

## CSR ARIANE

<b>Study No.:</b>	110147
<b>Title:</b>	ARIANE study: Arixtra and Platelet Monitoring
<b>Rationale:</b>	<p>Type II heparin-induced thrombocytopenia (HIT II) is an uncommon but serious and potentially fatal adverse reaction associated with heparin treatment. Although the risk for HIT II is lower with lower molecular weight heparins (LMWH) than with unfractionated heparin (UFH), regular platelet count monitoring is necessary in patients treated with LMWH according to the product labels.</p> <p>As fondaparinux does not bind to platelet factor 4 and does not cross-react with sera from patients with HIT II, platelet count monitoring is not required in patient treated with Arixtra®.</p> <p>Following the inscription of Arixtra® 2.5 mg on the list of reimbursed medicines, the Health Care Products Economic Committee (CEPS) requested a study to evaluate the rate of platelet monitoring in patients treated with Arixtra® 2.5 mg.</p> <p>To avoid methodological issues of potential bias in physicians' prescribing habits, the stated objective of the ARIANE study was enlarged to encompass broad questions around use of LMWH and Fondaparinux in the ambulatory care setting.</p>
<b>Phase:</b>	NA (observational study)
<b>Study Period:</b>	23 February 2008 - 9 August 2008
<b>Study Design:</b>	Observational, cross-sectional, pharmaco - epidemiological study
<b>Centres:</b>	470 participating General Practitioners (GP)
<b>Indication:</b>	<p>Prevention of Venous Thromboembolic Events (VTE) in medical patients who are judged to be 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.</p> <p>Prevention of Venous Thromboembolic Events (VTE) in patients who undergoing abdominal surgery who are judged to be at high risk of thromboembolic complications, such as patients undergoing abdominal cancer surgery.</p> <p>Prevention of Venous Thromboembolic Events (VTE) in patients who undergoing major orthopaedic surgery of the lower limbs such as hip fracture, major knee surgery or hip replacement surgery.</p>
<b>Treatment:</b>	Arixtra® 2.5mg / LMWH

<b>Objectives:</b>	<p><u>Primary objective:</u> To describe general practitioners' prescription patterns regarding use of Arixtra® 2.5 mg (sodium fondaparinux) and low molecular weight heparins (LMWH) for VTE prevention.</p> <p>The following data were used to describe prescription patterns :</p> <ul style="list-style-type: none"> <li>- Patient characteristics (demographics, medical history)</li> <li>- Presence of risk factors for VTE</li> <li>- Reason for venous thromboprophylaxis</li> <li>- Laboratory tests</li> </ul> <p><u>Secondary objective:</u> To compare prescription patterns regarding use of Arixtra® 2.5 mg and LMWH.</p>
<b>Main Outcome</b>	Rate of platelet monitoring in patients treated with Arixtra® 2.5 mg.
<b>Secondary Outcome</b>	Reasons for platelet monitoring; Descriptive variables of the group treated with Arixtra® 2.5 mg in comparison with group treated with LMWH including the following: duration of anticoagulant therapy, reason for venous thromboprophylaxis, at-risk for VTE
<b>Statistical Methods:</b>	<p>For quantitative and ordinal variables, the description in the Statistical Report includes the absolute number and frequency for each parameter. For quantitative variables, the description includes the absolute number, mean, standard deviation, median, quartiles and range. The number of missing data points is also stipulated. To compare the groups, the following tests were used:</p> <ul style="list-style-type: none"> <li>- Ranked analysis of variance for quantitative data</li> <li>- A chi<sup>2</sup> test (or an Exact Fisher test for small populations) for non-ordinal qualitative data.</li> <li>- A Kruskal-Wallis test for ordinal data.</li> </ul> <p>A significance threshold of 5% was set for these various tests. All statistical tests were carried out using SAS® software (V8.2. SAS Institute, North Carolina, USA).</p> <p>The study population was not perfectly representative of the registry population vis-à-vis indications. It was therefore decided to standardise the main focus of the study for groups of indications, taking into account the weight of each group of indications in the registry population. In practice, an imbalance may be generated by uneven distribution of the groups of indications in the registry population compared to that in the Study Population. Such an imbalance could affect the rate of prescription of platelet monitorings.</p> <p>Standardisation was carried out in both the Arixtra® 2.5 mg Group and the LMWH Group.</p>

<b>Study Population:</b>	<u>Inclusion criteria:</u> - Patients aged 18 years and over - Outpatients receiving Arixtra® 2.5 mg or LMWH, as an initial treatment or a newly introduced treatment after switch from another anticoagulant, to prevent venous thrombosis.
	<u>Non-inclusion criteria:</u> - Patients receiving a curative dose of Arixtra® (5, 7.5 or 10 mg) or LMWH - Patients taking part in another survey - Patients who refuse to take part in the study
	<u>Registry population:</u> Throughout the inclusion period, the study physician had to keep a registry of eligible patients prescribed Arixtra® 2.5 mg or LMWH to prevent thrombosis. This registry was used to check that the patients for whom the physician had filled out medical questionnaires constituted a representative sample.

Number of Subjects:	910		
Planned, N	1000		
Randomised, N	NA		
Completed, n (%)	837 (92%)		
Total Number Subjects Withdrawn, N (%)	73 (8.7%)		
Withdrawn due to Adverse Events n (%)	NA		
Withdrawn due to Lack of Efficacy n (%)	NA		
Registry	3134		
Withdrawn for other reasons n (%)	73 (8.7%)		
<b>Demographics</b>	Arixtra group	LMWH group	Total
N (ITT)	450	387	837
Females: Males	259 :191	205 :182	464 :373
Mean age, years (SD)	61.5 (17.3)	61.7 (17.8)	61.6 (17.5)
Race	Not collected		

## Results

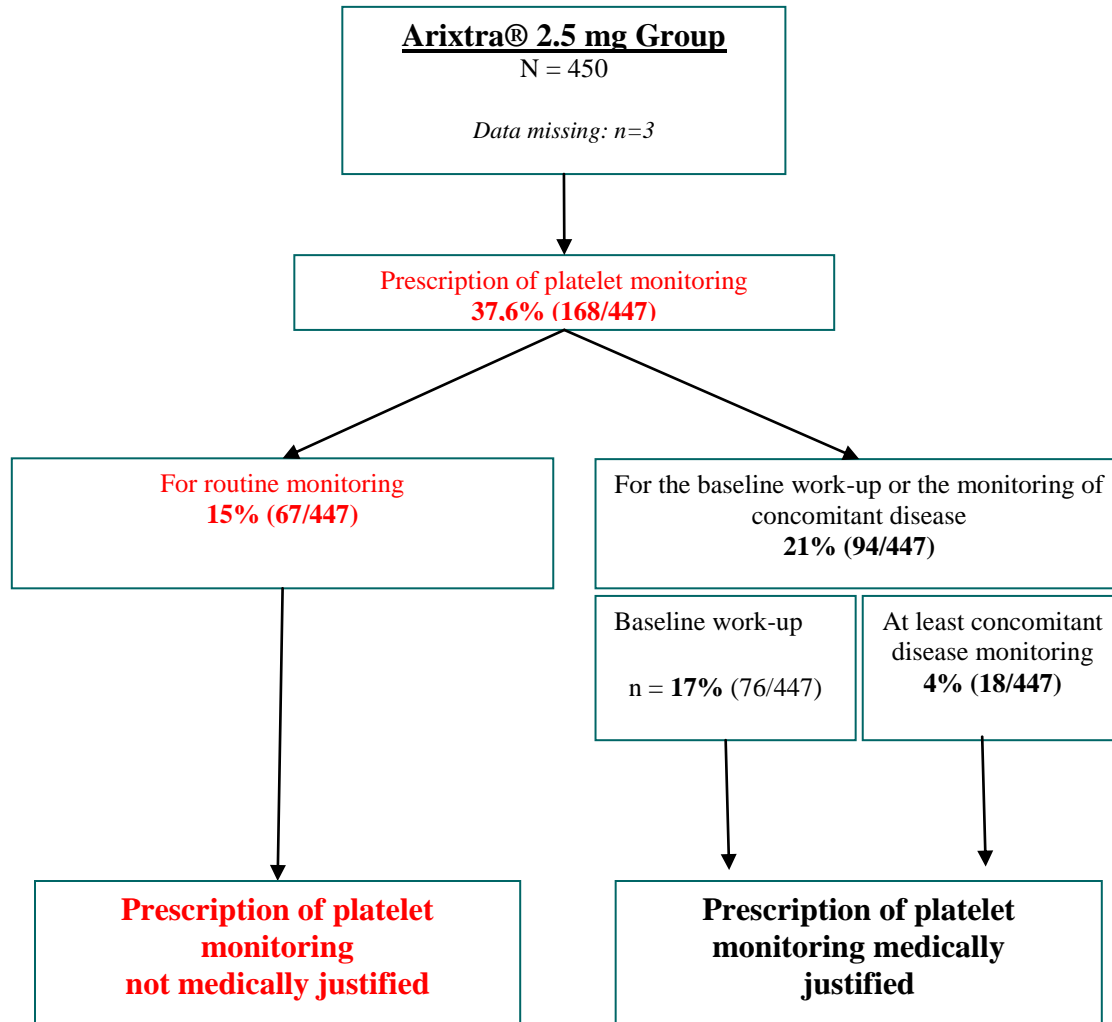
### Rate of platelet monitoring in the Arixtra® 2.5mg group:

In order to determine whether prescription of platelet monitoring medically justified or not in patients receiving Arixtra® 2.5 mg, the following algorithm was developed by the steering committee:

Platelet monitoring was considered as not medically justified if prescribed for routine monitoring.

It was considered as justified if done as part of the baseline work-up and/or during evaluation of a concomitant disease.

Based on these criteria, platelet monitoring was not medically justified in 15% of patients treated with Arixtra 2.5mg.



**Results on prescription of platelet monitoring in the LMWH group:**

Routine platelet count monitoring is necessary in all patients treated with LMWH at baseline of thromboprophylaxis and during the treatment.

In Ariane study, platelet monitoring was prescribed 81% of patients treated with LMWH.

Whereas a platelet count (PC) or a blood count (BC) are the most common platelet count prescribed in current practice, the rate of platelet monitoring in patients treated with LMWH was of 68.6%.

**Standardisation:**

The representativeness of patients included in the study (both the Arixtra® 2.5 mg and LMWH groups) was analysed by comparison to the registry data.

LMWH Group N=387 (data missing: n=2)		
	Platelet count for routine monitoring	Platelet count for baseline work up
At global	81% (312/385)	37.4% (144/385)
PC only or BC only	68.6% (264/385)	28% (108/385)

For both treatment groups, comparisons were made vis-à-vis age, gender, initial prescription setting, the indication for thromboprophylaxis, the type of drug and the length of the course of treatment, between patients included in the study and those exclusively listed in the registry.

After standardisation, the rate of platelet monitoring was:

- 37.7% [33.2% ; 42.2%] in the Arixtra® 2.5 mg Group
- 96.5% [94.6% ; 98.3%] in the LMWH Group

After standardisation, on the basis of the method used, platelet monitoring not medically justified, was about 14.7% (IC95%: [11.4%; 17.9%])

**Indications/ Risk factors for prescription of VTE prophylaxis by group**

<b>SPC<sup>1</sup> Arixtra® 2.5 mg / LMWH</b>	<b>Arixtra® 2.5 mg Group (n=450)</b>	<b>LMWH Group (n=387)</b>
<p><b>Indications:</b> To prevent VTE:</p> <ul style="list-style-type: none"> <li>- immobilization due to acute illness such as cardiac insufficiency and/or acute respiratory disorders and/or acute infectious or inflammatory disease</li> <li>- after major orthopaedic surgery of the lower limb</li> <li>- after high-risk abdominal surgery</li> </ul>	<p><b>SPC</b> <b>73.8%</b></p> <ul style="list-style-type: none"> <li>- Acute medical conditions or prolonged immobilisation 66.2%</li> <li>- Post-operative 7.6%</li> </ul> <p><b>Guidelines<sup>2</sup></b> <b>1.8%</b></p> <p><b>Non-recommended indications<sup>3</sup></b> <b>1.3%</b></p> <p><b>Unclassifiable<sup>4</sup></b> <b>23.1%</b></p>	<p><b>SPC</b> <b>78.1%</b></p> <ul style="list-style-type: none"> <li>- Acute medical conditions or prolonged immobilisation 69.3%</li> <li>- Postoperative 8.8%</li> </ul> <p><b>Guidelines</b> <b>1.8%</b></p> <p><b>Non-recommended indications</b> <b>1.0%</b></p> <p><b>Unclassifiable</b> <b>19.1%</b></p>
<p><b>Treatment duration:</b> 7 – 14 days</p>	<p>Mean: <b>15 days</b> (± 10.3). Median : 10 days</p> <p><b>54.0%</b> of patients had a treatment duration between <b>7 and 14 days</b></p>	<p>Mean: <b>17 days</b> (± 12.3). Median: 14 days</p> <p><b>48.6%</b> of patients had a treatment duration between <b>7 and 14 days</b></p>
<p><b>Dosage:</b> once daily</p>	<p>At least one injection of 2.5 mg daily in 100% of patients</p>	<p>At least one injection daily in 99.2% of patients</p>
<p><b>Creatinine clearance [20-50] ml/min<sup>5</sup></b></p>	<p>No patient had a creatinine clearance less than 20ml/min</p> <p>Patients with a creatinine clearance between 20 and 50 ml/min: 12.4% (14/113)</p>	<p>One patient had a creatinine clearance less than 20 ml/min: 0.9% (1)</p> <p>Patients with a creatinine clearance between 20 and 50 ml/min: 17.0% (18/106)</p>
<p><b>Elderly patients (&gt;75 years)</b></p> <p><b>Low body Weight (&lt; 50 kg)</b></p>	<p>26.2% (118).</p> <p>4.7% (21)</p>	<p>28.2% (109).</p> <p>3.1% (12)</p>

<sup>1</sup> SPC: Summary of Product Characteristics

<sup>2</sup> Guidelines: Pathologies mentioned in guidelines compiled by expert institutions

<sup>3</sup> Non-recommended indications (mentioned in neither the SPC nor expert guidelines)

<sup>4</sup> Unclassifiable: cases that cannot be assigned to an indication category because the physician has not provided sufficient data in the Case Report Form: these cases are impossible to define further without access to the patient's medical records

<sup>5</sup> In the MA of Arixtra® 2.5 mg in Europe (2007 modifications) there are precautions for use in patients who are at high risk of bleeding or VTE: elderly patients (>75 years), patients with body weight <50kg, patients with creatinine clearance between [20-50] ml/min (the dose should be reduced to 1.5 mg once daily in patients with creatinine clearance in the range of 20 to 50 ml/min).

**Safety / Efficacy Results:**

**not collected**

**Conclusion :**

Platelet monitoring was considered to be inappropriately prescribed in about **15%** of patients treated with Arixtra® 2.5 mg. However, this rate is much lower than that in patients treated with LMWH (approximately 96% overall).

Both Arixtra® 2.5 mg and LMWH were prescribed for venous thromboprophylaxis in accordance with labelled indications and/or recommended guidelines in at least 75% of cases.