HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
15 May 2013

ARIXTRA 2.5 mg/0.5 ml, solution for injection in pre-filled syringe

B/2 (CIP: 34009 359 225 4 0)
B/7 (CIP: 34009 359 226 0 1)
B/10 (CIP: 34009 563 619 7 7)

Applicant: GlaxoSmithKline

INN	fondaparinux sodium
ATC Code (year)	B01AX05 (Antithrombotic agent). Selective indirect factor Xa inhibitor
Reason for the review	**Re-assessment of the Actual Benefit and Improvement in Actual Benefit, at the request of the Committee (pursuant to Article R 163-21 of the French Social Security Code) following questions raised by the Afssaps (French Health Products Safety Agency) on 28 December 2011**
Lists concerned	**National Health Insurance reimbursement** (French Social Security Code L.162-17) **Hospital use** (French Public Health Code L.5123-2)
Indications concerned	**"- 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."**

Actual Benefit (AB)	**The Actual Benefit of ARIXTRA 2.5 mg is:** **- substantial when used as initial and prolonged thromboprophylaxis in adults after major orthopaedic surgery of the lower limbs such as hip fracture** **- substantial when used as initial thromboprophylaxis and insufficient in prolonged thromboprophylaxis after elective orthopaedic knee or hip surgery** **- substantial when used as thromboprophylaxis after abdominal surgery in adult patients who are judged to be at high risk of thromboembolic complications, such as patients undergoing abdominal cancer surgery** **- substantial when used as thromboprophylaxis in adults who are judged to be at high risk of venous thromboembolic events, i.e., adults who are immobilised due to acute illness such as cardiac insufficiency and/or acute respiratory disorders and/or acute infectious or inflammatory disease.**
Improvement in Actual Benefit (IAB)	**Given the risk of misuse that has been observed for many years with ARIXTRA 2.5 mg, the insufficiency assessment of ARIXTRA 2.5 mg in cases where prolonged thromboprophylaxis, the risk of serious or fatal haemorrhage in patients weighing less than 50 kg, in patients over 75 years of age and/or in renally impaired patients, the Committee considers that ARIXTRA 2.5 mg does not provide an improvement in actual benefit (IAB V, non-existent) in the prevention of venous thromboembolic events after major orthopaedic surgery of the lower limbs and in patients who are judged to be at high risk of thromboembolic complications after abdominal surgery or who are immobilised due to acute illness.**
Therapeutic use	**First line treatment**
Transparency Committee recommendations	**The Committee emphasises the absolute need, in view of the reported safety data, to respect the treatment durations and the indications stated in the Marketing Authorisation and highlights the precautions for use in patients at a high risk of bleeding.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Initial date (European centralised procedure): 21 March 2002 Extensions of the indication of thromboprophylaxis with ARIXTRA 2.5 mg: - to include patients undergoing surgery for hip fracture: 7 November 2003 - to include patients judged to be at high risk of venous thromboembolic events, i.e., who are immobilised due to acute illness: 25 January 2005 - to include abdominal surgery patients who are judged to be at high risk of thromboembolic complications, such as patients undergoing abdominal cancer surgery: 7 July 2005.
Prescribing and dispensing conditions / special status	List I ARIXTRA has a European Risk Management Plan (RMP) and, since January 2007, has had national pharmacovigilance monitoring.

ATC Classification	2012	
	B	Blood and blood forming organs
	B01	Antithrombotic agents
	B01A	Antithrombotic agents
	B01AX	Other antithrombotic agents
	B01AX05	Fondaparinux

02 BACKGROUND

In its 28 December 2011 letter to the HAS alerting them to the serious haemorrhagic accidents observed with ARIXTRA 2.5 mg in at-risk patients (the elderly, patients with low body weight or with renal impairment), the Afssaps questioned the HAS about the possibility of re-assessing the 1.5 mg dose, suggesting that it may be of benefit to these patients. The Committee decided to re-assess the actual benefit of ARIXTRA (all dosages with a Marketing Authorisation) in all of its indications.
In this Opinion, only the thromboprophylaxis indications for the 2.5 mg dosage will be re-assessed.

03 THERAPEUTIC 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 (see Pharmacodynamics)**
- **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 (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.
- Treatment of adults with acute symptomatic spontaneous superficial-vein thrombosis of the lower limbs without concomitant deep-vein thrombosis."

04 DOSAGE

"Patients undergoing major orthopaedic or abdominal surgery:
The recommended dose of fondaparinux is 2.5 mg once daily administered post-operatively by subcutaneous injection. The initial dose should be given 6 hours following surgical closure after checking that there is no active bleeding. Treatment should be continued until the risk of venous thromboembolism has diminished, usually until the patient is ambulant, at least 5 to 9 days after surgery.

Experience shows that in patients undergoing hip fracture surgery, the risk of Venous Thromboembolic Events continues beyond 9 days after surgery. In these patients, the use of prolonged prophylaxis with fondaparinux should be considered for up to an additional 24 days.

Medical patients who are at high risk of thromboembolic complications based on an individual risk assessment: the recommended dose of fondaparinux is 2.5 mg once daily administered by subcutaneous injection. A treatment duration of 6 to 14 days has been clinically studied in medical patients.

Special populations and situations:

- Elderly patients: elderly patients are at an increased risk of bleeding. A reduction in renal function generally occurs with age; elderly patients may present with a reduction in the elimination and an increase in plasma fondaparinux concentrations. In the elderly, fondaparinux is to be used with caution.
- Renal impairment and prevention of VTE (thromboembolic events): fondaparinux elimination is essentially renal. Fondaparinux should not be used in patients with creatinine clearance < 20 ml/min. The dose of fondaparinux should be reduced to 1.5 mg once daily in patients with creatinine clearance in the range of 20 to 50 ml/min. Patients with creatinine clearance below 50 ml/min are at increased risk of bleeding and of venous thromboembolic events, and are to be treated with caution. There is only limited available clinical data on patients with a creatinine clearance below 30 ml/min.
  No dosage adjustment is required for patients with mild renal impairment (creatinine clearance > 50 ml/min).

- Hepatic impairment and prevention of VTE: no dosing adjustment is necessary in patients with either mild or moderate hepatic impairment. In patients with severe hepatic impairment, fondaparinux should be used with care as this patient group has not been studied.
- Low body weight and prevention of VTE: patients with a body weight below 50 kg are at increased risk of bleeding. Elimination of fondaparinux decreases with weight. Fondaparinux should be used with caution in these patients.
- Prevention of venous thromboembolic events following surgery: In patients undergoing surgery, timing of the first fondaparinux injection requires strict adherence in patients 75 years and older, and/or with body weight below 50 kg and/or with renal impairment with creatinine clearance ranging between 20 to 50 ml/min. The first fondaparinux dose should be given not earlier than 6 hours following surgical closure. This injection should not be given before the absence of active bleeding has been verified.
- Spinal/epidural anaesthesia: in patients undergoing major orthopaedic surgery, epidural or spinal haematomas that may result in long-term or permanent paralysis cannot be excluded with the concurrent use of fondaparinux and spinal/epidural anaesthesia or spinal puncture. The risk of these rare events may be higher with post-operative use of indwelling epidural catheters or the concomitant use of other medicinal products affecting haemostasis."

05 THERAPEUTIC NEED

The aims of preventing venous thromboembolic disease (VTED) are:
- to avoid the two complications, which are pulmonary embolism and post-thrombotic syndrome
- to reduce the mortality associated with the occurrence of pulmonary embolism.

VTE prophylaxis is usually continued until the patient is totally ambulant.

In adults, after major lower limb orthopaedic surgery for a total hip or knee replacement or after surgery for hip fracture, thromboembolic risk is high and routinely requires the prescription of prophylactic measures. Thromboembolic risk is also high in patients who are judged to be at high risk of thromboembolic complications and who are immobilised due to acute illness or after abdominal surgery. Patients who are the most at risk are generally those who have a history of venous thromboembolic disease.

Thromboprophylaxis can be medicinal and or mechanical (the latter in particular for cases when medication is contraindicated). There are several alternative medicines available (see section 06).

The occurrence of a severe haemorrhage can be fatal and is the main risk associated with taking these medications.

Factors that increase the risk of haemorrhage are advanced age, low body weight and overdose as the result of accumulation following a deficiency in anticoagulant elimination. Since fondaparinux (ARIXTRA) is primarily excreted through the kidneys and its form remains unchanged, the risk of overdose is a very likely in patients with renal impairment. However there are alternatives available. In cases of moderate renal impairment, the alternatives are UFHs, LMWHs, ELIQUIS and XARELTO, if taken with caution. In cases of severe renal impairment, UFHs may be used in addition to the careful use of XARELTO and ELIQUIS, or mechanical methods may be used.

06 CLINICALLY RELEVANT COMPARATORS

06.1 Medicinal products

For initial thromboprophylaxis in major orthopaedic surgery of the lower limbs
Indirect thrombin and factor Xa inhibitors:
- Low molecular weight heparins (LMWHs) via SC injection:

Proprietary medicinal products	INN	AB [opinion]
FRAGMIN	Dalteparin sodium	Substantial [TC 5227 - 19/12/07]
FRAXIPARIN	Nadroparin calcium	Substantial [TC 2812 - 18/10/06]
INNOHEP	Tinzaparin sodium	Substantial [TC 6965 - 16/12/09]
LOVENOX	Enoxaparin sodium	Substantial [TC 7047 - 02/12/09]

- Unfractionated heparin (UFH) via SC injection

Proprietary medicinal products	INN	AB [opinion]
CALCIPARIN	Heparin calcium	Substantial [TC 4857 - 23/01/08]

Three oral anticoagulants are also indicated for "initial thromboprophylaxis in major orthopaedic surgery of the lower limbs" after total hip or total knee replacement surgery:

- Two direct factor Xa inhibitors:

Proprietary medicinal products	INN	AB (opinion)
ELIQUIS	Apixaban	Substantial [TC 11097 - 18/01/12]
XARELTO	Rivaroxaban	Substantial [TC 6017 – 21/01/09]

- One direct thrombin inhibitor:

Proprietary medicinal products	INN	AB (opinion)
PRADAXA	Dabigatran	Substantial [TC 5528 - 16/07/08]

For prolonged thromboprophylaxis in major orthopaedic surgery of the lower limbs
For LMWHs, the benefit of prolonged prophylactic treatment over 4 to 5 weeks after elective orthopaedic hip surgery has been established with enoxaparin (LOVENOX) and with dalteparin (FRAGMIN) up to 35 days. For other LMWHs, the recommended treatment duration in the majority of cases is 10 days, after which treatment with a vitamin K antagonist (VKA) should be considered.

XARELTO (rivaroxaban), ELIQUIS (apixaban) and PRADAXA (dabigatran etexilate) are also indicated after elective surgery (THR, TKR).

For initial thromboprophylaxis after abdominal surgery for adult patients who are judged to be at high risk of thromboembolic complications, such as patients undergoing abdominal cancer surgery
LMWHs and UFHs

For the prevention of Venous Thromboembolic Events (VTE) in adult medical patients who are judged to be at high risk of VTE and who are immobilised due to acute illness
Certain LMWHs: FRAGMIN and LOVENOX
UFHs

Other medicinal products may be used in these clinical situations. These medicinal products are second-line treatments.
Vitamin K antagonists (following initial treatment with LMWHs/UFHs): COUMADIN (warfarin), PREVISCAN (fluindione), SINTROM and MINI-SINTROM (acenocoumarol).
ORGARAN (danaparoid sodium): this medicinal product is indicated for not only thromboprophylaxis in cancer and orthopaedic surgery, but also in patients who require preventive parenteral antithrombotic treatment and who have acute type II heparin-induced thrombocytopenia (HIT) without thromboembolic complications or any documented history of type II HIT.
ARGANOVA (argatroban) is indicated for anticoagulation in adult patients with type II heparin-induced thrombocytopenia (HIT) who require parenteral antithrombotic therapy.

06.2 Other health technologies

Mechanical methods for preventing venostasis function by increasing the 'pump' action of the calf and the plantar arch in order to increase blood-flow in the lower limbs. Currently available mechanical methods are elastic support devices (compression stockings, socks or bandages), intermittent pneumatic compression (IPC) and plantar compression (PC). In the absence of a direct level 1 comparison with other prophylactic methods, mechanical compression alone is not recommended as first-line treatment (grade A). Mechanical methods are proposed, whenever possible, in association with antithrombotic treatments since combining their different effects is beneficial. When anticoagulants are contraindicated or the benefit/risk ratio does not favour the introduction of antithrombotic agents, in particular if there is a specific risk of haemorrhage, mechanical prevention can be of certain benefit [SFAR, 2005 and 2011].

◗ **Conclusion: There are several relevant comparator medicines available. The main anticoagulant comparators are LMWHs. UFHs are currently second-line treatments, except in cases of severe renal impairment, where they are used as the reference medicinal product because LMWHs (and fondaparinux) are contraindicated in such cases. Non-vitamin K antagonist oral anticoagulants (ELIQUIS, PRADAXA, and XARELTO) are also alternatives to fondaparinux, including in cases of renal impairment. Other anticoagulants (ORGARAN and ARGANOVA) are indicated, more specifically in the context of heparin-induced thrombosis (HIT). Mechanical methods are recommended in combination with medical treatment, unless pharmacological anticoagulant therapy is contraindicated.**

07 SUMMARY OF PREVIOUS ASSESSMENTS

07.1 Prevention of Venous Thromboembolic Events (VTE) in adults undergoing major orthopaedic surgery of the lower limbs such as hip fracture repair, major knee surgery or hip replacement surgery:

Initial assessment:

Date of Opinion (Inclusion on the list for hospital use)	16 October 2002
Indication	Prevention of Venous Thromboembolic Events (VTE) for a maximum treatment duration of 9 days in adults undergoing major orthopaedic surgery of the lower limbs such as hip fracture repair, major knee surgery or hip replacement surgery
Actual Benefit (AB) (wording)	Substantial
Improvement in Actual Benefit (IAB) (wording)	"The efficacy of fondaparinux (ARIXTRA) is superior to that of enoxaparin (LOVENOX) in terms of reducing radiological DVT within the context of a preventive treatment not lasting more than 9 days. The difference in curative treatment initiation between the two groups means that comparison is difficult. Given the current information, it is not possible to state the clinical benefit provided by fondaparinux (ARIXTRA) compared with enoxaparin (LOVENOX)."
Studies requested	

Second assessment: Following the extension of the indication for the duration of thromboprophylaxis after hip fracture, a re-assessment of Actual Benefit and Improvement in Actual Benefit in major orthopaedic surgery of the lower limbs were carried out. According to the 16 June 2004 Opinion:

Initial Thromboprophylaxis:

Date of Opinion (Inclusion on the list of medicines reimbursed by National Health Insurance and approved for hospital use)	16 June 2004
Indication	For initial thromboprophylaxis, i.e., for a maximum treatment duration of 9 days:
Actual Benefit (AB) (wording)	Substantial
Improvement in Actual Benefit (IAB) (wording)	"The improvement in actual benefit provided by fondaparinux (ARIXTRA 2.5 mg) is level III (moderate) compared with enoxaparin (LOVENOX) in terms of efficacy and only for patients with a history of venous thromboembolic disease (phlebitis and/or pulmonary embolism) who weigh over 50 kg and have a creatinine clearance above 50 ml/min. There is no improvement in actual benefit compared with enoxaparin (LOVENOX) (level V) for other patients."
Studies requested	

Thromboprophylaxis during the 19-23 days following an initial 1-week period:

- After elective hip replacement or knee surgery (re-assessment):

Date of Opinion (Inclusion on the list of medicines reimbursed by National Health Insurance and approved for hospital use)	16 June 2004
Indication	For thromboprophylaxis during the 19-23 days following an initial 1-week period after elective hip replacement or knee surgery surgery (re-assessment)
Actual Benefit (AB) (wording)	"For thromboprophylaxis during the 19-23 days following an initial 1-week period after elective hip replacement or knee surgery, the efficacy/adverse events ratio of fondaparinux could not be assessed due to the absence of data that evaluated fondaparinux in this clinical situation. The actual benefit of ARIXTRA 2.5 mg/0.5 ml, solution for injection is insufficient, given the absence of data in this clinical situation."
Improvement in Actual Benefit (IAB) (wording)	Not applicable
Studies requested	

- After surgery for hip fracture repair surgery (extension of the indication)

Date of Opinion (Inclusion on the list of medicines reimbursed by National Health Insurance and approved for hospital use)	16 June 2004
Indication	For thromboprophylaxis during the 19-23 days following an initial 1-week period after hip fracture repair surgery (extension of the indication):
Actual Benefit (AB) (wording)	Substantial
Improvement in Actual Benefit (IAB) (wording)	"Improvement in actual benefit level III (moderate) in terms of treatment efficacy only for patients weighing over 50 kg and with a creatinine clearance above 50 ml/min."
Studies requested	

07.2 Prevention of Venous Thromboembolic Events (VTE) in medical patients who are judged to be at high risk of 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.

Date of Opinion (Inclusion on the list of medicines reimbursed by National Health Insurance and approved for hospital use)	21 September 2005
Actual Benefit (AB)	Substantial
Improvement in Actual Benefit (IAB)	"Fondaparinux does not appear to expose patients to the risk of immuno-allergic thrombocytopenia (biologically plausible, however no cases observed to date), but this risk is very low with LMWHs. It has yet to be determined whether fondaparinux has an equivalent efficacy to the other two LMWHs since the ARTEMIS study versus placebo raises important questions regarding the observed venous thromboembolic events. Therefore, there is no strong clinical argument to justify prescribing fondaparinux instead of the other two LMWHs. ARIXTRA 2.5 mg/0.2 ml does not provide an improvement in actual benefit (IAB level V) compared with LMWHs in the prevention of acute Deep Vein Thromboses (DVT) and Pulmonary Emboli (PE) in adult medical patients who are judged to be at high risk of 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."
Studies requested	The Transparency Committee wanted "the results from a study whose objective was to better identify the population receiving this thromboprophylaxis and methods of use (in particular, treatment duration) in both community and hospital practices."

07.3 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.

Date of Opinion (Inclusion on the list of medicines reimbursed by National Health Insurance and approved for hospital use)	18 April 2007
Actual Benefit (AB)	Substantial
Improvement in Actual Benefit (IAB)	"ARIXTRA 2.5 mg/0.5 ml, solution for injection in pre-filled syringe does not provide an improvement in actual benefit (IAB level V) compared with dalteparin, the LMWH investigated in the PEGASUS study. Given the data currently available and its mechanism of action (biological plausibility), ARIXTRA does not appear to expose patients to a risk of immuno-allergic thrombocytopenia. However, an increased risk of major bleeding cannot be ruled out with fondaparinux compared with dalteparin based on the PEGASUS study, in which the duration of thromboprophylaxis was often less than 10 days, while thromboprophylaxis that continues beyond 10 days is likely to be required in the majority of these patients, especially in those treated for cancer."

Studies requested	None.

08 ANALYSIS OF NEW AVAILABLE DATA

08.1 Efficacy

8.1.1 Thromboprophylaxis after major orthopaedic surgery of the lower limbs (after THR and TKR or hip fracture)

There have been no new clinical data since the previous opinion.

The FONDACAST (FONDAparinux in patients with a plaster CAST) study conducted between 30 December 2008 and 4 July 2011 was carried out in an off-label context of non-surgical orthopaedic trauma. In this randomised, open-label, multi-centre superiority study, the efficacy and adverse events of ARIXTRA 2.5 mg x 1/day via SC injection (1.5 mg x 1/day in subjects with a creatinine clearance of 20 to 50 ml/min) were compared with those of nadroparin (LMWH) 2850 anti-Xa IU/0.3 ml x 1/day via SC injection. A total of 1,349 adult patients were included. These patients required rigid or semi-rigid immobilisation for a projected duration of at least 21 days and up to 45 days due to an isolated trauma involving a lower limb below the knee and not requiring surgery. The results of this study are not presented in this opinion.

8.1.2 Thromboprophylaxis in abdominal surgery for adult patients who are judged to be at high risk of thromboembolic complications, especially those undergoing abdominal cancer surgery

There have been no new clinical data since the previous opinion.

8.1.3 Thromboprophylaxis in adult patients immobilised due to acute illness and considered as being at a high risk of thromboembolic complications

There have been no new clinical data since the previous opinion.

08.2 Adverse events

Since its commercial launch (December 2001), eighteen PSURs have been submitted to the health authorities of the countries where ARIXTRA is registered. ARIXTRA has been marketed in France since December 2002 and has been the subject of National Pharmacovigilance led by the Regional Pharmacovigilance Centre (CRPV) of the Georges Pompidou European Hospital (HEGP) since 13 February 2007.
According to the last PSUR for the period between December 2010 and December 2011, total fondaparinux exposure was estimated to be 10.8 million patients. Cumulative fondaparinux exposure was estimated considering an ARIXTRA preventive treatment duration of 13 to 15 days (depending on the country) and a curative treatment duration of 7 days.
In France, according to national pharmacovigilance, the cumulative exposure from the time the product was first commercialised in France (December 2002) until 31 March 2013 is reportedly 3.66 million patients, half (1.87 million) of whom were exposed at a dose of 2.5 mg.

08.2.1 Risk of haemorrhage

2010-2011 PSUR data

In the PSUR from 7 December 2010 to 6 December 2011, 766 cases (1,839 adverse events) were reported internationally. Of these cases, 532 (69.5%) were considered serious.
The majority of the reports were observed in France (34%), in Japan (19%) in the United States (18%).

Since the commercial launch of ARIXTRA, a total of 3,394 cases of haemorrhage have been reported: 409 (16.9%) were associated with off-label use and 272 (8.0%) of these patients died; 40% of these reports came from France, 19% from Japan, 15% from the USA and 10% from Germany. In the majority of cases, the relationship between haemorrhage risk factors and age, weight or renal function was not able to be determined. It was noted, however, that 43.4% of the patients were over the age of 70 (15% missing data), 52% were women (10% missing data), 2% weighed less than 50 kg (75% missing data) and 9.2% had a creatinine clearance below 50 ml/min (84% missing data).

Of the 272 reported deaths, 72 observations confirmed that:

- 38 (52.8%) had been either the direct or the indirect result of a haemorrhagic event:
    - 17 after a cerebral haemorrhage (17 cases)
    - 5 after a gastrointestinal haemorrhage (5 cases)
    - 5 after a retroperitoneal haemorrhage (5 cases)
    - 8 after unspecified haemorrhage (8 cases)
    - 2 cases of haemorrhagic shock (2 cases)
    - 1 case of haemorrhage at a biopsy site.

  A haemorrhage risk factor was found for 25/38 cases linked either directly or indirectly to a haemorrhagic event. These risks factors were a product administration error, age >75 years, concomitant treatment increasing the risk of haemorrhage and off-label use.
- In 4 cases (5.5%), the cause of death was attributed to a pulmonary embolism; a lack of efficacy may potentially have been to blame (source: the applicant).
- In the 30 remaining cases, information was not available.

According to the cumulative analysis of cases observed since the commercial launch, haemorrhagic adverse events are the primary cause of death for patients (258/319; 80.9%).

National Pharmacovigilance

National Pharmacovigilance has been in place since commercialisation following the reports of haemorrhagic events occurring during treatment with ARIXTRA. The initial conclusions of the monitoring performed from commercial launch to 31 January 2007 were that: "*haematoma and haemorrhage represented the large majority of adverse events reported with ARIXTRA and several were severe cases affecting the elderly. The reporting rate was 5.5 haemorrhagic accidents for every 10,000 patients."* Misuse (e.g., inappropriate dose, off-label use) represented 40% of these observations.

At the Afssaps' request, a letter was sent to prescribers in June 2007. This letter reiterated the rules for correct use. Since this date, medical sales representatives have been required to provide healthcare professionals with a "good-use guide" summarising the indications, the contraindications and the special precautions for use in populations at risk of haemorrhage (elderly patients, patients with low body weight and patients with renal impairment).

A second report on the period from 1 February 2007 to 30 September 2008 described a reporting rate of 3 haemorrhagic events for every 10,000 patients treated versus 5.5/10 000 during the initial survey.
During this period, 319 of the 444 adverse events reported were haemorrhagic (72%). Regardless of the type of event, haemorrhagic or otherwise, the causal dose in 53% was "curative" and misuse was found in 42% of cases (use in an off-label indication, duration of treatment not compliant with the SPC or a dosing error). A different medicinal product was suspected with the same degree of causality as fondaparinux in 51 cases (16% of the total).

Haemorrhagic events affected elderly patients (73 years of age versus 58.5 years for other events); they included a severity criterion in 92% of cases and 25 deaths were considered linked to a haemorrhagic event.

A third report was based on the period from 1 October 2008 to 30 March 2011. During this period, 884 adverse events cases were analysed, including 554 haemorrhagic events (63% of cases) and 488 cases (88%) considered serious. Haemorrhagic events affected elderly patients with a mean age of 70 years who were female in 56% of cases. Fondaparinux was the only suspected product in 70% of cases.
When information was available (not assessable in 116, or in 20%, of the cases), the implicated dosage forms were 5 mg, 7.5 mg and 10 mg in 218 cases (40%) and 2.5 mg in the 219 other cases (40%). When the indication was assessable (for 459 cases, or 54% of the files), misuse was considered the cause in 250 cases. Misuse pertained to the indication (159 cases), the treatment duration (61 cases) and the dosage (30 cases).

According to the 27 September 2011 report by the National Pharmacovigilance Commission, the reporting rates for the period from October 2008 to February 2011 were as follows:

For the entire period and for a total of 1,562,455 patients who received ARIXTRA (654,533 as preventive treatment and 908,012 as curative treatment), the reporting rate was 884 adverse events, which **equals a reporting rate of 1 adverse event for every 1,767 patients treated.**

The reporting rate for haemorrhagic adverse events was 554 adverse events for the 1,562,454 treated patients, which **equals a reporting rate of 1 adverse event for every 2,820 patients treated,** broken down as follows: 1/3,363 patients treated curatively and 1/2,406 patients treated preventively.

Table 1: Rate of reporting on treated patients to the National Pharmacovigilance system

	Investigation 1 Dec 2002 to Feb 2007 (51 months)	**Investigation 2 March 2007 to Sept 2008 (20 months)**	**Investigation 3 Oct 2008 to March 2011 (29 months)**
Total number of treated patients	1,562,455		
	47,146 from 2003-2005 174,074 in 2006	992,123	1,562,455
Breakdown preventive curative	47,146*	626,353 365,770	654,533 908,012
Number of events Reporting rate	188 1/1,177	620 1/1,600	884 1/1,767
Number of haemorrhagic events Reporting rate	97 1/1,795	378 1/2,624	554 1/2,820
2.5 mg form Number of haemorrhagic effects Reporting rate	25 1/1,886 patients from 2003-2005	172 1/3,641 patients	272 1/2,406 patients
5 mg, 7.5 mg and 10 mg forms Number of haemorrhagic events Reporting rate	56 1/1,680	206 1/1,775	272 1/3,363

*only from 2003-2005

This report states that “since 2008, there has been a stabilisation in sales of the preventive dosage and an increase in sales for the curative forms with a concurrent stabilisation or decrease in the reporting rate, in particular for the curative forms. It is with the 2.5 mg form that an increase in reporting rate has been observed. Regarding the risk of haemorrhage, “in France over this period (October 2008-March 2011), the number of haemorrhagic events was similar to what has been observed since 2007, namely in that they represent the majority of adverse events reported, that they are serious events and that they require transfusions or even further interventions.” Age (>70 years) still appears to be a haemorrhagic risk factor. In this period, the use profile for fondaparinux appears to have changed since, unlike previously, curative doses were more commonly used; curative doses represented 58% of sales (this figure was 37% previously), although these doses were 'only' involved in 50% of the haemorrhagic events: there was an increase in the haemorrhagic event reporting rate for the 2.5 mg form, which only serves to reinforce the urgent need for a 1.5 mg form in France. Off-label use is still present, involved in more than 50% of haemorrhagic events and of all events. This increase in misuse needs to be put into perspective when examined vis-à-vis previous points, since cases of misuse with no adverse event have been sent by the applicant.” The report also indicates, “after discussion with the applicant and hospital practitioners, it appears that the message on how to correctly use fondaparinux needs to be circulated among community-based doctors. Community doctors are using the medicinal product off-label for cancer patients and for patients requiring long-term anticoagulation treatment, as well as in patients requiring medium- or even long-term preventive medical treatment. In these two situations, doctors prefer to start treatment with fondaparinux rather than with a vitamin K antagonist. It should be noted that international conferences recommend prophylaxis, in particular with fondaparinux, in surgical as well as medical situations, although these are officially off-label recommendations (thoracic surgery, bariatric surgery, cancer) *[Prevention of venous thromboembolism, American College of Chest physicians, Evidence based clinical practice guidelines 8th Edition Chest 2008]).”*

From this expert opinion, the rapporteurs have made the following proposals:

"- There is an urgent need for the 1.5 mg form in renally-impaired and/or elderly patients.
- The development of an antidote should be promoted.
- Section 4.8 of the SPC should be harmonised.
- Pharmacovigilance should continue, but with less intense monitoring."

The level of national pharmacovigilance monitoring for ARIXTRA has since been reduced from a monthly to a quarterly basis.

Discussions and conclusion on the analysis of haemorrhagic risk

Several haemorrhagic risk factors have been identified with fondaparinux treatment: renal impairment, advanced age (75 years), low body weight (< 50 kg) and timing of the first post-surgical injection.

Renal impairment:
The frequency of major haemorrhage among patients under fondaparinux treatment increases as creatinine clearance decreases. There are pharmacological arguments suggesting that there is a risk of accumulation when renal function is altered, especially in elderly patients, who represent a target population for preventive treatment.

According to pharmacovigilance data, 50% of reports involve the 2.5 mg dosage. However, the level of renal function was only identified in 80% of cases discussed according to the pharmacovigilance reports under consideration. In addition, there is no information on the timing of the onset of haemorrhage with respect to treatment initiation.

A dosage adjustment is proposed to reduce the risk of haemorrhage in patients with moderate renal impairment.

The initial assessment was primarily based on the results of a kinetics study[1]. To complete the dossier presented by the applicant for the 1.5 mg dose, the Transparency Committee had requested that an efficacy and safety clinical study be carried out with this dosage (see ARIXTRA 1.5 mg Opinion).

Low body weight:
There is no mention of any dose adjustment for patients with a low body weight in the SPC. The reduction in dosage to 1.5 mg/day is only proposed for patients with moderate renal impairment.

In practice, in clinical situations with a high risk of haemorrhage (low body weight, moderate renal impairment, advanced age), there are alternative non-medicinal (mechanical) methods and/or medicinal treatments available, such as UFH (CALCIPARIN in France).
These alternatives are recommended in these patients by several learned societies whose guidelines were updated in 2011/2012.
The 1.5 mg dosage is used primarily in Japan. Haemorrhages have been reported with this dose, however exposure data is not available (according to international pharmacovigilance data supplied by the applicant), which means that a conclusion cannot be drawn about the benefit of the 1.5 mg dose in reducing the risk of haemorrhage in the most at-risk patients. Fondaparinux does not have marketing authorisation in the United States. American guidelines recommend the use of alternatives rather than fondaparinux in these situations.

[1] Alexander G.G. Turpie et al. Pharmacokinetic and clinical data supporting the use of fondaparinux 1.5 mg once daily in the prevention of venous thromboembolism in renally impaired patients. Blood Coagulation and Fibrinolysis 2009, 20:114–121.

The occurrence of haemorrhage can be explained by the misuse of the medicinal product. The Afssaps/ANSM (French National Agency for Medicines and Health Products Safety, which replaced the Afssaps) has been observing misuse for several years now (see 28 December 2011 letter from their Director). Misuse was also found in several post-inclusion observational studies carried out on post-surgical thromboprophylaxis. According to this data, misuse primarily corresponds to use in indications not validated by a Marketing Authorisation and/or a duration of thromboprophylaxis longer than that found in the Marketing Authorisation. The treatment window for fondaparinux is narrow and there is also a risk of accumulation with prolonged treatment.

Advanced age:
There is no mention of any dose adjustment for patients with a low body weight in the SPC. The reduction in dosage to 1.5 mg/day is only proposed for patients with moderate renal impairment

Timing of the initial dosage:
For thromboprophylaxis, the risk of haemorrhage appears to arise quickly after administering the 2.5 mg dose, as seen in kinetic data on the onset of haemorrhage. This risk is reduced in major orthopaedic surgery when the first fondaparinux injection takes place 6 hours and not 4 hours after surgical closure (amendments to the SPC). In addition, the applicant and several clinical practice guidelines actually recommend waiting at least 8 hours.

In conclusion, for patients with renal impairment and creatinine clearance < 50 ml/min, ARIXTRA should not be used at the 2.5 mg once-daily dosage.
In patients 75 years of age or over or with a body weight < 50 kg, the use of fondaparinux should only be considered with great caution given the risk of haemorrhage and the inability to adjust the dosage.

08.2.2 Other adverse events

Other adverse events have received special monitoring, and a cumulative analysis has been carried out since the commercial launch of ARIXTRA. According to the last PSUR (period from 7 December 2010 to 6 December 2011):

- Off-label use: following the alert issued by the AFSSAPS during the launch of the French national monitoring programme and the detection of a warning from the disproportionality analysis carried out by the applicant, it was decided, in agreement with CHMP/AFSSAPS, to circulate a DHCPL (Dear Health Care Professional Letter) in France only (the large majority of cases [60%] were observed in France). This letter informed the prescribers of the risks associated with the off-label use of fondaparinux, understanding that the majority (61%) of adverse events reports associated with off-label use were of a haemorrhagic nature.
- Treatment failure: a cumulative analysis carried out since 2001 revealed that 471 observations have been reported. The reporting rate for these events has diminished from 64/100,000 (PSUR no. 4, period of June 03-Dec 03) to 1.4/100,000 in the latest PSUR.
- Heparin-induced thrombocytopenia (HIT): since of the commercial launch of ARIXTRA, the applicant has confirmed 66 spontaneous observations of HIT, including 17 with no confounding factors, indicating that treatment with fondaparinux may be associated with a disorder similar to HIT, but no causal relationship between fondaparinux treatment and the onset of HIT has been established.
- Catheter-related thrombosis (in patients treated for acute coronary syndrome): 14 cases have been reported to GSK so far (OASIS 8 post-marketing safety study).
- Anaphylaxis: 5 cases have been reported since the commercial launch of ARIXTRA.

08.3 Usage data

Current data from the DOREMA and Thalès panels do not enable the prescriptions of ARIXTRA to be analysed by indication.

The applicant extracted the breakdown of prescriptions by dosage and by mean treatment duration for the various dosages from the Thalès database. In order to estimate the breakdown of prescriptions by whether they were curative or preventive, a prescription for the 2.5 mg dosage was assumed to be preventive while the other dosages were assumed to be curative (see Table 1). This overestimates the number of preventive prescriptions.

Table 2. Distribution of ARIXTRA prescriptions per dosage (source: Thalès)

	Period: January to March 2012*	
	Number	**Percentage**
PREVENTIVE ARIXTRA 2.5 mg	**19,440**	**31.6%**
CURATIVE	**42,120**	**68.4%**
ARIXTRA 5 mg	8,370	13.6%
ARIXTRA 7.5 mg	30,510	49.6%
ARIXTRA 10 mg	3,240	5.3%
TOTAL ARIXTRA Prescriptions	**61,560**	**100.0%**

***: Data provided by the applicant**

The mean treatment duration (moving annual total, March 2012) for the 2.5 mg dosage was 14.5 days with a median duration of 10 days.

08.4 Study programmes

The risk management plan (CHMP validation: August 2010) stipulates that the collection of spontaneous reports continue with an ongoing periodic review of data. Heightened monitoring of spontaneous cases of haemorrhage and off-label use is in progress.

The Transparency Committee and CEPS have requested that several studies be conducted (ARISTOTE and ARCHIMED Community and Hospital studies).
Several post-inclusion studies have been carried out by the applicant on ARIXTRA 2.5 mg in response to requests by the Transparency Committee and the CEPS. The studies were in the following indications: "Prevention of Venous Thromboembolic Events (VTE) in major orthopaedic surgery of the lower limbs" [Opinion of 16/06/2004; Aristote study], "Prevention of Venous Thromboembolic Events (VTE) in patients immobilised due to acute illness" [Opinion of 29/09/2005 Archimed study (2 arms - community and hospital)] and [CEPS Opinion of 27/07/2006; Ariane study], and "Treatment of SVT", [Opinion of 22/06/2011, Study in progress].

No studies have been requested in the other ARIXTRA 2.5 mg indications. The above studies were evaluated by the ISPEP group. Their purposes corresponded to the requests from both the Committee and the CEPS. The wording of the requests, the purposes of the studies and the summary of the results are presented in Appendix 1 (Summary_EPI). The study reports (Archimed: community arm [Appendix 2] and hospital arm [Appendix 3]) are in the Appendix of the Opinion of 18/11/2009 (Aristote and Ariane).

The results from these studies provide some elements in response to the Committee's requests:

- They show that although there is compliance with the dosage and contraindications stated in the Marketing Authorisation for ARIXTRA 2.5 mg, the frequency of non-compliance with the registered indications and the mean treatment duration is noteworthy:
  - For the "Orthopaedic surgery" indication (Aristote study), non-compliance with the Marketing Authorisation mainly takes the form of extending the recommended treatment duration in THR and TKR cases, since nearly 1/3 of patients have a mean treatment duration of ≥ 15 days and 16% of patients have a treatment duration of > 35 days. Even though the percentage of patients with a treatment duration ≥ 15 days is higher (38%) in cases of hip fracture, this percentage is still 30% in THR (without fracture) and TKR cases [Appendix 1, Summary Table 2]. The percentage of patients with a treatment duration of > 35 days is approximately 21%, 17% and 12% respectively in cases of hip fracture, THR (without fracture) and TKR.

  The comparison of the duration (prolonged/shortened) with the frequency of haemorrhagic events occurring during the follow-up period of the ARISTOTE study is not presented. However, 11/13 major bleeds occurred in the 10 days following administration.

  Indication non-compliance was only seen in 2% of cases. Furthermore, non-compliance with the 6-hour wait between a procedure and administration was only seen in 14% of cases.
  - For the "Prevention in patients immobilised due to acute illness" indication, there was also non-compliance with the Marketing Authorisation in terms of extending the duration of treatment and in terms of the indication:

- A treatment duration beyond that recommended in the SPC (6-14 days) was seen in approximately 1/3 to 40% of cases [Archimed (community, hospital) and Ariane] [Appendix 1, Summary Table 2].

- In terms of non-compliance with the Marketing Authorisation indication [Appendix 1, Summary Table 3]:
  - The indication stated in the SPC was only followed (strictly) for half of patients in the two Archimed studies (community and hospital) and for ¾ of patients in the Ariane study.
  - The indication was one that was not recommended (by the SPC or learned societies) or that was not for a disorder in 8.2% of patients in the Archimed community study and 22.1% for the Archimed hospital study.
  - The indication did not correspond to the SPC but did correspond to one of the disorders for which a prescription for an antithrombotic agent is recommended by learned societies [lower back pain, acute lumbar sciatica or progressive cancer] for nearly 15% of patients in the Archimed community and hospital studies.

  It should be noted that since there was no follow-up in these studies on the occurrence of events (in compliance with the Committee's request), and in the occurrence of haemorrhages in particular, an analysis of the frequency of these events according to duration of treatment or non-compliance with the indications was not possible.

- A noticeable proportion of patients treated with ARIXTRA 2.5 mg presented with risk factors (haemorrhage) [Appendix 1, Summary Table 4]:
  - Approximately 20-25% of Archimed (community and hospital) and Aristote study patients and 12.4% of Ariane study patients had a creatinine clearance of 20 to 50 ml/min.
  - Patients aged 75 and over represented over half of all Archimed hospital study patients and 1/3 and 1/4 of all Archimed community and Ariane study patients respectively. Approximately 60% of patients included in the Aristote study were over 70 years of age.
  - In the Archimed hospital study, 13.7% of patients weighed less than 50 kg, and 4% to 5% of patients in the other studies weighed less than 50 kg.
  - It should be noted that very few patients in these studies had a platelet count of less than 50,000 (0 to 3 pts).

- The results for the frequency of VTE and haemorrhagic events correspond to those found in the clinical trials, with a VTE frequency of 2.4% at 6 weeks (and 1.5% in cases of symptomatic

events) and a frequency of major haemorrhages of 1.9% at Day 10 and 2.2% at 6 weeks. The frequency of haemorrhage was higher in cases where creatinine clearance <50 ml/min [Appendix 1, Summary Table 1].

08.5 Summary & discussion

In terms of thromboprophylactic efficacy, there is no new efficacy data for fondaparinux (ARIXTRA 2.5 mg) in the clinical situations validated by a Marketing Authorisation.
The medicinal product's efficacy was previously assessed in comparison with a LMWH (enoxaparin) after THR and TKR and with placebo after hip fracture. The benefit of prolonged thromboprophylaxis with fondaparinux after a hip replacement has yet to be assessed and its benefit compared with other oral non vitamin K antagonist anticoagulants (ELIQUIS, PRADAXA and XARELTO) has yet to be determined.

In terms of safety, post-inclusion study and pharmacovigilance data both confirm the existence of misuse (in terms of duration of thromboprophylaxis and off-label use) and a risk of haemorrhage.

The risk of haemorrhage is higher in patients with known risk factors, such as elderly patients, those with low body weight and/or those with renal impairment, in whom the treatment window appears to be very narrow. There is a risk of overdose and, due to the risk of accumulation, the risk of overdose is higher with prolonged use. Clinical situations where the prophylactic use of ARIXTRA 2.5 mg would be critical for these patients appear to be rare, as there are alternative medicinal products available (e.g., LMWHs, UFHs). When the clinical situation contraindicates the use of fondaparinux (or any other anticoagulant), treatment with mechanical methods should be considered.

In summary, in patients with no haemorrhagic risk factors (i.e., patients > 50 kg, > 75 years of age and without renal impairment), ARIXTRA 2.5 mg is used as first-line treatment when the indications and the thromboprophylaxis duration validated by the marketing authorisation are respected.

09 THERAPEUTIC USE

The French SFAR 2005[2] guidelines were updated in 2011[3] and the 2008[4] guidelines of the American College of Chest Physicians (ACCP) were updated in 2012.[5] There are also 2009 Afssaps guidelines for thromboprophylaxis in medicine (excluding surgery).

09.1 Thromboprophylaxis after major orthopaedic surgery of the lower limbs

[2] SFAR (Société Française d'Anesthésie et de Réanimation) [French Society of Anaesthesia and Intensive Care]. Prévention de la maladie thromboembolique veineuse péri-opératoire et obstétricale. Recommandations pour la pratique clinique. Short text, 2005.
http://www.sfar.org/article/209/prevention-de-la-maladie-thromboembolique-veineuse-perioperatoire-et-obstetricale-rpc-2005.
[3] Samama CM, Gafsou B, Jeandel T, Laporte S, Steib A, Marret E, Albaladejo P, Mismetti P, Rosencher N. Prévention de la maladie thromboembolique veineuse postopératoire. Update 2011. Short text. Ann Fr Anesth Reanim 2011;30:947-51.
[4] Geerts WH, Samama CM, Lassen MR, Colwell CW, Bergqvist D, Pineo GF, Heit JA. Prevention of Venous Thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:381-453.
[5] Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schünemann HJ for the American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive Summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012a; 141 (suppl): 7S-47S.

According to the French SFAR guidelines (2011), “LMWHs at a high prophylactic dose, fondaparinux, dabigatran, rivaroxaban and apixaban are the five first-line prophylactic treatments (grade 2-). High prophylactic dose LMWHs are the reference treatment (grade 1+).
Fondaparinux, an indirect anti-Xa, at a subcutaneous dose of 2.5 mg/day is superior to LMWHs in terms of efficacy for major VTEs. However, there is a higher incidence of major haemorrhage with fondaparinux compared with LMWHs, suggesting that this dose of fondaparinux not be used in patients at a high risk of haemorrhage (grade 2-)”.

These guidelines state that the 2.5 mg dose should not be used in patients at a high of haemorrhage (Grade 2-) after THR and TKR and after hip fracture, and that LMWHs should be used instead of ARIXTRA 2.5 mg in cases with concomitant haemorrhagic risk factors, especially patients with moderate renal impairment (Grade 2+).

To reduce the risk of haemorrhage, SFAR experts indicate that the first injection of fondaparinux should not be given before eight hours have lapsed after surgery, and may be given up to 18 hours after surgery (grade 1+).

According to ACCP guidelines (2012), “in patients having THR or TKR surgery: prophylaxis is recommended for at least 10 to 14 days using one of the following methods: LMWH, fondaparinux, apixaban, dabigatran, low dose UFHs, titrated doses of AVK, aspirin (Grade 1B) or a CPI (Grade 1C).

In patients having surgery to repair a hip fracture (HF): prophylaxis for at least 10 to 14 days using one of the following methods is recommended: LMWHs, fondaparinux, low dose UFHs, titrated doses of AVK, aspirin (Grade 1B) or a CPI (Grade 1C).

LMWHs are preferred over other treatments (Grade 2B or 2C) due to the potential limitations of the other agents: possible increased risk of haemorrhage (fondaparinux, rivaroxaban), possible lower efficacy (UFHs, AVK, aspirin and CPI) and the absence of long-term safety data (apixaban, dabigatran and rivaroxaban).”

“It is suggested to continue with thromboprophylaxis up to 35 days after surgery, regardless of the type of surgery or the agents used (Grade 2B).”

09.2 Thromboprophylaxis in patients judged to be at high risk of thromboembolic complications after abdominal surgery

According to French SFAR guidelines (2005, 2011), “in abdominal surgery patients with moderate risk but with an abnormally long surgical duration, or in cases of major, high-risk abdominal surgery (i.e., of the liver, pancreas, colon, inflammatory disease or cancer of the gastrointestinal tract), the SFAR recommends using high doses of LMWHs or ARIXTRA 2.5 mg/day (Grade 1+). The SFAR recommends extending the duration of thromboprophylaxis to one month after major abdominopelvic surgery (Grade 1+)”.

According to the ACCP recommendations (2008, 2012), “in patients undergoing abdominopelvic surgery who are at a high thromboembolic risk, ARIXTRA 2.5 mg is no longer suggested when LMWHs or UFHs (Grade 2C) are contraindicated or unavailable”, while in 2008, ARIXTRA 2.5 mg was recommended (Grade 1A) for moderate or high risk major abdominal surgery patients.

09.3 Thromboprophylaxis in patients who are judged to be at high risk of thromboembolic complications and who are immobilised due to acute illness

According to Afssaps guidelines (2009) on the medical prevention and treatment of VTED, "ARIXTRA 2.5 mg is a first-line treatment like LMWHs and UFHs (Grade A). The recommended prescription duration is 7 to 14 days (grade A). LMWHs and fondaparinux are preferable to UFHs, given their greater ease of use (1 injection/day for LMWHs and fondaparinux, no need to monitor platelet count and no increased risk for fondaparinux), their lower haemorrhagic risk (LMWHs), the reduction in induced thrombocytopenia (with LMWH and especially with fondaparinux) and the absence of haemorrhagic risk with fondaparinux compared with placebo in this medical context."

According to ACCP guidelines (2008, 2012), "for patients hospitalised for an acute illness who are at increased thrombotic risk, the ACCP recommends thromboprophylaxis with LMWHs, low dose UFHs two or three times per day or fondaparinux (Grade 1B). It is suggested to discontinue thromboprophylaxis beyond the immobilisation or hospitalisation period (Grade 2B).

In patients with significant haemorrhagic risk, ACCP recommends thromboprophylaxis using compression stockings or CPI (Grade 2C) and to initiate medicinal thromboprophylaxis only when the risk of haemorrhage diminishes (Grade 2B)."

Specific clinical situations

Thromboprophylaxis in vulnerable patients (low weight, advanced age, renal impairment)
See Re-assessment Opinion for the 1.5 mg dosage of ARIXTRA.

Cases of delayed hypersensitivity to heparins
According to a recent review[6,7], delayed hypersensitivity (DHS) to heparins affects 7.5% of patients treated. DHS to heparins occurs 7 to 10 days after the injection, with reactions at the injection site (localised itching, erythema and even eczema), and even generalised effects in 5% to 10% of patients. Serious reactions are rare (maculopapular rash, DRESS or toxic epidermal necrolysis). Risk factors are being overweight, being female and prolonged exposure. When a skin reaction occurs under heparin treatment, HIT should be ruled out first; then the heparin should be discontinued. If a substitute anticoagulant is required, fondaparinux is the medicinal product with the lowest cross allergy risk (10%) compared with LMWHs (74%), UFHs, danaparoid or hirudins, thereby representing an alternative.

[6] See Pharmacovigilance letter BIP n°3, 2012.
[7] Nosbaum A, Pralong P, Rozieres A, Dargaud Y, Nicolas JF, Bérard F. Delayed-type hypersensitivity to heparin: diagnosis and therapeutic management. Ann Dermatol Venereol. 2012;139(5):363-8.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

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

010.1 Re-assessment of the Actual Benefit

◗ Venous thromboembolic disease is one of the primary causes of cardiovascular death (along with myocardial infarction and stroke): it can be a serious and potentially life-threatening condition (potentially fatal pulmonary embolism) or lead to significant sequelae (post-thrombotic syndrome).
Patients undergoing major orthopaedic surgery for elective total hip or knee replacement, patients who have experienced a hip fracture, and patients judged as being at high risk of thromboembolic complications following abdominal surgery or who are immobilised due to an acute medical disorder are the population at high thromboembolic risk and who require thromboprophylaxis.
◗ In these clinical situations, and apart from patients with renal impairment, ARIXTRA 2.5 mg (fondaparinux sodium) is a treatment for preventing venous thromboembolic events.

◗ Public health benefit:
The public health burden of venous thromboembolic disease (VTED) is significant, and in particular in the sub-population of patients undergoing major orthopaedic surgery or immobilised due to acute illness. The burden of patients undergoing abdominal surgery and at high risk of thromboembolic complications is moderate.
In venous thromboembolic prophylaxis, having effective and well-tolerated treatments with a low risk for bleeding and that are not likely to cause heparin-induced thrombocytopenia, especially in at-risk patients, constitutes a public health need.
The available results of the observational studies (in particular the ARISTOTE study, the ARCHIMED community study, the ARCHIMED hospital study and the ARIANE study) show that the Marketing Authorisation conditions of use for ARIXTRA 2.5 mg are not respected in terms of treatment duration (too long for approximately one third of patients) both for THR and TKR patients and in patients immobilised for acute illness. It should be noted that, except for hip fracture patients, the benefit of prolonged thromboprophylaxis has yet to be established. Furthermore, for patients immobilised due to an acute illness, fairly frequent non-compliance with the Marketing Authorisation has been observed.
These results confirm the risk of misuse noted during the pharmacovigilance monitoring follow-up.
However, the profile of patients treated with ARIXTRA 2.5 mg included in these observational studies corresponds with what would be expected in real life, i.e., they are patients more at risk of adverse events, mainly haemorrhagic events, due to their higher mean age, their renal impairment and their low body weight, than those patients included in the studies.
As a result, ARIXTRA 2.5 mg does not have an additional impact in terms of morbidity and mortality, and therefore does not meet an identified public health need.
Consequently, available data shows that ARIXTRA 2.5 mg does not provide a public health benefit in the prevention of VTED in these three indications.

◗ There are medicinal alternatives, both oral (dabigatran etexilate [PRADAXA], rivaroxaban [XARELTO], apixaban [ELIQUIS] and vitamin K antagonists) and injectable (LMWHs and CALCIPARIN).

◗ ARIXTRA 2.5 mg is a first-line thromboprophylactic treatment in these clinical situations.

Given the aforementioned, the Committee considers that:

the Actual Benefit (AB) of ARIXTRA 2.5 mg is:
- significant in initial and prolonged thromboprophylaxis in adults after major orthopaedic surgery of the lower limbs such as hip fracture repair
- significant in initial thromboprophylaxis and insufficient in prolonged thromboprophylaxis after elective orthopaedic knee or hip surgery

- significant in thromboprophylaxis after abdominal surgery in adult patients who are judged to be at high risk of thromboembolic complications, such as patients undergoing abdominal cancer surgery

- significant in thromboprophylaxis in adults who are judged to be at high risk of venous thromboembolic events, i.e., who are immobilised due to acute illness such as cardiac insufficiency and/or acute respiratory disorders and/or acute infectious or inflammatory disease.

The Committee emphasises the absolute need, given the reported safety data, to respect the treatment durations and the indications stated in the Marketing Authorisation and draws attention the precautions for use regarding patients at an increased risk of bleeding.

◗ **Proposed reimbursement rate: 65 %.**

010.2 Re-assessment of the Improvement in Actual Benefit (IAB)

Given the risk of misuse that has been observed for many years with ARIXTRA 2.5 mg, the insufficiency assessment of ARIXTRA 2.5 mg in cases of required prolonged thromboprophylaxis, the risk of serious or fatal haemorrhage in patients weighing less than 50 kg, in patients over 75 years of age and/or in renal impaired patients, the Committee considers that ARIXTRA 2.5 mg does not provide an improvement in actual benefit (IAB V, non-existent) in the prevention of venous thromboembolic events after major orthopaedic surgery of the lower limbs and in patients who are judged to be at high risk of thromboembolic complications after abdominal surgery or who are immobilised due to acute illness.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends the continued inclusion of ARIXTRA 2.5 mg on the list of medicines reimbursed by National Health Insurance and on the list of medicines approved for hospital use, except for when indicated in prolonged thromboprophylaxis after elective orthopaedic knee or hip surgery.

◗ **Packaging:** The packaging is appropriate for the prescription conditions according to the indications, the dosage and the treatment duration.

APPENDICES

APPENDIX I - Summary of available results from previous assessments:

A- Prevention of Venous Thromboembolic Events (VTE) for a maximum treatment duration of 9 days in adults undergoing major orthopaedic surgery of the lower limbs such as hip fracture repair, major knee surgery or hip replacement surgery

"The superiority of fondaparinux (ARIXTRA) was established for the composite endpoint versus enoxaparin (LOVENOX) (reduction of 54% [95% CI: 44% - 63%] in the incidence of venous thromboembolic events in the 11 days following the procedure). The majority of events observed were asymptomatic and distal. The implementation of a curative treatment was twice as common in the enoxaparin group (LOVENOX) (351/3,670, or 9.56%) than in the fondaparinux group (ARIXTRA) (199/3,659, or 5.44%). The frequency in occurrence of symptomatic thromboembolic events (DVT and pulmonary embolism) was low and did not differ between the fondaparinux (ARIXTRA) and enoxaparin (LOVENOX) groups at Day 11 and Day 49. Patients aged 75 years and older, those with a body weight below 50 kg and those with moderate renal impairment were more at risk of major bleeding. For these patients, complying with the recommended timing for the administration of the first injection of fondaparinux (ARIXTRA) (i.e., no less than 6 hours after the surgical procedure) is particularly important" (Opinion of 16 October 2002).

Following the indication extension pertaining to the duration of thromboprophylaxis after hip fracture, a re-assessment of Actual Benefit and Improvement in Actual Benefit in major orthopaedic surgery of lower limbs was carried out. According to the Opinion of 16 June 2004:

For initial thromboprophylaxis, i.e., a maximum duration of 9 days, "regarding elective major orthopaedic surgery of lower limbs, the results of the indirect comparison carried out between the enoxaparin studies in elective hip surgery and the PENTHIFRA PLUS study in surgery after hip fracture do not enable the level of efficacy and safety of ARIXTRA 2.5 mg to be established in prolonged thromboprophylaxis after elective hip surgery, as the populations treated in these two indications are different (10 years difference in age and 15 kg difference in weight)."

For thromboprophylaxis during the 19-23 days following an initial period lasting one week:

- There is no clinical data for thromboprophylaxis in patients post-elective hip replacement surgery or knee surgery (re-assessment): "the results of the indirect comparison carried out between the enoxaparin studies in elective hip surgery and the PENTHIFRA PLUS study in surgery after hip fracture do not enable the level of efficacy and safety of ARIXTRA 2.5 mg to be established in prolonged thromboprophylaxis after elective hip surgery, as the populations treated in these two indications are different (10 years difference in age and 15 kg of difference in weight)."
- After surgery for hip fracture (indication extension), "in comparison with placebo, the PENTHIFRA PLUS study showed that fondaparinux (ARIXTRA 2.5 mg) provides a clinical benefit. No low molecular weight heparin has been assessed in prolonged prophylaxis in the surgery for hip fracture indication."

B- Prevention of Venous Thromboembolic Events (VTE) in adult medical patients who are judged to be at high risk of 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

ARIXTRA was more effective than placebo in reducing the incidence of venous thromboembolic events in patients immobilised due to acute illness such as cardiac insufficiency and/or acute respiratory disorders and/or acute infectious or inflammatory disease. The safety profile is the same as for those patients on placebo. Enoxaparin, dalteparin and fondaparinux appear to have an efficacy and a safety profile that is comparable overall for these patients (Opinion of 21 September 2005).

C- 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

"The extension of the indication for fondaparinux (ARIXTRA) is based on the results of a single study, the PEGASUS study. This randomised study compared fondaparinux 2.5 mg/day to dalteparin 5,000 IU/day for a maximum of 10 days in patients who had undergone abdominal surgery who were at a high risk of venous thromboembolic events. The efficacy was evaluated based on a composite endpoint combining different relevant clinical events collected from only 70% of included patients. The majority of events observed were radiological (asymptomatic distal VTE). A superiority and a non-inferiority analysis were both carried out on this study. It was apparent from these analyses that fondaparinux was not more effective than dalteparin in a thromboprophylaxis period lasting a maximum of 10 days. However, the non-inferiority of fondaparinux compared with dalteparin was demonstrated. Furthermore, an exploratory, post-hoc sub-group analysis carried out suggested that fondaparinux would be more effective than dalteparin in cancer surgery patients (especially those patients at risk of VTED). Concerning safety (see discussion in the EPAR European evaluation report), the high risk of major bleeding cannot be ruled out with fondaparinux in comparison with dalteparin given the incidence data observed in the PEGASUS study" (Opinion of 18 April 2007).

APPENDIX 4 - Good Clinical Practice Guidelines for thromboprophylaxis

Table 1. SFAR guidelines (2011) on the use of VTED prophylaxis after major total hip or knee replacement (THR or TKR) orthopaedic surgery

Excerpts from the guidelines	Grade
LMWHs given at high prophylactic doses, **fondaparinux**, **dabigatran**, **rivaroxaban** and **apixaban** are the five first-line prophylactic treatment methods.	**1+**
High prophylactic dose **LMWHs** the standard treatment.	**1+**
Fondaparinux, an indirect anti-Xa, at a subcutaneous dose of 2.5 mg/day is superior to **LMWHs** in terms of efficacy for major VTEs. However, there is a higher incidence of major haemorrhage with **fondaparinux** compared with **LMWHs**, suggesting that this dose of fondaparinux should not be used in patients at high risk of haemorrhage.	**2-**
Dabigatran, an oral, direct anti-IIa at a dose of 220 mg/day or 150 mg/day is not inferior to **LMWH** in terms of efficacy for major VTEs. The incidence of major haemorrhage appeared to be lower with the 150 mg/day dose, although this was not significant. For patients over the age of 75 years and patients with moderate renal impairment, the 150 mg/day dose is suggested.	**2+**
In cases of increased thromboembolic risk (patient-related risk, apart from advanced age), it is suggested to refrain from using **dabigatran** at the 150 mg/day dose.	**2-**
Rivaroxaban, an oral, direct anti-Xa at a dose of 10 mg/day is superior to **LMWHs** in terms of efficacy and symptoms for major VTEs with a tendency to increase the risk of haemorrhage. In cases of increased thromboembolic risk (patient-related risk), the use of **rivaroxaban** is suggested.	**2+**
In cases of high haemorrhagic risk (patient-related risk), the use of **rivaroxaban** is not suggested.	**2-**
Apixaban, an oral, direct anti-Xa, at a dose of 5 mg/day (2.5 mg x 2/day) is superior to **LMWHs** for major VTEs, although it does not reduce symptomatic events. The incidence of haemorrhage is not different from what is observed with **LMWHs**. Consequently, in cases of increased thromboembolic risk (patient-related risk), the use of **apixaban** is suggested.	**2+**

Table 2. SFAR guidelines (2011) on treatment initiation and duration for the various anticoagulant treatment options available for the prevention of VTED after total hip or total knee replacement (THR or TKR) surgery

Excerpts from the guidelines	Grade
Given the common use of locoregional anaesthetic techniques, pre-operative administration should be avoided. Initial post-operative prophylaxis with **LMWHs** is preferred.	**2+**
Prolonged prophylaxis with **LMWHs**, **fondaparinux**, **dabigatran**, **rivaroxaban** or **apixaban** up to the 35th post-surgical day reduces the risk of major VTE after THR without increasing the risk of major haemorrhage. It is recommended to prescribe medicinal thromboprophylaxis up to the 35th day THR post-operative day.	**1+**
Prophylaxis with **LMWHs**, **fondaparinux**, **dabigatran**, **rivaroxaban** or **apixaban** up to the 14th TKR post-operative day.	**1+**
It is therefore suggested to prescribe medicinal thromboprophylaxis up to the 35th TKR post-operative day.	**2+**

Table 3. SFAR guidelines (2011) on the use of the different available treatments for the prevention of VTED after HF surgery

Excerpts from the guidelines	Grade
LMWHs and **fondaparinux** are the two first-line prophylactic treatment methods. Dabigatran, rivaroxaban and apixaban are not indicated for HF.	**1+**
Fondaparinux at a dose of 2.5 mg/day is more effective than **LMWH** on asymptomatic DVT (distal and proximal), but the downside is an increase in the risk of major haemorrhage. In patients with concomitant haemorrhage risk factors (and especially moderate renal impairment patients), the use of **LMWH** is often suggested.	**2+**
In cases of elective surgery, **fondaparinux** cannot be administered pre-operatively; **LMWH** should be administered pre-operatively in such cases, and more than 12 hours should be allowed to lapse between the last **LMWH** injection and the surgical procedure.	**1+**

Prophylaxis with **fondaparinux** up to 35th post-surgical day reduces thromboembolic risk after HF without increasing the risk of major haemorrhage. It is recommended to prescribe medicinal thromboprophylaxis up to the 35th post-surgical day in HF cases.	**1+**

Table 4. AFSSAPS guidelines (2009) on the use of the different available treatments for VTED in cases of acute illness

Recommendations	Grade
Treatment with **UFHs** or with **LMWHs** (only **enoxaparin** and **dalteparin** have a Marketing Authorisation in this indication) or with **fondaparinux** is recommended to reduce VTEs, symptomatic or otherwise, in patients over the age of 40 admitted to hospital for a scheduled period of >3 days due to: • acute heart or respiratory failure or • severe infection, an acute inflammatory rheumatoid disorder or an inflammatory gastrointestinal disorder when they have a concomitant VTED risk factor: 75 years or older, cancer, history of venous thromboembolic events, hormone treatment, chronic heart or respiratory failure or myeloproliferative disorders.	**A**
Through extrapolation, prophylaxis is proposed for non-hospitalised patients with an acute illness, as defined above, of the same degree of severity leading to a restriction in mobility for more than 3 days.	**Professional agreement**
LMWHs and **fondaparinux** are preferred to **UFHs**, given: • their greater ease of use (1 injection/day for **LMWHs** and **fondaparinux**, no need to monitor platelet count and no increased risk for **fondaparinux**) • the lower risk of haemorrhage (**LMWHs**), • the lower risk of induced thrombocytopenia (with **LMWHs** and in particular with **fondaparinux**) • the absence of the haemorrhagic risk with **fondaparinux** compared with placebo in this medical context.	**B**
The recommended prescription duration is 7 to 14 days.	**A**
Beyond 14 days, prophylaxis is proposed in cases where there is a continued risk of VTED.	**Professional agreement**
Prophylaxis with elastic venous compression (20 to 30 mmHg) is proposed in all cases for the same duration (7 to 14 days), especially in cases where medicinal treatment is contraindicated.	**Professional agreement**