HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

22 June 2011

ARIXTRA 2.5mg/0.5 mL, solution for injection in prefilled syringe
B/2 prefilled 0.5 mL glass syringe(s) with needle (CIP code: 359 225-4)
B/7 prefilled 0.5 mL glass syringe(s) with needle (CIP code: 359 226-0)
B/10 prefilled 0.5 mL glass syringe(s) with needle (CIP code: 563 619-7)

Applicant: GLAXOSMITHKLINE

fondaparinux sodium
ATC code: B01AX05

List I

Date of Marketing Authorisation (Centralised European procedure) for extension of indication: 31 August 2010.

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance (B/2 and B/7) and approved for hospital use (B/10) in the extension of indication: **"Treatment of adults with acute symptomatic spontaneous superficial-vein thrombosis of the lower limbs without concomitant deep-vein thrombosis"**.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Fondaparinux sodium[1]

1.2. Background

Fondaparinux is the first anticoagulant with a Marketing Authorisation used to treat superficial-vein thrombosis.

1.3. Indications

Extension of indication that is the subject of this opinion:

"Treatment of adults with acute symptomatic spontaneous superficial-vein thrombosis of the lower limbs without concomitant deep-vein thrombosis"

Reminder of the other Marketing Authorisation indications:
- "Prevention of Venous Thromboembolic Events (VTE) in adults undergoing major orthopaedic surgery of the lower limbs such as hip fracture, major knee surgery or hip replacement surgery.

- Prevention of Venous Thromboembolic Events (VTE) in adults undergoing abdominal surgery who are judged to be at high risk of thromboembolic complications, such as patients undergoing abdominal cancer surgery

- Prevention of Venous Thromboembolic Events (VTE) in adult medical patients who are judged to be at high risk for VTE and who are immobilised due to acute illness such as cardiac insufficiency and/or acute respiratory disorders, and/or acute infectious or inflammatory disease.

- Treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in adults for whom urgent (< 120 min) invasive management (percutaneous coronary intervention-PCI) is not indicated.

- Treatment of ST segment elevation myocardial infarction (STEMI) in adults who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy"

1.4. Dosage in the treatment of superficial venous thrombosis (see SPC)

"The recommended dose of fondaparinux is 2.5 mg once daily, administered by subcutaneous injection. Treatment should be continued for a minimum of 30 days and up to a maximum of 45 days in patients at high risk of thromboembolic complications.

Method of administration

- Patients may self-administer the medicine if they so wish and are able to do so. Doctors will provide clear instructions for self-injection.

- ARIXTRA 2.5 mg is administered by deep subcutaneous injection while the patient is lying down. Sites of administration should alternate between the left and the right anterolateral and left and right posterolateral abdominal wall.

[1] Fondaparinux is a synthetic and selective inhibitor of activated Factor X (Xa). Its antithrombotic activity is the result of antithrombin III (ATIII)-mediated selective inhibition of Factor Xa. By binding selectively to ATIII, fondaparinux potentiates (about 300 times) the innate neutralisation of Factor Xa by ATIII. Neutralisation of Factor Xa interrupts the blood coagulation cascade and thus inhibits both thrombin formation and thrombus development. Fondaparinux does not inactivate thrombin (activated Factor II) and has no effects on platelets.

To avoid the loss of medicinal product when using the prefilled syringe do not expel the air bubble from the syringe before the injection. The whole length of the needle should be inserted perpendicularly into a skin fold held between the thumb and the forefinger; the skin fold should be held throughout the injection.

Special populations and/or situations;

- Renal impairment: fondaparinux should not be used in patients with creatinine clearance <20 mL/min.

The dose should be reduced to subcutaneous injection of 1.5 mg once daily in patients with creatinine clearance in the range of 20 to 50 mL/min; the tolerance and efficacy of 1.5 mg has not been studied.

No dosage reduction is required for patients with mild renal impairment (creatinine clearance >50 mL/min).

- Severe hepatic impairment: the tolerance and efficacy of fondaparinux in patients has not been studied, therefore fondaparinux is not recommended for use in these patients.

- Low body weight: the tolerance and efficacy of fondaparinux in patients with body weight less than 50 kg has not been studied, therefore fondaparinux is not recommended for use in these patients."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

B	Blood and blood-forming organs
B01	Antithrombotic agents
B01A	Antithrombotic agents
B01AX	Other antithrombotic agents
B01AX05	Fondaparinux

2.2. Medicines in the same therapeutic category

Antithrombotic inhibitor of Factor Xa: none.

2.3. Medicines with a similar therapeutic aim: none.

No other medicine has a Marketing Authorisation.

According to the AFSSAPS November 2009 guidelines (published before the results of the CALISTO study became available) for the treatment of superficial-vein thrombosis: venous compression is recommended in the acute phase of superficial-vein thrombosis in a limb, if there are no contraindications (Professional Agreement). Surgery is not recommended (Grade C) except for extensive superficial-vein thromboses at the saphenofemoral junction (Professional Agreement). Low-molecular-weight-heparin (Grade C) and fondaparinux (Professional Agreement) at prophylactic doses against VTE may prevent the risk of thromboembolic complications.

3 ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The assessment of the clinical benefit of ARIXTRA 2.5 mg in adults for the treatment of superficial-vein thrombosis (SVT) of the lower limbs without concomitant deep-vein thrombosis (DVT) is based on the results of a European phase III multicentre clinical study, the CALISTO study.

The applicant GSK also submitted the results of:

- a Cochrane review (Di Nisio, 2007 *[sic]*) evaluating the efficacy and tolerance of cutaneous, medical and surgical treatments for SVT of the leg;
- a randomised study that compared two doses of enoxaparin and an NSAID (tenoxicam) with placebo (STENOX Group, 2003);
- an epidemiological study (POST study, Decousus, 2010) which studied how SVT was treated by vascular physicians in France, and estimated the incidence of complications of isolated SVT.

3.1.1 CALISTO study

Methodology

This was a randomised, double-blind clinical study in 3002 patients aged over 18 years with isolated acute symptomatic spontaneous lower-limb superficial-vein thrombosis, at least 5 cm long, as confirmed by compression ultrasonography.

Non-inclusion criteria:

- patients who:
  - had been treated for cancer within the previous six months;
  - had severe renal failure with creatinine clearance < 30 mL/min;
  - weighed < 50 kg;
  - had a high risk of bleeding;
  - had an SVT located within 3 cm of the saphenofemoral junction, SVT associated with sclerotherapy or placement of an intravenous catheter, history of SVT (< 90 days) or DVT or pulmonary embolism (PE) (< 6 months).

The primary aim was to compare the efficacy in terms of preventing thromboembolic complications of 2.5 mg once daily[2] of sodium fondaparinux (ARIXTRA 2.5 mg) with that of placebo in patients with isolated acute lower-limb SVT. Treatment was administered for 45 days (± 2 days). Patients were followed-up for 30 days after this treatment (D75 ± 2 days). Patients were encouraged to use graduated compression stockings and were allowed to take analgesic medicines in the form of oral paracetamol, combined with topical NSAIDs if pain persisted under paracetamol.

The primary efficacy endpoint was a composite of symptomatic deep venous thrombotic complication (DVT or PE) or symptomatic extension or recurrence[3] of SVT or death from any cause by D47.

[2] The 2.5 mg once daily dose of sodium fondaparinux was chosen on the basis of results of studies available for sodium fondaparinux and the STENOX and VESALIO studies (with low-molecular-weight heparin, LMWH) suggesting that the efficacy of preventive and curative doses was similar; patients with a high bleeding risk were excluded from the study.

Secondary endpoints were onset by D47 and D77 of the individual criteria of the primary efficacy endpoint, the composite of symptomatic DVT and/or PE, the composite of symptomatic extension and/or symptomatic recurrence, and surgery for SVT. The (secondary) tolerance criteria were incidence by D47, D77 and up to four days after the last dose of study treatment of bleeding (major, non-major but clinically significant or minor bleeding), and death from any cause.

In addition, any other adverse effect up to four days after the last dose of study treatment was included in the analysis.

The number of subjects was originally calculated as 2500 (1250 in each group). This was based on the following assumptions: incidence of primary efficacy endpoint events of 4% in the ARIXTRA 2.5 mg group and 8% in the placebo group at the end of the treatment period for a power of 98.7% in detecting this difference (Fisher's exact test) and a power of at least 80% in detecting an absolute difference of 2% for level of bleeding between the two arms.
As the global number of thromboembolic events was lower than anticipated, the scientific committee decided to increase the sample size to 3000 subjects (1500 in each treatment group) in order to retain the statistical power of the study. Efficacy analyses were performed on data from the intention-to-treat population.

Results:

Study population

Between March 2007 and May 2009, a total of 3002 patients were enrolled at 171 centres in 17 countries - 1502 in the fondaparinux group (ARIXTRA 2.5 mg) and 1500 in the placebo group. Populations were similar in both treatment groups (see Table 1). In France, 174 patients were included by 16 investigating centres.
Median age was 58 years, with 64% women, and 4.4% of patients had creatinine clearance < 50 mL/min.

Table 1: characteristics of ITT populations at inclusion

Patient characteristics	ARIXTRA N=1502	Placebo N=1500	p
Mean age (years)	57.1±13.3	56.9±13.6	0.69
Gender (% female)	64.8	62.9	0.29
BMI (mean)	29.2±5.2	29.0±5.4	0.32
BMI≥30 (%)	38.2	35.7	0.16
Varicose veins (%)	88.6	88.6	1.00
Previous SVT (%)	11.9	11.9	1.00
Previous DVT or PE (%)	7.0	6.9	1.00
History of cancer (%)	2.1.	1.9	0.80
Known thrombophilia (%)	1.3	1.2	0.87
Cardiovascular disease (%)	4.7	4.4.	0.73

- Characteristics of SVT at inclusion were similar in both groups. Mean time between start of SVT symptoms and randomisation was 7.1 days. Mean length of SVT was 20.5 cm. Most (89%) SVTs were located in varicose veins; in 93% of subjects, the vein involved was the great saphenous vein. In this case, the SVT was located above the knee in 47% of patients and more than 10 cm from the saphenofemoral junction (SJ) in 82% of patients.

- The study treatment was self-administered by more than 90% of patients in both groups. A higher proportion of patients[4] from the ARIXTRA group adhered to treatment (95.5% vs 88.6%) (see Table 2).

Table 2: data concerning adherence to treatment and treatment modalities in the intention-to-treat population

	Fondaparinux	Placebo
At least one injection of study drug	1499 (99.8%)	1488 (99.2%)
Mean duration of treatment (days)	43.6±7.3	41.2±11.0
≤ 10 days	35 (2.3%)	95 (6.4%)
[11-30] days	26 (1.7%)	66 (4.4%)
[31-45] days	1161 (77.5%)	1091 (73.3%)
> 45 days	277 (18.5%)	236 (15.9%)
Self-administered treatment	1360 (90.7%)	1364 (91.7%)

- Other treatments received (see Table 3).

Table 3: Main concomitant treatment in the ITT population during the study

Treatment	Fondaparinux	Placebo
Support (graduated compression stockings)	83.0%	83.1%
Analgesic agents	27.7%	28.5%
Topical NSAIDs	41.5%	41.8%
Oral NSAID or COX-2 inhibitor	2.1%	3.7%
Oral or parenteral anticoagulant	1.1%	6.4%
• High (therapeutic) dose of anticoagulant	0.7%	4.1%
• Intermediate dose of anticoagulant	0.1%	0.4%
• Low (prophylactic) dose of anticoagulant	0.4%	2.9%
Aspirin or other antiplatelet agent	21.4%	22.6%

[4] Patients were considered not to have adhered to treatment if they received fewer than 36 of the 45 (80%) injections planned, or if the last day of treatment was before D40. This included patients who discontinued treatment because of an adverse event or thromboembolic event.

Efficacy outcomes:

Table 4: Efficacy outcomes in the CALISTO study

Efficacy	Fondaparinux (N=1502) n (%)	Placebo (N=1500) n (%)	Absolute risk reduction with ARIXTRA % (95% CI)	Relative risk (95% CI)	P value ***
Efficacy by D47					
Primary efficacy endpoint	*13 (0.9)*	88 (5.9)	-5.0 (-6.3 to -3.7)	0.15 (0.08 to 0.26)	<0.001
Death*	2 (0.1)	1 (0.1)	0.1 (-0.2 to 0.3)	1.99 (0.18 to 21.87)	1.000
PE†	0 (0.0)	5 (0.3)	-0.3 (-0.6 to 0.0)	-	0.031
DVT**	3 (0.2)	18 (1.2)	-1.0 (-1.6 to -0.4)	0.17 (0.05 to 0.56)	<0.001
Extension of SVT to saphenofemoral junction	4 (0.3)	51 (3.4)	-3.1 (-4.1 to -2.2)	0.08 (0.03 to 0.22)	<0.001
Recurrence of SVT	5 (0.3)	24 (1.6)	-1.3 (-2.0 to -0.6)	0.21 (0.08 to 0.54)	<0.001
DVT or PE	3 (0.2)	20 (1.3)	-1.1 (-1.8 to -0.5)	0.15 (0.05 to 0.50)	<0.001
Surgery for SVT	11 (0.7)	57 (3.8)	-3.1 (-4.1 to -2.0)	0.19 (0.10 to 0.37)	<0.001
Efficacy by D77					
Composite outcome	18 (1.2)	94 (6.3)	-5.1 (-6.4 to -3.7)	0.19 (0.12 to 0.32)	<0.001
Death*	2 (0.1)	1 (0.1)	0.1 (-0.2 to 0.3)	1.99 (0.18 to 21.87)	1.000
PE†	0 (0.0)	6 (0.4)	-0.4 (-0.7 to -0.1)	-	0.015
DVT	4 (0.3)	19 (1.3)	-1.0 (-1.6 to -0.4)	0.21 (0.07 to 0.62)	0.001
Extension of SVT to the sapheno-femoral junction	5 (0.3)	54 (3.6)	-3.3 (-4.3 to -2.3)	0.09 (0.04 to 0.23)	<0.001
Recurrence of SVT	8 (0.5)	26 (1.7)	-1.2 (-2.0 to -0.4)	0.31 (0.14 to 0.68)	0.002
DVT or PE	4 (0.3)	22 (1.5)	-1.2 (-1.9 to -0.5)	0.18 (0.06 to 0.53)	<0.001
Surgery for SVT	15 (1.0)	61 (4.1)	-3.1 (-4.2 to -1.9)	0.25 (0.14 to 0.43)	<0.001

**There were two deaths from cancer in the fondaparinux group and one death from acute heart failure in the placebo group.*
† No instance of pulmonary embolism was fatal.
***Proximal DVT: 1 in the fondaparinux group and 10 in the placebo group.*
****Nominal p value (not adjusted for multiple comparison)*

Conclusions and comments on the efficacy data from the CALISTO study

In the CALISTO study, sodium fondaparinux (ARIXTRA) given at a dose of 2.5 mg once daily for 45 days was more effective than placebo in preventing thromboembolic complications in patients with isolated lower-limb SVT. The proportion of patients experiencing a VTE event was 5.9% in patients receiving placebo compared with 0.9% of patients receiving 2.5 mg fondaparinux once daily, i.e. a 5% reduction in absolute risk (95% CI: - 6.3, - 3.7) and an 85.2% reduction in relative risk (95% CI: 73.7%-91.7%, $p < 0.001$).

The incidence of each thromboembolic component of the primary efficacy endpoint was also lower in patients receiving fondaparinux. The number of patients who died was small and was similar between both treatment groups.

Efficacy was maintained up to D77 and in both subgroups studied (see Appendix 1). Fondaparinux 2.5 mg once-daily reduced the rate of surgery for SVT, including ligation of the saphenofemoral junction; by D77, eight patients in the fondaparinux group (0.5%) had undergone surgery compared with 52 patients in the placebo group (3.5%).

3.2. Other submitted data

3.2.1. Data from a Cochrane review (2007)[5]

The aim of this review was to assess the efficacy and tolerance of topical, medical, and surgical treatments in patients presenting with SVT of the legs diagnosed by clinical signs and confirmed by venous compression ultrasonography. Data from twenty-four studies involving 2469 participants were included in this review. The methodological quality of most of the studies was poor, particularly in relation to method of allocation or randomisation, absence of a placebo group and a high incidence of premature dropouts from the studies. The rate of complications in the form of DVT and/or PE was only given for nine of the 24 studies, and extension or recurrence of SVT was only reported for six. The rate of adverse events was only reported for nine studies. The quality of only four of the 24 studies was judged to be satisfactory (grade A). Eight of the 24 studies reviewed enrolled fewer than 50 patients and only six enrolled more than 100 patients.

Ten of these studies[6] included a group receiving LMWH.

The authors of the review felt that an intermediate dose of LMWH for at least a month might be advised. However, neither the clinical benefit in terms of preventing symptomatic venous thromboembolic complications nor the appropriate dosage regimen (dose and treatment duration) have been established.

3.2.2. Findings the STENOX study

Methodology

This randomised, double-blind study in four parallel arms evaluated the efficacy of two doses of an anticoagulant (LMWH) with that of an NSAID versus placebo in 427 patients older than 18 years with SVT of at least 5 cm recorded with lower-limb ultrasonography. Patients received either enoxaparin (40 mg once daily or 1.5 mg /kg/day SC), or oral tenoxicam (20 mg once daily) or placebo, for 8-12 days. Compression lower-limb ultrasonography was performed routinely in all patients between D8 and D12 to look for deep- or superficial-vein thrombosis. The primary efficacy endpoint of the study was incidence of symptomatic or asymptomatic DVT (detected by routine ultrasonography) and PE on D12. Secondary endpoints were incidence of symptomatic or asymptomatic DVT and PE by D97 or a composite endpoint including extensions and asymptomatic or symptomatic SVT recurrence up to D12 and up to D97. Extension was defined as proximal extension of at least 2 cm (rather than extension up to the saphenofemoral junction, as in the CALISTO study).

Results:

On D12, there was no difference between the four arms for the primary efficacy endpoint (see Table 5):

[5] Di Nisio M, Wichers IM, Middeldorp S. Treatment for superficial thrombophlebitis of the leg. Cochrane Database of Systematic Reviews 2007, Issue 2. Article No.: CD004982. DOI: 10.1002/14651858.CD004982.pub3.

[6] The studies included in the Cochrane meta-analysis were: Belcaro 1989; Belcaro 1990; Belcaro 1999; Gorski 2005; Katzenschlager 2003; Lozano 2003; Marchiori 2002; Stenox Group 2003; Titon 1994; Vesalio Group 2005.

Table 5: STENOX study: incidence of primary efficacy endpoint (symptomatic or asymptomatic PE or DVT) by D12

	Placebo (n=112)	Enoxaparin 40 mg (n=110)	Enoxaparin 1.5 mg/kg (n=106)	Tenoxicam 20 mg (n=99)
PE or DVT	4 (3.6%)	1 (0.9%)	1 (1.0%)	2 (2.1%)
PE	0	0	0	1
Symptomatic DVT	1	1	0	0
Asymptomatic DVT	3	0	1	1

Differences between groups were not significant: P=0.37 for the two enoxaparin groups versus placebo and P=0.39 for tenoxicam versus placebo; RR = 0.24 for the comparison enoxaparin 40 mg versus placebo; RR = 0.27 for the comparison enoxaparin 1.5 mg/kg versus placebo; RR = 0.57 for the comparison tenoxicam 20 mg versus placebo.

On D12, each of the three active treatments was associated with a reduction in risk of onset of the secondary efficacy outcome combining deep- and superficial-vein thromboembolic events (symptomatic or asymptomatic PE or DVT or extension or recurrence of symptomatic or asymptomatic SVT). The proportion of extensions of SVT reaching the saphenofemoral junction was not given (see Table 6).

Table 6. Incidence of (secondary) endpoints combining deep- and superficial-vein thromboembolic events (symptomatic or asymptomatic PE or DVT or extension or recurrence of symptomatic or asymptomatic SVT) by D12

	Placebo (n=112)	Enoxaparin 40 mg (n=110)	Enoxaparin 1.5 mg/kg (n=106)	Tenoxicam 20 mg (n=99)
Deep- or superficial-vein thromboembolic venous event (TEVE)*	34 (30.6%)	9 (8.3%)*	7 (6.9%)*	14 (14.9%)*
Symptomatic or asymptomatic DVT	4	1	1	2
Recurrence or extension of symptomatic SVT	27	5	3	9
Recurrence or extension of asymptomatic SVT	6	4	3	4

*Differences were significant between the groups receiving enoxaparin and placebo (p<0.001) and between the tenoxicam group and placebo (p=0.008).

By D97, incidence of symptomatic or asymptomatic DVT or PE was 4.5% in the placebo group, 5.7% in the enoxaparin 40 mg group, 3.9% in the enoxaparin 1.5 mg/kg group and 4.3% in the tenoxicam 20 mg group.

3.2.3. POST observational study[7]

Methodology

This study had two objectives, namely to describe the current practice of French vascular physicians in treating SVT, and to determine the incidence of thromboembolic complications of isolated SVT. The population consisted of adult patients with symptomatic SVT of the lower limbs that was at least 5 cm long on compression ultrasonography. Patients who had undergone surgery within the previous 10 days or who had had SVT following sclerotherapy within the past 30 days were excluded, as were patients who could not be followed

[7] DECOUSUS H *et al.* For the POST (PROSPECTIVE OBSERVATIONAL SUPERFICIAL THROMBOPHLEBITIS) STUDY GROUP. Superficial venous thrombosis and venous thromboembolism: a large, prospective epidemiologic study. Ann Intern Med 2010; 152: 218-24.

up. Bilateral complete ultrasonographic examination of the proximal and distal veins was performed on D10. A follow-up visit was scheduled at three months.
A total of 844 patients were enrolled by 96 centres (17 public hospitals and 79 office practices or private clinics) between March 2005 and October 2006. Ultrasonographically-confirmed DVT or symptomatic PE was diagnosed in 24.9% of patients. Findings included proximal DVT in 9.7% and symptomatic PE in 3.9% of the total population; 634 patients were enrolled with isolated lower-limb SVT and 586 of these patients were followed up to three months.

Results:
Of the 597 patients, 90.5% received anticoagulant therapy, 36.7% at a prophylactic dose and 62.9% at a curative dose. Patients were treated for a median of 11 days for the curative dose and 11 days for the prophylactic dose. Seventeen percent (17%) of patients also received a vitamin K antagonist, for a median of 81 days. In addition, 97.7% used graduated compression stockings, 47.2% used topical NSAIDs (applied to the skin) and 8.2% took oral NSAIDs; 10.2% of patients underwent surgery (such as ligation or stripping).

Fifty-eight (58; 10.2%) of the 586 patients analysed experienced a venous thromboembolic event within three months of the diagnosis of SVT. Complications were symptomatic in 46 patients (8.3%): distal DVT in eight cases, proximal DVT in seven cases and pulmonary embolism in three cases. There were 18 symptomatic recurrences of SVT and 10 extensions of SVT. One death was considered to be possibly caused by PE.

3.3. Adverse effects

3.3.1. Post marketing pharmacovigilance data on fondaparinux

According to the most recent periodic safety update report (PSUR), at 30 September 2009 the estimated cumulative exposure to fondaparinux was 5.43 million patients. This estimate was calculated from sales figures available on 30 September 2009, based on the assumptions that ARIXTRA was taken for 13 and 15 days (depending on the country) as preventive therapy and for seven days as curative therapy. In France, national pharmacovigilance monitoring figures show that estimated cumulative exposure is 2.91 million patients, using the same method, from the time the product was placed on the French market (December 2002) up to 31 May 2010; the dose was 2.45 mg in two thirds of these cases (1.9 million).

- Adverse effects involving bleeding: since ARIXTRA was placed on the market, there have been a total of 2 416 spontaneous notifications of bleeding: 409 (16.9%) were associated with off-label use, with 181 (7.5%) ending in the patient's death; 38.6% of the notifications came from France (25.9% from Japan, 15.2% from the United States and 10% from Germany). The majority of notifications did not contain the information needed for an accurate determination of effect of bleeding risk factors (age, weight and renal function); nevertheless, it can be seen that 46.7% of patients were aged over 70 years (24% missing data), 56.5% were women (15% missing data), 4.5% weighed under 50 kg (68.3% missing data) and 9.3% had creatinine clearance below 50 mL/min (86.5% missing data).

- One hundred and thirty (130) deaths have been notified since the product was placed on a market, 96 of which were related to adverse effects in the form of bleeding. Most of the patients involved had a bleeding risk factor.

- In France, national pharmacovigilance monitoring was started in January 2007 following the notification of bleeding events occurring during treatment with ARIXTRA. This first monitoring programme concerned all effects reported since the product had been placed on the market up to 31 January 2007, and concluded that "haematoma and bleeding accounted for the great majority of adverse effects reported with ARIXTRA, and that these were serious cases affecting elderly patients". Misuse (inappropriate dose, off-label indication) accounted for

40% of this type of case. A letter was sent to prescribers in June 2007, reminding them of the rules for correct use.

According to French data reported between 1 February 2007 and 30 September 2008, 444 adverse effects were reported including 319 cases of bleeding (72%) and 125 (28%) other effects (lack of efficacy, bleeding disorders, cutaneous effects).

- Bleeding events affected elderly patients (73 years vs 58.5 years for other types of effect).
- Bleeding events were serious in 92% of cases.
- 25 deaths directly related to a bleeding event were reported.
- Irrespective of the type of bleeding or other event, in 53% of cases the dose in question was curative and misuse occurred in 42% of cases (off-label use, duration not in accordance with SPC or wrong dose given).
- In 51 cases (16% of the total) another medicine was under suspicion to the same extent as fondaparinux.

There was a reduction in notification rate in the second survey: 3 bleeding events per 10 000 patients treated compared with a rate of 5.5/10 000 in the first survey.

A new report concerning the period from 1 October 2008 to 31 March 2011 is currently being prepared by the Georges Pompidou European Hospital Regional Pharmacovigilance Centre, the national monitoring rapporteur for France, due to be submitted to the Pharmacovigilance Technical Committee on 10 May 2011, which will decide whether or not it should be passed to the National Pharmacovigilance Committee.

3.3.2. Information from the CALISTO clinical study

- Bleeding risk (see Table 6).

Table 6: Bleeding by treatment group at D47* and up to D77 in the CALISTO study

	ARIXTRA (N=1499)	Placebo (N=1488)
D47*	%	%
Major bleeding‡	1 (0.1)	1 (0.1)
Clinically significant non-major bleeding	5 (0.3)	8 (0.5)
Minor bleeding	9 (0.6)	6 (0.4)
All bleeding	15 (1.0)	14 (0.9)
D77		
Major bleeding	1 (0.1)	1 (0.1)
Clinically significant non-major bleeding	6 (0.4)	9 (0.6)
Minor bleeding	9 (0.6)	6 (0.4)
All bleeding	16 (1.1)	15 (1.0)

**D47 or up to four days after the last dose of the study treatment if after D47.*
. ‡P=1.00 by Fisher's exact test. Intra-retinal bleeding resolved with no functional sequelae after withdrawal of the study treatment in the fondaparinux group; epistaxis requiring medical intervention resolved without sequelae in the placebo group

- Other adverse effects: there was no difference between the two treatment groups for other adverse events (see Table 6). The incidence of serious adverse events was 0.7% with ARIXTRA 2.5 mg and 1.1% with placebo.

The mortality rate was low and similar for both treatment groups, with two deaths (0.1%) in the fondaparinux group and 1 (0.1%) in the placebo group. Major bleeding[8] occurred during treatment in one patient receiving fondaparinux (0.1%) and one patient receiving placebo (0.1%). Clinically significant non-major bleeding occurred in five patients receiving

[8] Bleeding was classed as major if it was fatal and/or if it occurred in a critical region or organ (e.g. intracranial; spinal cord bleeding; intraocular; retroperitoneal; intra-articular; pericardial; or intramuscular with compartment syndrome; and/or was associated with a fall in haemoglobin concentration of at least 20 g/L or led to transfusion of two or more units of packed red blood cells or of whole blood.

fondaparinux (0.3%) and in eight patients receiving placebo (0.5%). Patients whose bleeding risk was considered to be high were not enrolled.

The tolerance of fondaparinux was not studied in patients with superficial-vein thrombosis after sclerotherapy or as a complication of placement of an intravenous catheter, in patients with a history of superficial-vein thrombosis during the previous three months, patients with a history of thromboembolism within the previous six months or in patients with active cancer. Similarly, patients with severe hepatic impairment, creatinine clearance < 30 mL/min or weighing under 50 kg were not enrolled in the study.

3.3.3 Risk management plan

A study of actual use to assess "prescriber compliance with SPC information concerning prescription of ARIXTRA in SVT" is planned.

3.4. Conclusion

The assessment of ARIXTRA in the treatment of superficial-vein thrombosis (SVT) is based on the results of one study (CALISTO) which compared fondaparinux (ARIXTRA) at a daily subcutaneous dose of 2.5 mg for 45 days with placebo in adults with acute symptomatic spontaneous lower-limb SVT, without concomitant deep-vein thrombosis. The primary efficacy endpoint was symptomatic deep venous thromboembolic complication (DVT or PE) or extension or recurrence[9] of SVT or death from any cause by D47. Fondaparinux reduced this composite endpoint (0.9% vs 5.9% with placebo) i.e. a 5% reduction in absolute risk [95% CI: - 6.3 , - 3.7] and 85.2% reduction in relative risk [95% CI: 73.7%-91.7%, $p < 0.001$].

Fondaparinux also reduced the incidence of each thromboembolic component of the primary efficacy endpoint, but above all, those components whose relevance has not been established in reducing progression towards a deep venous thromboembolic event (extension to the saphenofemoral junction and recurrence of SVT). The number of deaths was low and was similar in both the fondaparinux (n=2) and placebo (n=1) groups.

Efficacy was maintained up to D77 in the population enrolled and in the subgroups studied (see Appendix 1). Fondaparinux reduced surgical procedures for SVT, including ligation of the saphenofemoral junction performed by D77 in 0.5% of patients in the fondaparinux group compared with 3.5% of patients in the placebo group.

Major bleeding during treatment occurred in one patient (0.1%) in each group. Non-major but clinically significant bleeding occurred in five patients receiving fondaparinux (0.3%) and in eight patients receiving placebo (0.5%).

Comments:

- This study was carried out using a rigorous methodology (randomisation, double-blind, analysis by intention-to-treat).

- Clinical benefit is anticipated in the population of patients in the CALISTO study.

- However, the choice of composite primary efficacy endpoint is debatable as it consisted of events which were of equal clinical relevance; although there is no problem with symptomatic PE and DVT, it has not been established that extension to the saphenofemoral junction is a risk factor for proximal DVT; and it has not been shown that recurrence of SVT is a predictive factor of progression towards a deep venous thromboembolic event (DVT and/or PE). As the findings of the study mainly concern reduction in recurrence or extension of SVT, they are likely to reduce the amount of anticipated clinical benefit.

[9] Extension of SVT was defined as progression of the initial thrombus by at least 2 cm and to within 3 cm or less of the saphenofemoral junction. Recurrence was defined as occurring in a different superficial vein from the initial event (i.e. at inclusion), or located in the same superficial vein but separated from the index thrombus by at least 10 cm.

In addition, the inclusion criteria probably selected a population at low risk of thrombosis (as active cancer, recent surgery, and the most "proximal" cases of SVT were excluded). This explains the low level of deep thromboembolic complications by D45 in the placebo group (1.3%).

Furthermore, it is not possible to objectively identify those cases of SVT with a clear indication at inclusion for surgery and there is no information about cases of SVT excluded from the study on this criterion, nor on the proportion.

- The SPC recommends that the dosage of fondaparinux be reduced from 2.5 mg daily to 1.5 mg daily in patients with moderate to severe renal failure (creatinine clearance 20-50 mL/min): the CALISTO study does not provide any evidence of this dose adjustment.

An observational study (POST) demonstrated the wide range of treatments proposed in the management of isolated lower limb SVT and professional practice, without providing supporting evidence of their appropriateness for the patient's clinical situation. Despite the treatment prescribed, the incidence of symptomatic DVT/PE was reported as 3.3% at three months without any details of the type and duration of treatment received (preventive/curative LMWH, vitamin K antagonist, or no antithrombotic). This population is probably more at risk than that of the observational study.

Overall, the CALISTO study does not provide sufficient evidence to confirm the clinical benefit of treatment with ARIXTRA for 30-45 days in all patients with SVT (notably irrespective of patient profile and anatomical location of the thrombus). In view of the non-inclusion criteria, it cannot be assumed that the results of the CALISTO study could be transposed to a population of patients at high risk of thrombosis and/or bleeding. In the CALISTO clinical study, the inclusion criteria probably selected a population with low bleeding risk (as severe renal impairment, low body weight and recent surgery were excluded). This explains the low level of bleeding complications in the fondaparinux group (0.1%). Most of the adverse effects reported with ARIXTRA in the above indications involved bleeding, with serious cases more frequently affecting elderly patients and situations involving misuse, which was the reason for the AFSSAPS information of 2007.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit (AB) in the treatment of SVT

SVT is generally not serious, but may be complicated by thromboembolic venous events (symptomatic DVT or PE), which may be life-threatening (potentially fatal pulmonary embolism) or cause major sequelae (post thrombotic syndrome).

In acute symptomatic spontaneous superficial-vein thrombosis of the lower limbs without concomitant deep-vein thrombosis, ARIXTRA at a 2.5 mg daily dosage is intended to prevent onset of thromboembolic complications. However, this type of complication is rare (1.5% of symptomatic events in the CALISTO study placebo group).

In the CALISTO study, patients were at low risk of thrombosis or haemorrhage, and as there was little difference in clinically significant complications (symptomatic DVT and PE), fondaparinux has a moderate efficacy to adverse effects ratio. In addition, the benefit of 45 days of treatment (compliance, moderate anticipated clinical benefit) has not been firmly established.

There are no alternative medicinal products with a marketing authorisation in this indication. Although types of LMWH are used, their benefit has been poorly established.

Public health benefit

The public health burden of venous thromboembolism (VTE) is substantial. The public health burden of isolated superficial-vein thrombosis (SVT) is considered to be low in view of its low level of severity [low incidence of complications (DVT, PE) and smaller number of patients concerned.
The availability of treatment for SVT by an anticoagulant with demonstrated efficacy against thromboembolic complications and with documented tolerance in use is a therapeutic need. However, improvement in the treatment of SVT has not been explicitly identified as a public health need, as the indicator given in the Appendix of the French law on public health for the objective in question, no. 69, was formulated in terms of reduced mortality.
The results of the placebo-controlled CALISTO study demonstrate a substantial reduction in onset of symptomatic thromboembolic complications measured using a global composite efficacy endpoint; this efficacy can still be measured by onset of DVT or pulmonary embolism, but the absence of effect on mortality was also noted. The incidence of bleeding events in treated patients was not increased. So a moderate impact is anticipated from the proprietary medicinal product ARIXTRA 2.5 mg in terms of reduction in morbidity and mortality related to complications of isolated SVT.

It is not certain that it will be possible to transpose the results of the CALISTO study into everyday practice:

- In the CALISTO study, patients at risk of poor tolerance of ARIXTRA 2.5 mg were excluded, while patients treated in everyday practice are likely to have a higher risk profile; as a result the tolerance of ARIXTRA 2.5 mg in everyday practice is uncertain;
- it is unclear whether the patients taking part in the international study who were treated in France (174 patients enrolled in France) were representative, with possible differences related to the profile of treated patients, practice in France, prior treatment or concomitant therapy for SVT, timing of treatment, investigations (ultrasonography) and use of specialists (vascular).
- The most appropriate treatment period has still not been formally established.

A favourable but unquantified impact on the organisation of care could be anticipated in terms of reduction in surgery for SVT. However, nursing care is sometimes needed for certain patients, which could increase costs, with a probably non-negligible impact because of the long treatment period proposed.
Consequently, in the current state of knowledge, public health benefit is anticipated for the proprietary medicinal product ARIXTRA 2.5 mg in this new indication. However, this benefit is low.

The actual benefit of ARIXTRA 2.5 mg is moderate.

4.2. Improvement in actual benefit (IAB) in the treatment of SVT

The Committee considers that ARIXTRA 2.5 mg does not contribute any improvement in actual benefit (level V) in the treatment strategy in view of the uncertainty regarding the clinical benefit of a 45-day treatment period in the very varied population of patients with isolated SVT.

4.3. Therapeutic use

The aim of treatment of acute symptomatic superficial-vein thrombosis is to relieve pain and to prevent extension of thrombosis to the deep-vein system and onset of pulmonary embolism.

According to the AFSSAPS guidelines of November 2009[10], (produced before the results of the CALISTO study became available) in a patient with SVT:

- Venous compression, preferably with elastic or inelastic compression (depending on the clinical situation and the practitioner's preference) is recommended in the acute phase of superficial-vein thrombosis of a limb (Professional Agreement)
- NSAIDs are not recommended (Grade C).
- curative doses of anticoagulants are not recommended in venous thromboembolism (Grade C), except in cases of SVT extending to the saphenofemoral junction, which may require curative doses of an anticoagulant. Low-molecular-weight-heparin (Grade C) and fondaparinux (Professional Agreement) at prophylactic doses to prevent thromboembolism may reduce the risk of thromboembolic complications. If one of these treatments is started, it is suggested that treatment should be given for 7 to 30 days (Professional Agreement).
- Surgery is not recommended (Grade C), but may be considered for SVT extending to the saphenofemoral junction (Professional Agreement).

Role of fondaparinux 2.5 mg daily in the management of SVT

When anticoagulation is being considered to treat SVT, the medicine that has been most evaluated is subcutaneous sodium fondaparinux 2.5 mg daily.

Adult patients likely to benefit from sodium fondaparinux should have isolated acute symptomatic spontaneous superficial-vein thrombosis of the lower limbs, at least 5 cm long and confirmed by ultrasonographic examination. Treatment should be started as soon as possible after diagnosis and after exclusion of concomitant deep-vein thrombosis (DVT) or superficial-vein thrombosis within 3 cm or less of the saphenofemoral junction. Fondaparinux should not be given within the 24-hour period before surgery. Fondaparinux therapy should not be resumed for at least six hours after the procedure, provided that haemostasis is effective. The Committee notes that fondaparinux 2.5 mg daily is contraindicated in patients with severe renal failure defined as creatinine clearance < 50 mL/min: the Committee points out that the 1.5 mg daily dose of fondaparinux has not been assessed in this clinical situation.

The Committee notes that treatment requiring a daily subcutaneous injection for 45 days is restrictive for the patient and that the benefit of this treatment period has only been established in patients with the same profile as those enrolled in the CALISTO study and provided that they comply with the treatment.

4.4. Target population

Indication: treatment of adults with acute symptomatic spontaneous superficial-vein thrombosis of the lower limbs without concomitant deep-vein thrombosis

According to the Marketing Authorisation, patients eligible for treatment with fondaparinux 2.5 mg should have isolated acute symptomatic spontaneous lower-limb SVT at least 5 cm in length and confirmed by ultrasonography or other objective methods. Treatment should be started as soon as possible after diagnosis and after exclusion of concomitant deep-vein thrombosis (DVT) or superficial-vein thrombosis within 3 cm or less of the saphenofemoral junction.

Incidence of symptomatic SVT confirmed by Doppler ultrasonography

The incidence of SVT in France has not been clearly established. According to Wichers *et al*.[11], the incidence of SVT is thought to be greater than that of DVT.

[10] *Prévention et traitement de la maladie thrombo-embolique veineuse en médecine* [Prevention and treatment of venous thromboembolism in medicine - in French only]. Good practice guidelines, AFSSAPS, November 2009.

[11] Wichers IM. Treatment of superficial vein thrombosis to prevent deep vein thrombosis and pulmonary embolism: a systematic review. Haematologica. 2005;90:672-7

However, in the OPTIMEV observational study carried out in 333 vascular medicine clinics between November 2004 and January 2006[12], 1848 of the 8256 patients enrolled with a suspected thromboembolic event had lower-limb DVT and 788 had SVT confirmed by Doppler ultrasonography. So in this study there were 2.3 times as many cases of DVT as SVT confirmed by Doppler ultrasonography. The study did not give SVT length (+/- 5 cm).
In the EPI-GETBO study[13], the estimated annual incidence of DVT in the general population was 1.24 per 1000 (95% confidence interval, 1.12-1.36), which would represent between 73 000 and 88 000 individuals a year in France[14].
In the absence of reliable epidemiological data allowing precise assessment of the incidence of SVT, the estimated number of patients with ultrasonographically-confirmed symptomatic SVT is at least 30 000 per year (incidence of DVT / 2.3) and the estimated total number of patients with symptomatic SVT is about 88 000 a year (calculation basis proposed by the applicant on the assumption that incidence of SVT is at least the same as that of DVT).
There are insufficient data to provide an estimate of the proportion of extensive SVT (at least 5 cm).

The following should also be subtracted from the target population for ARIXTRA:

- The proportion of patients with concomitant DVT: the estimated frequency of occurrence of patients with SVT who have concomitant DVT/pulmonary embolism (PE) was 24.9% in the POST study[15] and 28.8% in the OPTIMEV study[12]
- The proportion of patients with isolated SVT in which the head of the thrombus was located less than 3 cm from the saphenofemoral junction: in the POST study, the estimated percentage of patients with isolated SVT in which the head of the thrombus was located less than 3 cm from the saphenofemoral junction was 8.4%.
- The proportion of patients with moderate or severe renal failure (creatinine clearance ≤ 50 mL/min): in the CALISTO study, 4.4% of patients enrolled had creatinine clearance of 30-50 mL/min.

At present, there are insufficient epidemiological data on the incidence of SVT to allow a precise estimate of the target population for ARIXTRA 2.5 mg in the treatment of ultrasonographically-confirmed symptomatic lower-limb SVT. Based on the data available to us, this population would be between 20 000 and 60 000 patients per year. The Committee is not able to identify those patients likely to benefit from 45 days of treatment.

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines refundable by the French National Health Insurance (B/2 and B/7) and on the list of medicines approved for hospital use and various public services (B/10) in the indication "Treatment of adults with acute symptomatic spontaneous superficial-vein thrombosis of the lower limbs without concomitant deep-vein thrombosis" and at the dosage in the Marketing Authorisation.

The Committee makes its recommendation on the condition that a post-listing study should be carried out.

[12] Galanaud JP. Predictive factors for concurrent deep-vein thrombosis and symptomatic venous thromboembolic recurrence in case of superficial venous thrombosis. The OPTIMEV study. Thromb Haemost 2011;105:1.
[13] Oger E. Incidence of venous thromboembolism: a community-based study in Western France. Thromb Haemost 2000;83:657-60.
[14] Estimated total French population on 1 January 2011: 65 026 885 (www.insee.fr)
[15] Decousus H. Superficial venous thrombosis and venous thromboembolism: a large, prospective epidemiologic study. Ann Intern Med 2010; 152: 218-24.

The transparency Committee requests that a cohort be established to study patients treated in France for superficial-vein thrombosis (SVT) in non-hospital practice (general practice or vascular medicine) to provide the following information:

- characteristics of patients treated for SVT, and in particular details of patients treated with ARIXTRA 2.5 mg. This will make it possible to produce a comparison of patient profiles by treatment received,
- treatments prescribed (including ARIXTRA) and their actual conditions of use
- the impact on morbidity and mortality (particularly in terms of onset of VTE and major haemorrhage) of these treatment strategies (particularly treatment with ARIXTRA). A comparative analysis of this impact will be performed according to observed treatment strategies for SVT.
- together with the impact on organisation of care, globally and by treatment strategies for SVT.

For this purpose, the following data should be collected and analysed:

- characteristics of patients treated: age, gender, weight/BMI, indication for treatment, clinical and ultrasonographic characteristics of SVT (size, location), ultrasonography examination (results, date), duration of SVT, comorbidities (including varices, DVT, PE, renal failure), other risk factors for clinical venous thromboembolism events [VTE] (contraceptive, HRT, immobility, etc.), relevant clinical events (including VTE) or surgery, previous treatment*
- actual conditions of use of ARIXTRA: dosage, treatment duration, compliance with dosage regimen, concomitant therapies**, any changes in therapy (proprietary medicinal product, date) etc.,
- characteristics of doctors (prescriber's specialty, prior diagnosis by GP referring the patient to a vascular specialist for confirmation of diagnosis),
- frequency of onset of VTE [recurrence of SVT, extension of SVT, DVT, PE etc.] with details of whether or not these events were confirmed by ultrasonographic examination,
- death during follow-up,
- frequency of and reason for treatment withdrawals,
- frequency of use of care facilities: hospitalisations, surgery or sclerotherapy,
- safety, particularly in terms of major bleeding,
- impact on organisation of care (use of care, level of prescription of platelet monitoring, level of use of nursing procedures and attendance, etc.).

***drug therapy** (name of proprietary medicinal product, dosage, date) including NSAIDs, anticoagulant, platelet antiaggregation **or other** (type, date): notably elastic compression stockings, sclerotherapy, surgery (stripping, ligation, thrombectomy etc.)

****drug therapy** (name of proprietary medicinal products, dosage, date) including NSAIDs, anticoagulant etc. **or other** (type, date), notably elastic compression stockings

The study duration should be at least three months and justification should be provided by an independent scientific committee. In addition, it is important to ensure that the population of patients taking ARIXTRA is sufficient [appropriate period for collection of data].

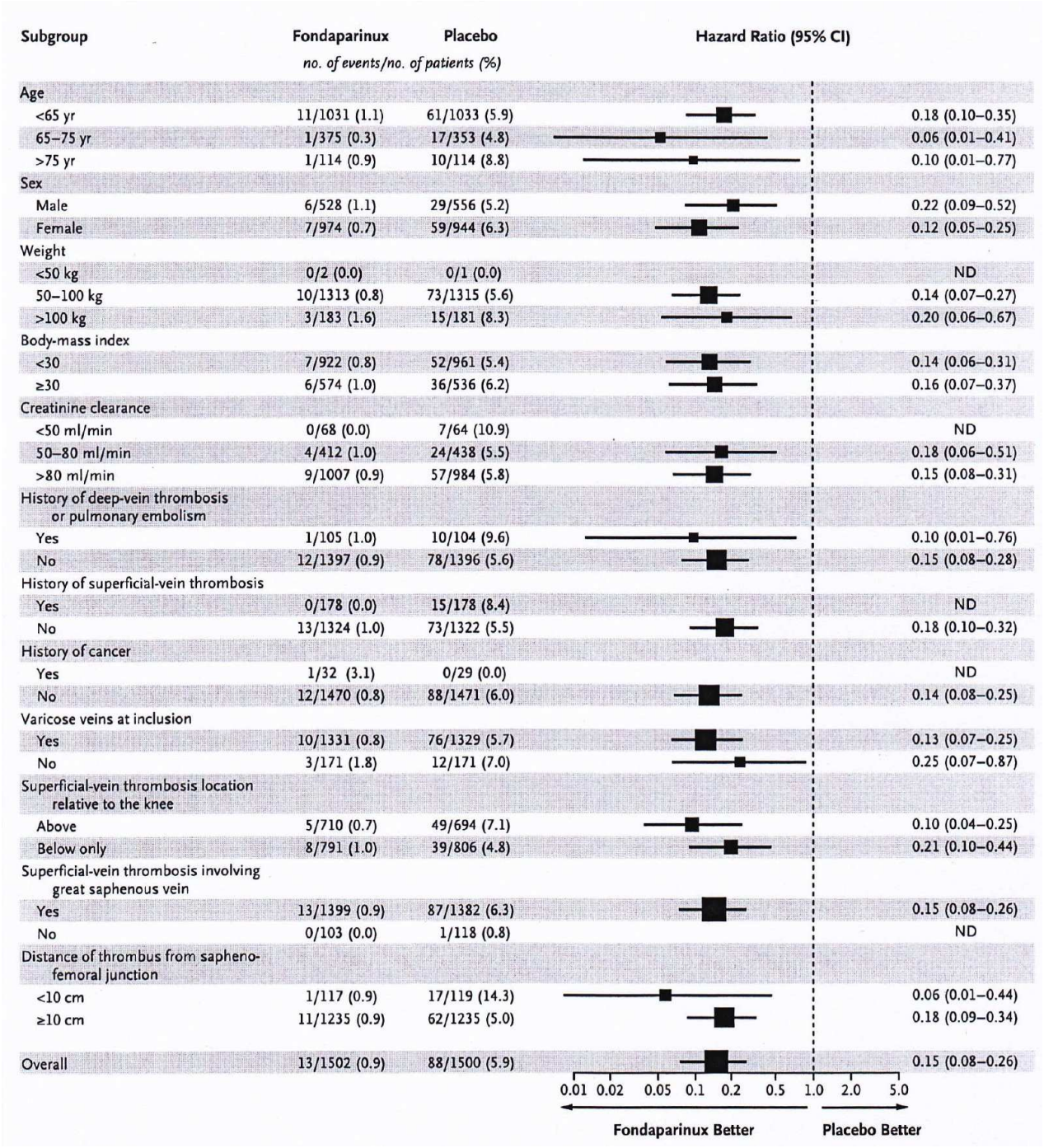
If the studies that are planned or currently in progress, notably as part of the EU Risk Management Plan, are unable to answer the questions posed by the Transparency Committee, a specific study will need to be carried out.

The Committee would like to have the results of this study in two years' time at the latest, and states that it will re-evaluate the actual benefit of ARIXTRA 2.5 mg in this indication at the end of this period.

Packaging: Appropriate for the prescription conditions given in the Marketing Authorisation.

Reimbursement rate: 35%

APPENDIX 1 - <u>Efficacy results in the CALISTO study by D47, by subgroup</u>



Subgroup	Fondaparinux	Placebo	Hazard Ratio (95% CI)
	no. of events/no. of patients (%)		
Age			
<65 yr	11/1031 (1.1)	61/1033 (5.9)	0.18 (0.10–0.35)
65–75 yr	1/375 (0.3)	17/353 (4.8)	0.06 (0.01–0.41)
>75 yr	1/114 (0.9)	10/114 (8.8)	0.10 (0.01–0.77)
Sex			
Male	6/528 (1.1)	29/556 (5.2)	0.22 (0.09–0.52)
Female	7/974 (0.7)	59/944 (6.3)	0.12 (0.05–0.25)
Weight			
<50 kg	0/2 (0.0)	0/1 (0.0)	ND
50–100 kg	10/1313 (0.8)	73/1315 (5.6)	0.14 (0.07–0.27)
>100 kg	3/183 (1.6)	15/181 (8.3)	0.20 (0.06–0.67)
Body-mass index			
<30	7/922 (0.8)	52/961 (5.4)	0.14 (0.06–0.31)
≥30	6/574 (1.0)	36/536 (6.2)	0.16 (0.07–0.37)
Creatinine clearance			
<50 ml/min	0/68 (0.0)	7/64 (10.9)	ND
50–80 ml/min	4/412 (1.0)	24/438 (5.5)	0.18 (0.06–0.51)
>80 ml/min	9/1007 (0.9)	57/984 (5.8)	0.15 (0.08–0.31)
History of deep-vein thrombosis or pulmonary embolism			
Yes	1/105 (1.0)	10/104 (9.6)	0.10 (0.01–0.76)
No	12/1397 (0.9)	78/1396 (5.6)	0.15 (0.08–0.28)
History of superficial-vein thrombosis			
Yes	0/178 (0.0)	15/178 (8.4)	ND
No	13/1324 (1.0)	73/1322 (5.5)	0.18 (0.10–0.32)
History of cancer			
Yes	1/32 (3.1)	0/29 (0.0)	ND
No	12/1470 (0.8)	88/1471 (6.0)	0.14 (0.08–0.25)
Varicose veins at inclusion			
Yes	10/1331 (0.8)	76/1329 (5.7)	0.13 (0.07–0.25)
No	3/171 (1.8)	12/171 (7.0)	0.25 (0.07–0.87)
Superficial-vein thrombosis location relative to the knee			
Above	5/710 (0.7)	49/694 (7.1)	0.10 (0.04–0.25)
Below only	8/791 (1.0)	39/806 (4.8)	0.21 (0.10–0.44)
Superficial-vein thrombosis involving great saphenous vein			
Yes	13/1399 (0.9)	87/1382 (6.3)	0.15 (0.08–0.26)
No	0/103 (0.0)	1/118 (0.8)	ND
Distance of thrombus from sapheno-femoral junction			
<10 cm	1/117 (0.9)	17/119 (14.3)	0.06 (0.01–0.44)
≥10 cm	11/1235 (0.9)	62/1235 (5.0)	0.18 (0.09–0.34)
Overall	13/1502 (0.9)	88/1500 (5.9)	0.15 (0.08–0.26)