two treatment groups, the incidence of major and clinically significant but non-major haemorrhages (primary safety endpoint) was slightly higher for patients in the 12 months sub-group compared with the 6 months sub-group, which may suggest an increase in the risk of haemorrhaging depending on the duration of anticoagulant treatment.

Table 12: incidence of primary safety endpoint according to the predetermined treatment duration (safety population)

n/N (%)	Rivaroxaban	Enoxaparin/VKA
Treatment duration = 3 months	9/125 (7.2)	13/122 (10.7)
Treatment duration = 6 months	129/1383 (9.3)	142/1382 (10.3)
Treatment duration = 12 months	111/904 (12.3)	119/901 (13.2)

Analysis for the sub-group of vulnerable patients:
According to a post-hoc analysis, the incidence of the primary safety endpoint for those patients aged over 75 years and/or with a body weight ≤50 kg and/or a creatinine clearance <50 ml/min was similar in the two groups. No interaction was established (p for interaction = 0.118).

Table 13: incidence of major and clinically significant but non-major haemorrhages according to the vulnerability of the patients

n/N (%)	Incidence		Hazard Ratio	95% CI	p interaction
	Rivaroxaban	Enoxaparin/VKA			
Non-vulnerable patients	184/1,904 9.7	194/1,929 10.1	0.969	0.792-1.185	0.118
Vulnerable patients	64/508 12.6	80/476 16.8	0.716	0.515-0.994	

Analysis as a function of patient characteristics and the presence of haemorrhage risk factors:
There is no heterogeneity of the results in these sub-groups with those for the overall population, in particular according to age (<65 years or >75 years), the presence of cancer, the status of renal function (creatinine clearance ≥80 ml/min, 50 to <80 ml/min and <50 ml/min) or a previous treatment with heparin or fondaparinux before randomisation.

Antidote for rivaroxaban
There is no specific antidote for rivaroxaban available in cases of haemorrhagic complications.[12] Given the strong bond that rivaroxaban has with plasma proteins, the product is not likely to be able to be dialysed.

Monitoring of coagulation
According to the SPC, the routine monitoring of coagulation parameters is not necessary during treatment with rivaroxaban. However, if monitoring is clinically indicated, plasma concentrations of rivaroxaban can be measured using calibrated quantitative factor Xa inhibitor tests (examinations carried out in specialist laboratories or hospitals).

Death
A total of 114 deaths (rivaroxaban: 63 [2.6%]; enoxaparin/VKA: 51 [2.1%]) were reported in the safety population. The four most common causes of death reported in the two treatment groups were: cancer (rivaroxaban: 0.9%; enoxaparin/VKA: 1.0%), infectious disease (rivaroxaban: 0.4%; enoxaparin/VKA: 0.2%), unexplained death for which PE could not be ruled out (rivaroxaban: 0.3%; enoxaparin/VKA: 0.2%), and haemorrhage (rivaroxaban: 0.2%; enoxaparin/VKA: 0.2%).

Hepatic safety
No sign of hepatic toxicity was detected. An increase in ALAT levels of more than 3 times the normal value was observed for 1.9% (45/2,351) of patients treated with rivaroxaban and for 3.0% of those treated with enoxaparin/VKA (70/2,324).
It should be noted that the SPC states that XARELTO is contraindicated “in cases of hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C.”

NB. The applicant has provided the pooled results from the EINSTEIN EP and TVP studies, which in terms of safety confirm the results from the EINSTEIN EP study, a lowering in major haemorrhagic events with XARELTO and a similar level of events for the primary safety endpoint combining major haemorrhages and clinically significant but non-major haemorrhages.

[12] According to the SPC, the route to take in cases of haemorrhagic complications includes the following measures: the use of active charcoal to limit absorption in cases of overdose of rivaroxaban l; delay the next administration of rivaroxaban or discontinue treatment, depending on needs, knowing that the final half-life of rivaroxaban is 7 to 11 hours; appropriate symptomatic treatment e.g. mechanical compression, surgical intervention, vascular filling and haemodynamic correction and blood or blood products transfusion. If these measures are inadequate or in case of a life-threatening situation for the patient, the administration of recombinant factor VIIa may be considered, although this recommendation is based on limited non-clinical data and the use of recombinant factor VIIa in patients treated with rivaroxaban is yet to be documented.

08.2.2 Information from the SPC

-In patients with moderate (creatinine clearance of 30 to 49 ml/min) or severe renal impairment (creatinine clearance of 15 to 29 ml/min) patients should be treated with two doses per day of 15 mg for the first three weeks. Then, the recommended dose is 20 mg in a single dose per day.
The SPC states that a reduction of the 20 mg dose taken once per day to the 15 mg dose taken once daily should be considered if the patient's assessed risk of bleeding outweighs the risk of recurrent DVT or PE. However the 15 mg dose is recommended on the basis of a pharmacokinetic model and has not been studied in this clinical situation.
For patients with severe renal impairment (creatinine clearance 15 to 29 ml/min) clinical data are limited but indicate that rivaroxaban plasma concentrations are significantly increased. In these patients, XARELTO should therefore be used with caution.

The use of rivaroxaban is not recommended in patients with creatinine clearance of <15 ml/min.

08.2.3 Pharmacovigilance data

XARELTO 10 mg has been marketed in France since 6 May 2009 in the indication "prevention of venous thromboembolic events (VTE) in adult patients undergoing elective hip or knee replacement surgery (total hip or total knee replacement)." XARELTO 15 mg and 20 mg obtained European Marketing Authorisation in the indications "deep vein thrombosis (DVT)" and "non-valvular atrial fibrillation (NVAF)" on 9 December 2011 and have been marketed in France since 17 August 2012.
Between 1st October 2008 (start of commercialisation) and 15 September 2012, according to information from the applicant, XARELTO 10, 15 or 20 mg has been prescribed, worldwide, to approximately 3,800,000 patients and for an estimated mean duration of 24.5 days. During this period, 7,762 new medically confirmed pharmacovigilance cases were reported, which is a notification incidence of 2/1,000. Thrombocytopenia was reported in 96 patients, which is an incidence of 0.0025%. A total of 89 cases of impaired renal function were reported, which is an incidence of 2.3 cases for every 100,000 patients (cumulative data). Fifty seven cases of angioedema (cumulative notification) were reported, the majority of which (30) were serious.

08.3 Summary & discussion

Results from the EINSTEIN-PE clinical study

Efficacy:

A randomised non-inferiority study (EINSTEIN-PE) “openly” compared rivaroxaban (30 mg/day over 3 weeks then 20 mg/day) with enoxaparin followed by a vitamin K antagonist (warfarin or acenocoumarol) in 4,832 patients with PE. Before randomisation, the protocol authorised the administration of treatment with heparin or fondaparinux. The treatment duration was (3, 6, 12 months) decided by the investigator depending on the risk factors for the patient and local recommendations.

The non-inferiority of rivaroxaban was demonstrated versus enoxaparin/VKA for the primary efficacy endpoint (occurrence of recurrent, fatal or non fatal DVT or PE).

- In the PP population, the incidence of the primary efficacy endpoint was 1.7% in the rivaroxaban group and 1.6% in the enoxaparin/VKA group (HR 1.045 [0.662-1.648]). The upper limit of the confidence interval was below the predefined non-inferiority limit set as 2.0 (p non-inferiority (unilateral test) = 0.0026). The results obtained ensure the conservation of at least 78.4% for the efficacy of enoxaparin/VKA treatment.
- In the ITT population.
- In contrast, the superiority of rivaroxaban compared with enoxaparin/VKA was not established, p = 0.5737.

The results were in agreement and uniform regardless of the predefined treatment duration (3, 6 or 12 months) and in all sub-groups analysed, taking into account factors such as age, body weight, creatinine clearance, history of DVT or PE, cancer, as well as in the vulnerable patient sub-group (age >75 years, weight <50 kg or creatinine clearance <50 ml/min).

The incidence in the ITT population for the endpoint combining the primary efficacy endpoint events and overall mortality was 4.0% (97/2,419) in the rivaroxaban group and 3.4% (82/2,413) in the enoxaparin/VKA group (HR =1.156; [0.862-1.552]).

Safety

In the rivaroxaban group compared with the enoxaparin/VKA group the incidence

- of major haemorrhages and clinically significant but non-major haemorrhages was not different: 10.3% vs. 11.4% (HR = 0.900, p superiority = 0.2305).
- of major haemorrhages was lower: 1.1% vs. 2.2%. This difference is to be considered with caution due to the fact that the hierarchical analysis was discontinued.
- of clinically significant but non-major haemorrhages was not different: 9.5% vs. 9.8%.

The results were uniform in the various predefined sub-groups according to demographic characteristics and the presence of haemorrhagic risk factors. No sign of cardiovascular or hepatic toxicity was apparent in this study.

The net clinical benefit, evaluated through an endpoint combining recurrence of DVT or PE and major haemorrhages according to the Cox proportional risk model (HR = 0.849, 95% CI [0.633-1.139]) does not show superiority for rivaroxaban over enoxaparin/VKA.

Main discussion points regarding the data from the EINSTEIN-PE study

1) Methodology:
There were no specific issues with the methodology, apart from the absence of double-blinding.

2) Transferability
The patients included had a lower mean age, a greater mean body weight, and a higher creatinine clearance than those expected in actual medical practice; the transferability of results to an older population and/or with impaired renal function is therefore not certain. Furthermore, 92% of patients randomised received an LMWH, a UFH or fondaparinux before randomisation in the treatment of PE; the results from the rivaroxaban group are, in truth, those of rivaroxaban preceded by a heparin or fondaparinux. The transferability of the results to a population of patients only receiving rivaroxaban is not certain.

3) Data in real life conditions of use of rivaroxaban (XARELTO) are required, in particular, due to the absence of an antidote (in cases of needing rapid discontinuation of the effect of anticoagulation) and monitoring of haemostasis.

08.4 Study programmes

Risk Management Plan (RMP)

The European RMP is primarily based on the clinical studies in progress, a prescription-monitoring study and on usage data from European databases. The plan was updated following the extension of the indication in the treatment of pulmonary embolism. The risk of “increasing bilirubin and hepatic enzymes" has been removed from the RMP.

In France, a national pharmacovigilance programme is also run by the regional Pharmacovigilance centre in Angers.

Data required by the RMP involves:

- "identified significant risks": haemorrhages.
- "potential significant risks”: embryo-foetal toxicity.
- "missing information" regarding:
    - on the one hand, patients:
        - undergoing major orthopaedic surgery other than THR or TKR,
        - with atrial fibrillation and a valve implant,

- with severe impairment in hepatic function,
- aged at least 18 years.

- and on the other hand, the use of rivaroxaban in the long-term, under conditions of current medical practice, in the treatment of DVT, PE and SPAF in true life situations.

09 THERAPEUTIC USE

Depending on the severity, treatment of pulmonary embolism either requires admission to hospital (in intensive care) or can be treated on an outpatient basis. The reference anticoagulant treatment is a UFH administered via IV, regardless of the level of severity. A follow-up treatment with oral anticoagulants is quickly implemented.
For patients with a pulmonary embolism and no complications, and who do not have haemodynamic failure, an LMWH (in particular tinzaparin) is an alternative to UFHs. If there is no significant risk of haemorrhage (which excludes patients with a low body weight, with moderate to severe renal impairment and the very elderly), fondaparinux via SC injection (ARIXTRA) is also an alternative.
LMWHs and fondaparinux are easier to use and there is a lower risk of thrombocytopenia with them than with UFH.
In cases of pulmonary embolism with a high risk of haemodynamic instability, an increased risk of haemorrhage, severe renal impairment and in perioperative situations, UFHs remain the treatment of choice.[13,14]
The treatment duration, which is at least 3 months, should be agreed on a case per case basis as a function of the clinical picture (occurrence of PH, presence of a major transient trigger factor, relapsing idiopathic form etc.).

<u>The therapeutic use of rivaroxaban (XARELTO) in the treatment of pulmonary embolism</u>
XARELTO is an alternative to a treatment combining enoxaparin and VKA. The Committee emphasises that available data (EINSTEIN-PE study) are based on patients who [in the majority] received an LMWH, a UFH or fondaparinux in the acute phase before randomisation for 24 to 36 hours.

The therapeutic use of XARELTO over fondaparinux is unknown and experience with its use for a treatment duration of longer than 12 months is limited.
The theoretical advantage of rivaroxaban (XARELTO) is that there is no need for additional treatment with a VKA or to monitor platelet counts.
The lack of possibilities to monitor its biological efficacy routinely could complicate the management of certain patients, for example those who are poorly compliant. In cases of haemorrhage there is no antidote available.
An assessment of rivaroxaban in current practice would therefore be particularly useful in order to obtain a better estimate of the incidence of bleeding and its management, in particular as there is no antidote.[15]

[13] Bertoletti L et Mismetti P. Traitement anticoagulant initial de l'embolie pulmonaire. Revue des maladies respiratoires. 2011; 28:216-226.
[14] Prévention et traitement de la maladie thromboembolique veineuse en médecin. Recommandations de bonne pratique. Afssaps, December 2009.
[15] Committee Opinion of 14 March 2012 given for XARELTO in the treatment of DVT and the prevention of recurrent DVT and PE.

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual Benefit (AB)

◗ Venous thromboembolic disease is one of the primary causes of cardiovascular deaths (along with myocardial infarction and stroke): it is a serious and potentially life-threatening condition through potentially fatal pulmonary embolism and/or it can have significant sequelae (post-thrombotic syndrome).

◗ XARELTO (rivaroxaban) is a curative therapy for pulmonary embolism and a preventive therapy for recurrent DVT or PE.

◗ This medicinal product is a first-line therapy.

◗ Public health benefit:

The public health burden of venous thromboembolic disease is significant. The burden of pulmonary embolism (PE) is also considered as significant.

In the treatment of pulmonary embolism and in the secondary prophylaxis of venous thromboembolic events and pulmonary embolism, the availability of effective treatments, which are safe with respect to bleeding, particularly in at-risk patients, is a public health need.

In view of the available data, in particular the randomised, open-label study demonstrating the non-inferiority of XARELTO versus enoxaparin followed by a VKA (without demonstrated superiority) in terms of efficacy, with similar safety, it is not expected that XARELTO will provide an additional impact on morbidity and mortality linked to pulmonary embolism in comparison with current treatments. The impact on the quality of life is not documented.

There is no guarantee that the data from this trial can be carried over into current practice, particularly due to the fact it was an open-label trial and the profile of patients included was different to that expected in actual practice: (lower age, higher body weight and better renal function for patients included). Furthermore, there is uncertainty regarding the consequences of the absence of laboratory monitoring and the absence of an antidote.

An impact on the organisation of healthcare could be expected, particularly because there is no need for specific monitoring of the blood values and there is no dosage adjustment phase, in contrast to VKA. This potential impact merits being documented.

Therefore, XARELTO does not appear to provide an additional contribution to an identified public health need.

Consequently, it is not expected that XARELTO will benefit public health in this indication in the treatment of pulmonary embolism and in the prevention of recurrence (DVT and PE) following an acute PE in adults.

◗ The efficacy/adverse effects ratio of rivaroxaban is high.

◗ There are treatment alternatives: UFH followed by a VKA, LMWHs supplemented by a VKA or not and fondaparinux (ARIXTRA) supplemented with VKA.

Consequently, the Committee considers that the actual benefit of XARELTO is substantial in this extension of the indication. The Committee emphasises that the available data (EINSTEIN-EP study) are based on patients who mainly received an LMWH, a UFH or fondaparinux in the acute phase (24-36 hours) of pulmonary embolism.

The Committee recommends inclusion on the list of medicines reimbursed by National Health Insurance and on the list of medicines approved for hospital use in this extension of the indication and at the dosages in the Marketing Authorisation.

◗ Proposed reimbursement rate: 65%

010.2 Improvement in actual benefit (IAB)

The Committee considers that XARELTO does not provide an improvement in actual benefit (IAB V, non-existent) in the treatment of pulmonary embolism (PE) and in the prevention of recurrent DVT and PE in adults.

010.3 Target population

The target population for XARELTO 15 and 20 mg is defined as adult patients with pulmonary embolism who are not haemodynamically unstable or are unlikely to receive thrombolysis or pulmonary embolectomy.

Estimation
The number of patients with a pulmonary embolism can be assessed from 2011 PMSI data: a total of 64,413 adult patients were admitted to hospital in 2011 with a primary diagnosis, associated or linked to pulmonary embolism:

- 53,137 adult patients with a primary diagnosis, associated or linked to pulmonary embolism without mention of acute cardiopulmonary involvement (code I26.9),
- 11,276 adult patients with a primary diagnosis, associated or linked to pulmonary embolism with mention of acute cardiopulmonary involvement (code I26.0), not meeting the requirements for indication of rivaroxaban (XARELTO).

Conclusion: by using the hypothesis that all pulmonary embolisms are treated in a hospital environment in France, the target population for XARELTO can be estimated each year at 53,000 patients.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging
They are appropriate for the prescription conditions according to the indication, the dosage and the treatment duration.