

## CSR Aristote

Study No.:	<b>104326</b>
Title:	ARISTOTE Study: French cohort Study conducted to determine how ARIXTRA® 2.5 mg is used in every day practice, and to document the incidence of Venous Thromboembolic Events (VTEs) and major bleeding after orthopaedic surgery
Rationale:	ARIXTRA®, a synthetic selective factor Xa inhibitor, is indicated for the prevention of VTE after major orthopedic surgery of the lower limbs. As part of its evaluation process of ARIXTRA® 2.5 mg, the French High Health Authority (HAS) requested that a prospective cohort study be set up to describe the conditions of use of ARIXTRA® 2.5 mg and to evaluate its clinical effectiveness in terms of the incidence of symptomatic VTE and tolerance in terms of the incidence of bleeding events in the real-world clinical practice setting.
Phase:	Pharmaco-epidemiological study
Study Period:	4th January 2006 – 25th January 2007
Study Design:	Prospective, longitudinal, multicentre pharmaco-epidemiological study
Centres:	48 centres (Departments of Orthopaedic Surgery) included at least one patient
Indication:	Prevention of VTE after major orthopaedic surgery of the lower limbs, such as hip fracture surgery, total hip replacement or total knee replacement.
Treatment:	ARIXTRA® 2.5 mg
Objectives:	<ul style="list-style-type: none"> <li>-To describe the conditions of prescription of ARIXTRA® 2.5 mg in clinical practice.</li> <li>-To evaluate the incidence of VTE occurring during the six weeks following the initiation of the prescription of ARIXTRA® 2.5 mg</li> <li>- To evaluate the incidence of major bleeding events occurring during the six weeks following the initiation of the prescription of ARIXTRA® 2.5 mg</li> </ul>
Primary Outcome/Efficacy Variable:	<p>- <b>Descriptive analysis</b> of the conditions of prescription of ARIXTRA® 2.5 mg was carried out using variables related to indication, total treatment duration, and other patient characteristics. Variables were compared with the SmPC in terms of indication, duration of treatment and contra-indications.</p> <p>-<b>Incidence of VTE occurring during the hospital stay and during the post-discharge follow-up.</b> The incidence of VTE was estimated at Day 10 (for comparison with the historical phase III clinical trial data with ARIXTRA® 2.5 mg ; Day 0 was the date of the surgery) and on Day 42 after the initiation of ARIXTRA® 2.5 mg. VTE was defined as Deep Venous Thrombosis (DVT) and/or Pulmonary Embolism (PE) and/or deaths due to PE. DVT and PE were confirmed by an additional examination with a high diagnostic probability (venous Doppler ultrasonography or phlebography for DVTs, spiral chest CT-scan and/or ventilation-perfusion scintigraphy and/or pulmonary angiography for PE). Documentation (including autopsy report if available) was requested for fatal PE.</p> <p>- <b>Incidence of major bleeding events during the hospital stay and the post-discharge follow-up.</b> The incidence of major bleeding was evaluated at Day 10 and Day 42 after the initiation of ARIXTRA® 2.5 mg. Major bleeding events were defined according to the definition used in the phase III ARIXTRA® 2.5mg trials: fatal bleeding, bleeding in a critical organ, (retroperitoneal, intracranial, intraspinal, or involved any other critical organ), bleeding leading to reoperation, or overt bleeding with a Bleeding Index of 2 or more. The bleeding index was calculated as: number of units of packed red blood cells or whole blood transfused plus prebleeding haemoglobin concentration (g/dL) minus postbleeding haemoglobin concentration (g/dL).</p> <p style="text-align: center;">All events were adjudicated by an independent committee.</p>
Secondary Outcome/Efficacy Variable(s):	The incidence of minor bleeding (including clinically relevant non-major bleeding events): during the hospital stay and the post-discharge follow-up. The incidence of minor bleeding

	<p>was also evaluated at Day 10 and Day 42 after the initiation of ARIXTRA® 2.5 mg. Clinically relevant non-major bleeding events were defined as episodes of epistaxis or bleeding gums requiring an intervention, a haematoma of over 25 cm<sup>2</sup> or visible haematuria lasting over 24 hours.</p>
<b>Statistical Methods:</b>	<p>All patients fulfilling the inclusion and exclusion criteria and who were operated on between 1st January and 30th November 2006 were analysed.</p> <p>The analysable population was described according to the type of the orthopaedic surgery. The following tests were used for statistical comparisons between the groups:</p> <ul style="list-style-type: none"> <li>•For qualitative data, comparisons were made using Pearson's Chi<sup>2</sup> Test or, if the theoretical (calculated) numbers were below 5, Fisher's Test.</li> <li>•For quantitative data, if the distribution approached normal (using the Kolmogorov-Smirnoff Test), Student's test or analysis of variance was performed. Otherwise, i.e. if the distribution was not normal, non-parametric tests were carried out (Mann &amp; Whitney and Kruskal &amp; Wallis).</li> <li>•Crude relative risk was calculated to identify variables that may be predictive of VTEs and bleeding. The variables analysed were: age of over 75; weight below 50 kg; BMI of less than 30 kg/m<sup>2</sup>; creatinine clearance of less than 20 ml/min or less than 50 ml/min; an interval of less than 6 hours between the end of the surgical procedure and the first injection of ARIXTRA® 2.5 mg; preoperative use of a drug that might entail a risk of bleeding; and the presence of at least two risk factors as identified by the Study Physicians.</li> </ul> <p>Statistical analyses were carried out using SAS® software (Version 9.1). The significance threshold was fixed at 5% (two-tailed) for inter-group comparisons.</p>
<b>Study Population:</b>	<p><u>Inclusion criteria</u></p> <ul style="list-style-type: none"> <li>•Patients aged 18 years and over</li> <li>•Patients in a hospital orthopaedic surgery department who were prescribed ARIXTRA® 2.5 mg</li> </ul> <p><u>Exclusion criteria</u></p> <ul style="list-style-type: none"> <li>•Patients who refused to take part in the Study</li> </ul>
Number of Subjects:	608
Planned, N	600
Randomised, N	None
Completed, n (%)	594
Total Number Subjects Withdrawn, N (%)	14 (2.3%)
Withdrawn due to Adverse Events n (%)	0
Withdrawn due to Lack of Efficacy n (%)	0
Withdrawn for other reasons n (%)	14 (2.3%)
<b>Demographics</b>	
N (ITT)	594
Females : Males	391 : 203
Mean Age, years (SD) , median, range	71.5 (12.7), 73.5, 25-97
Race, n (%)	Not collected
<b>Results:</b>	<p>Patients were divided into four groups: 178 patients (30%) had a hip fracture (HF), 245 patients (41.4%) had a total hip replacement (THR), 155 patients (26.1%) had a total knee replacement (TKR); and 13 patients (2%) had an other type of surgery and for 2 patients the procedure was unknown.</p> <p>No major differences were observed among the 3 types of surgery (THR/TKR/HF) in the incidence of VTE or the incidence of bleeding events (table 1).</p>
<b>VTE (table1):</b>	<p>Altogether 14 patients (2.4%; 95%CI: 1.3%-3.9%) had a VTE during the whole study period, including 9 symptomatic events and 5 patients with asymptomatic VTE. 13 patients (2.2% ; IC95% : 1,2%-3,7%) had a VTE between Day 0 and Day 42. Nine patients experienced a VTE (1.5% ; 95%CI: 0.7%-2.9%) between</p>

Day 0 and Day 10 (including 4 symptomatic VTE and 5 asymptomatic VTE).

**Major Bleedings (table 1):** 13 patients had a total of 13 major bleeding events during the whole study period (mean follow-up 50.8 days) (and at Day 42), i.e. 2.2% of the 594 enrolled patients (95%CI: 1.2%-3.7%). Types of major bleeding were as follows: 1 fatal, 3 involving a critical organ, and 9 with a Bleeding Index  $\geq 2$ . 11 patients (1.9% ; 95%CI: 0.9%-3.3%) had a major bleeding event between Day 0 and Day 10. If the events defined only by surgical site bleeding with a bleeding Index  $\geq 2$  are excluded, the rate of bleeds is **0.5%** (n=3) at Day 10 and 0.8% (n=5) at Day 42. The fatal bleeding event and the 3 bleeding events in a critical organ occurred in patients operated for hip fracture surgery.

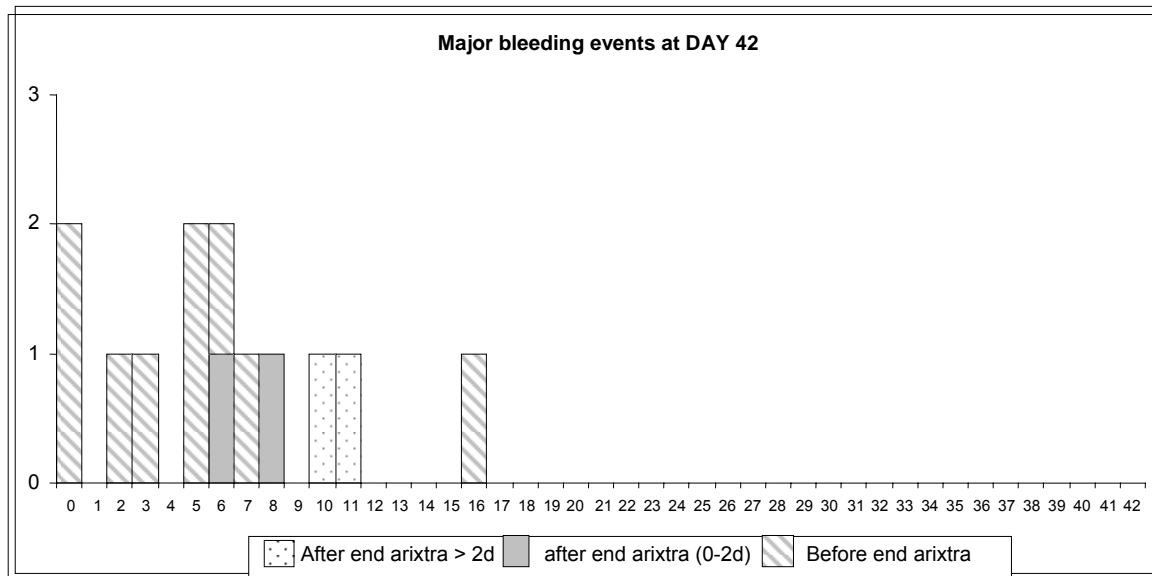
On average, the major bleeding events occurred approximately 6 days after the surgical procedure and the first injection of ARIXTRA® 2.5 mg. (Figure 1).

Table 1: Complications observed during all the study period.

Complications	Whole population (N=594)*
<b>VTE</b>	
% (N)	2,4% (14)
IC95%	1,3%-3,9%
<b>VTE</b>	
% (N) Symptomatic	1,5% (9)
% (N) Asymptomatic	0,8% (5)
<b>Major bleeds</b>	
% (N)	2.2% (13)
95%CI	1.2%-3.7%
<b>Type of major bleed</b>	
% (N) Fatal bleed	0.2% (1)
% (N) Non-fatal in a critical organ*	0.5% (3)
% (N) Leading to a reintervention	0
% (N) With bleeding index $\geq 2$	1.5% (9)
<b>Minor Bleeding</b>	
% (N)	6,1% (36)
IC95%	4,3%-8,3%
<b>Death</b>	
% (N)	2,7% (16)
IC95%	1,6%-4,3%

\*1 intracranial hemorrhage and 2 duodenal bleeds

**Figure 1: Occurrence of major bleeding events compared to start of treatment by ARIXTRA®, at DAY 42 (13 events occurring in 13 patients)**



**Minor Bleeding:** 36 patients (6.1% ; 95%CI: 4.3%-8.3%) had 41 minor bleeding events throughout the whole study follow-up (mean follow-up 50.8 days). Between Day 0 and Day 10, 30 patients (5.1%; 95%CI: 3.4%-7.1%) had 33 minor bleeding events. Eighteen (18) of the 36 cases of minor bleeding were qualified as clinically significant bleeding by the independent adjudication committee.

**Deaths:** 16 patients died during the whole study period i.e. 2.7% (95%CI: 1.6%-4.3%) of the enrolled 594 patients. The causes of death were as follows:

- Heart disease: 5 cases
- Rhabdomyolysis causing heart and kidney failure: 1 case
- Sepsis: 3 cases
- Stroke: 1 case
- Failure to thrive syndrome: 2 cases
- Mesenteric infarct: 1 case
- Acute pulmonary oedema: 1 case
- Vomiting then cardiorespiratory arrest: 1 case
- Mesenteric infarct + haemorrhage: 1 case: *Female 80 years, 50 kg, HF surgery. Received low molecular weight heparin (LMWH) the day before the operation, ARIXTRA® 2.5 mg during 5 days and an additional injection of LMWH on day of last ARIXTRA injection (day 5). On day 6, mesenteric infarction with haemorrhagic shock.*

Between Day 0 and Day 42, 12 deaths (2.0%; 95%CI: 1.1%-3.5%) occurred, all in the HF group. Four (4) deaths (0.7% ; 95%CI: 0.2%-1.7%) occurred between Day 0 and Day 10.

#### **Results on conditions of utilisation:**

Overall, 84% of patients received ARIXTRA® 2.5 mg for less than 35 days, the median duration of the treatment was 10 days.

Regarding the warnings of the SmPc , 47.5% of the subjects were more than 75 years old, 22.5% had a creatinine clearance between 20 and 50 ml/min and 38.6% of the patients received a treatment able to increase the risk of bleeding (VKA, NSAID/cox 2 inhibitor, antiplatelet drugs) before surgery.

**Safety Results:** Pharmacovigilance retained 44 cases: 10 reported by the study physicians and 34 derived from the adjudicators' conclusions. The causality relation with ARIXTRA® ("imputability") was considered to be possible in 3 cases, probable in 3 cases, almost certain in 1 case and unlikely in 2 cases. In the 35 other cases, the imputability of ARIXTRA® could not be determined.

Of the 13 major bleedings, only one was considered almost certainly related to ARIXTRA® and 12 were not determined. Of the 16 deaths, 2 were clearly not related to ARIXTRA® by the investigator and 14 were not determined.

Most Frequent Adverse Events	n (%)
Subjects with any AE(s),	44 (7.4%)
<i>Most Common AEs: (n ≥ 4):</i>	
Haemoglobin decreased	32
Incision site haemorrhage	22
Haematoma	9
Intentional drug misuse	9
Incision site haematoma	7
Subcutaneous haematoma	5
Anemia	5
Post procedural haemorrhage	4
Operative haemorrhage	4
Incorrect drug administration	4
Serious Adverse Events n [n considered by the investigator to be related to study medication or unknown causality]	
<b>Subjects with non-fatal SAEs, n (%)</b>	<b>14(%)</b>
Anaemia	3 [3]
Cardiac disorder	1 [1]
Cerebral haematoma	1 [1]
Deep vein thrombosis	1 [1]
Disorientation	1 [1]
Duodenal ulcer perforation	1 [0]
Dyspnoea	1 [1]
Gastrointestinal haemorrhage	1 [1]
Haemoglobin decreased	1[1]
Haemorrhage	4 [4]
Hepatocellular injury	1 [1]
Hypokalaemia	1 [1]
Hypovolaemia	1 [1]
Incision site haematoma	6 [6]
Incision site haemorrhage	22[21]
Operative haemorrhage	4 [4]
Phlebitis	1 [1]
Post procedural haematoma	1 [1]
Post procedural haemorrhage	4 [4]
Pulmonary embolism	1 [1]
Renal failure	2 [2]
Renal failure acute	1 [1]

Subdural haematoma	1 [1]
Thrombocytopenia	1 [1]
Thrombosis	1 [1]
Wound haemorrhage	1 [1]
<b>Fatal Serious Adverse Events</b>	
<b>Subjects with fatal SAEs, n (%)</b>	<b>5</b>
Acute pulmonary oedema	1 [0]
Atrial fibrillation	1 [0]
Failure to thrive	2 [1]
Gastrointestinal pain	1 [0]
Hypotension	1 [0]
Intestinal infarction	1 [0]
Ischaemic stroke	1 [1]
Peritonitis	1 [0]
Pneumonia aspiration	1 [1]
Respiratory distress	1 [1]
Sepsis	1 [0]
Shock haemorrhagic	1 [1]

#### **Conclusion:**

The ARISTOTE Study, a French, multicenter, prospective pharmacoepidemiological, cohort study of patients receiving ARIXTRA® 2.5 mg to prevent venous thromboembolic events following major orthopaedic surgery of the lower limbs, showed that ARIXTRA® 2.5 mg was used according to the SmPC and in line with current Guidelines in the majority of patients.

The median treatment duration of ARIXTRA® 2.5 mg was 10 days. As expected, the population in this study was different from that in the phase III clinical trial program with ARIXTRA® 2.5 mg and that of other anticoagulant drugs in recent clinical trials: in particular, the population in ARISTOTE appeared to be at greater risk of venous thromboembolic and bleeding events because of differences in age, kidney function, history of venous thromboembolism, and concomitant treatments.

Nevertheless, the incidences of venous thromboembolic and major bleeding events in the ARISTOTE Study were similar to those observed in the Phase III programme:

- the incidence of symptomatic VTEs was comparable to those reported in the clinical trials with ARIXTRA® 2.5 mg (overlapping 95% confidence intervals), and there were only 4 symptomatic VTE, all distal DVT, at Day 10
- the incidence of major bleeding events (ARIXTRA® 2.5 mg phase III definition) was comparable to that observed in the phase III clinical trials with ARIXTRA® 2.5mg , i.e. 1.9% at Day 10 and 2.2% throughout the entire Study (mean follow-up 50.8 days).

Furthermore, If the events defined only by surgical site bleeding with a bleeding Index  $\geq 2$  are excluded, the rate of bleeds is 0.5% (n=3) at Day 10 and 0.8% (n=5) at Day 42.

Bleeding risk factors observed in the ARISTOTE Study were consistent with those identified in the SmPC, in particular weight < 50 kg, age > 75, and creatinine clearance less than 50 ml/min. It should be noted that age did not emerge as a predictive factor for major bleeding events, but this was probably due to the limited number of cases observed.

The mortality rate observed in the ARISTOTE Study was also comparable to that observed in the phase III clinical trials with ARIXTRA® 2.5 mg.



## CTR Approval Form

Product Trade Name: ARIXTRA® 2.5 mg

Generic Name: Fondaparinux

**Study Number** as it appears on study summary: **104326**

**Indication as it appears on study summary:**

- Prevention of venous thromboembolic events in major orthopaedic surgery of the lower limbs, such as hip fracture, total hip replacement or total knee replacement.

Please supply key words for future search facility: ARIXTRA, fondaparinux, venous thromboembolic events, major bleeding, major orthopaedic surgery, deep vein thrombosis, pulmonary embolism

Population:	Adult patients in a hospital Orthopaedic Surgery Department who were prescribed ARIXTRA® 2.5 mg
Study design:	Prospective, longitudinal, multicentre pharmaco-epidemiological study
Other:	

Was this study used as an arm to support a combination product? No

If yes, please indicate the name of the combination product and study number:

Product: Study Number:

This summary was reviewed by the following personnel:

BDS Representative	
GCSP Reviewer (if applicable)*	
CIP Legal Representative	

*\*GCSP reviews apply to CMD locally sponsored studies only.*