HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

Opinion

15 May 2013

ARIXTRA 1.5 mg/0.3 ml, solution for injection in pre-filled syringe

B/2 (CIP: 34009 363 500 6 9)
B/7 (CIP: 34009 363 501 2 0)
B/10 (CIP: 34009 564 989 2 5)

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

Actual Benefit (AB)	**Insufficient AB upheld**
Improvement in Actual Benefit (IAB)	**Not applicable**
Therapeutic use	**Not applicable**
Recommendations	**Non-reimbursement recommendation upheld**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Initial date (European centralised procedure): 24 October 2003
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.

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

N.B. The 1.5 mg dose does not have Marketing Authorisation for acute coronary syndromes (NSTEACS and STEACS).

04 DOSAGE OF FONDAPARINUX IN CASES OF RENAL IMPAIRMENT

For the prevention of VTE (venous thromboembolic events):

“Fondaparinux should not be used in patients with creatinine clearance <20 ml/min (contraindication).
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.
No dosage reduction is required for patients with mild renal impairment (creatinine clearance >50 ml/min)."

According to the special warnings and precautions for use section in the SPC, "fondaparinux is known to be mainly excreted by the kidney. Patients with creatinine clearance <50 ml/min are at increased risk of bleeding and VTE and should be treated with caution. There are limited clinical data available from patients with creatinine clearance less than 30 ml/min."

According to the pharmacokinetic properties section in the SPC, "compared with patients with normal renal function (creatinine clearance > 80 ml/min), plasma clearance is 1.2 to 1.4 times lower in patients with mild renal impairment (creatinine clearance 50 to 80 ml/min) and on average 2 times lower in patients with moderate renal impairment (creatinine clearance 30 to 50 ml/min). In severe renal impairment (creatinine clearance < 30 ml/min), plasma clearance is approximately 5 times lower than in normal renal function. Associated terminal half-life values were 29 h in moderate and 72 h in patients with moderate and severe renal impairment.”

Treatment of superficial-vein thrombosis:

“Fondaparinux should not be used in patients with creatinine clearance <20 ml/min (contraindication).

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 (see Special warnings and precautions for use and Pharmacokinetic properties sections of SPC). No dosage reduction is required for patients with mild renal impairment (creatinine clearance >50 ml/min).

The safety and efficacy of the 1.5 mg dose has not been studied.”

NB. ARIXTRA 2.5 mg is also indicated in the treatment of coronary syndromes (unstable angina/NSTEMI/STEMI). It should not be used in patients with creatinine clearance <20 ml/min (contraindication). No dosage reduction is required for patients with creatinine clearance > 20 ml/min.

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 orthopaedic surgery of the lower limb for a total hip or knee replacement and after surgery for hip fracture, thromboembolic risk is high and requires the routine 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 (VTED). Thromboprophylaxis can be medicinal and/or mechanical (the latter in particular for cases when medication is contraindicated).

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 (in particular in cases of renal impairment).

Since fondaparinux (ARIXTRA) is primarily excreted through the kidneys and its form remains unchanged, the risk of overdose is a therefore likely in patients with renal impairment. ARIXTRA 1.5 mg/day has a Marketing Authorisation in patients with moderate to severe renal impairment (creatinine clearance between 20 and 50 ml/min). Alternatives are 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, a UFH 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

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

Initial thromboprophylaxis:
Indirect thrombin and factor Xa inhibitors*****: Low Molecular Weight Heparins (LMWHs) and Unfractionated Heparins (UFHs), via SC injection:

Proprietary medicinal products	INN	AB (date of Opinion)
FRAGMIN	Dalteparin sodium	Substantial (19/12/07)
FRAXIPARIN	Nadroparin calcium	Substantial (18/10/06)
INNOHEP	Tinzaparin sodium	Substantial (16/12/09)
LOVENOX	Enoxaparin sodium	Substantial (02/12/09)
CALCIPARIN	Heparin calcium	Substantial (23/01/08)

***: see Table 1 below: usage guidelines - as a function of creatinine clearance – of the various injectable anticoagulants.**

Table 1: Comparison of the guidelines for use of the various injectable anticoagulants, based on creatinine clearance

<table>
<tr><th>Creatinine clearance (ml/min)</th><th>< 20</th><th>≥ 20 Cl and < 30</th><th>≥ 30 and < 50
(moderate renal impairment)</th><th>≥ 50 and < 80
(mild renal impairment)</th></tr>
<tr><td>UFH</td><td>Indicated</td><td>Indicated</td><td rowspan="3">Indicated
(UFH, LMWH)</td><td rowspan="3">Indicated (UFH, LMWH)</td></tr>
<tr><td>LMWH</td><td colspan="2">Relative contraindication in preventive LMWH indications</td></tr>
<tr><td>REVASC, ORGARAN[1]</td><td colspan="2">Contraindicated</td></tr>
<tr><td>ARIXTRA 1.5 mg</td><td>Contraindicated</td><td colspan="2">1.5 mg dose indicated
as a replacement for the 2.5 mg dose</td><td>Indicated (2.5 mg dose)</td></tr>
<tr><td>XARELTO 10 mg</td><td>Not recommended if Cl < 15</td><td colspan="2">Indicated
Limited clinical data
Use with caution</td><td>Indicated</td></tr>
</table>

[1] ORGARAN is contraindicated in cases of severe renal impairment, except if the patient presents with HIT and there is no treatment alternative.

PRADAXA	Contraindicated	Contraindicated	Indicated but little clinical data use with caution at a reduced dose (75 mg dose)	Indicated (110 mg dose)
ELIQUIS	Not recommended if Cl < 15	Indicated Limited clinical data Use with caution	Indicated	Indicated

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

Prolonged thromboprophylaxis

- For LMWHs, the benefit of prolonged prophylactic treatment over 4 to 5 weeks after 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.

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

- FRAGMIN, FRAXIPARIN, INNOHEP and LOVENOX.
- CALCIPARIN

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

- FRAGMIN, FRAXIPARIN and LOVENOX.
- CALCIPARIN

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

No other medicinal product has a Marketing Authorisation in this indication.

According to Afssaps November 2009 guidelines (prior to the results of the CALISTO study) on SVT treatment, unless contraindicated, venous compression is recommended in the acute phase of superficial-vein thrombosis of a limb (Professional Agreement). Surgery is not recommended

(Grade C) except for SVT extending towards the saphenofemoral junction (Professional Agreement). When creatinine clearance is > 30 ml/min, LMWHs (Grade C) at the dose used for VTED prophylaxis may prevent thromboembolic complications.

Other medicinal products may be used in these clinical situations. These medicinal products are second-line treatments.

- Vitamin K antagonists (as an alternative to 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 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 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 combination with antithrombotic treatments since combining their different effects is beneficial. When anticoagulants are contraindicated or the benefit/risk balance 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 comparator medicines that can be prescribed in patients with renal impairment:**
- moderate impairment: UFHs, LMWHs, ELIQUIS and, with caution, XARELTO
- severe impairment: UFHs, and with caution, XARELTO and ELIQUIS.

07 SUMMARY OF PREVIOUS ASSESSMENTS

A summary of the conclusions of data analyses that have already been assessed can be found in the Appendix of this opinion.

Initial assessment: inclusion, ARIXTRA is contraindicated in patients with renal impairment

Date of Opinion (Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use)	16 June 2004
Indications	- Prevention of Venous Thromboembolic Events (VTE) in 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 patients 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 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) (wording)	Given the absence of a clinical evaluation of the 1.5 mg fondaparinux dosage, the efficacy/adverse events ratio cannot be assessed. The actual benefit of ARIXTRA 1.5 mg/0.3 ml, solution for injection is insufficient.
Transparency Committee recommendations	The Committee does not recommend inclusion on the list of medicines reimbursed by National Health Insurance or on the list of medicines approved for use by hospitals and various public services.
Studies requested	A clinical evaluation of this dose “in real-life situations”, and not on the basis of pharmacokinetic modelling, is necessary.

Second assessment: A re-assessment was performed following the removal of the contraindication in cases of severe renal impairment if creatinine clearance is above 20 ml/min, as long as the new 1.5 mg dose of fondaparinux is used, and a re-assessment of AB and IAB in major orthopaedic surgery of the lower limbs was performed.

Date of Opinion (Inclusion on the list of medicines refundable reimbursed by National Health Insurance and approved for hospital use)	5 December 2007
Indications	- Prevention of Venous Thromboembolic Events (VTE) in 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 patients 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 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) (wording)	The actual benefit of ARIXTRA 1.5 mg should be considered insufficient in the absence of satisfactory clinical data evaluating its thromboprophylactic efficacy in patients with renal impairment.
Transparency Committee recommendations	The Committee does not recommend including ARIXTRA 1.5 mg/0.3 ml, solution for injection in pre-filled syringe on the list of medicines reimbursed by

	National Health Insurance and on the list of medicines approved for use by hospitals and various public services in the indications and at the dosages in the Marketing Authorisation since the clinical efficacy data to justify the use of fondaparinux at a dose of 1.5 mg in patients with renal impairment is insufficient.

Third assessment: re-assessment following the presentation of new clinical data

Date of Opinion (Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use)	10 March 2010
Indications	- Prevention of Venous Thromboembolic Events (VTE) in 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 patients 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 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) (wording)	The efficacy/safety ratio for fondaparinux at a dose of 1.5 mg/day was not satisfactorily evaluated. When thromboprophylaxis is needed for patients with a creatinine clearance of 20 to 50 ml/min, a UFH (CALCIPARIN) or an LMWH may be prescribed if creatinine clearance is above 30 ml/min (see SPC for LMWHs), or oral dabigatran etexilate (PRADAXA) or rivaroxaban (XARELTO) (after total knee or total hip surgery) may be considered. The actual benefit of ARIXTRA 1.5 mg should be considered insufficient in the absence of satisfactory clinical data.
Transparency Committee recommendations	The Transparency Committee does not recommend the inclusion of ARIXTRA 1.5 mg/0.3 ml, solution for injection in pre-filled syringe on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals.

08 ANALYSIS OF NEW AVAILABLE DATA

08.1 Efficacy

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 in this indication.

N.B. 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 located below the knee and not requiring surgery. The results of this study are not presented in this opinion since this use of fondaparinux in this clinical situation is off-label.

The only new data comes from a new pharmacokinetic modelling study, the results of which were published in 2010.[2] This model suggested that the administration of fondaparinux 2.5 mg leads to an accumulation of this product not only in cases of altered renal function, but also in cases of low body weight. This risk is also reported to exist in elderly patients, since renal function and body weight decline with age. Weight, creatinine clearance and age therefore influence the pharmacokinetics of fondaparinux. According to the authors of this modelling study, the relationship between fondaparinux accumulation and the occurrence of bleeding has yet to be confirmed, and it still has not been determined whether or not lower exposure reduces the risk of bleeding while still ensuring the same medicinal product efficacy.

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

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

Treatment of adults with acute symptomatic spontaneous superficial-vein thrombosis of the lower limbs without concomitant deep-vein thrombosis
There have been no new clinical data in these indications.

[2] Xavier Delavenne, Paul Zufferey, Denis Baylot, Philippe Nguyen, Jeanne-Yvonne Borg, Michaela Fontenay, Beatrice Deygas, Patrick Mismetti, Silvy Laporte for the GETHCAM study group and POP-A-RIX investigators*Population pharmacokinetics of fondaparinux administered at prophylactic doses after major orthopaedic surgery in everyday practice. Thromb Haemost 2010; 104: 252–260.

08.2 Adverse events

ARIXTRA 1.5 mg is not marketed in France. The applicant states that safety data available is not specifically related to a particular dosage.

ARIXTRA 1.5 mg does not have a Marketing Authorisation in the USA, but it is available in Japan. International pharmacovigilance data (PSUR covering the period from 7 December 2001 to 6 December 2011) pertains to all ARIXTRA dosages (1.5 mg - 2.5 mg - 5 mg - 7.5 mg – 10 mg). This data does not enable the difference in the occurrence of haemorrhagic events between the 1.5 mg and 2.5 mg doses to be determined.

In Japan, haemorrhages have been reported with fondaparinux 1.5 mg; however exposure data is not available and thus conclusions cannot be drawn regarding the benefit of the 1.5 mg dosage in reducing the occurrence of haemorrhage in high-risk patients.

08.3 Summary & discussion

Since the last Committee opinion, there has been no new efficacy, safety or usage clinical data for the 1.5 mg dose.

It should be reiterated that the Marketing Authorisation granted for the 1.5 mg dose in cases of moderate to severe renal impairment in lower limb orthopaedic surgery was primarily based on a pharmacokinetic model[3]. According to results from a new model, it would appear that the risk of accumulation with the 2.5 mg dose (and therefore, of overdose) is increased not only in cases of renal impairment, but also in patients weighing less than 50 kg (and indirectly in elderly patients). The relationship between fondaparinux accumulation and the occurrence of bleeding should be confirmed before recommending a potential dosing adjustment. However, it still has not been determined whether or not lower exposure reduces the risk of bleeding while still ensuring the same medicinal product efficacy.

09 THERAPEUTIC USE

The aims of preventing venous thromboembolic disease are to ward off two complications, i.e., pulmonary embolism and post-thrombotic syndrome, while controlling the occurrence of haemorrhage. In patients with moderate renal impairment, the following medicinal products can be prescribed: UFH (CALCIPARIN), LMWH, and, for elective hip and knee surgery, apixaban (ELIQUIS), and, with caution, dabigatran etexilate (PRADAXA) or rivaroxaban (XARELTO).

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

The therapeutic use of the 1.5 mg dose of fondaparinux is not specified in any of these guidelines.

[3] 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.
[4] See Appendix at the end of this opinion.

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 (AB)

◗ 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, ARIXTRA 1.5 mg (fondaparinux sodium) would be a first-line preventive treatment for venous thromboembolic events.

◗ Public health benefit:
The public health burden of venous thromboembolic disease (VTED) is significant. Having access to safe, effective treatments to prevent VTED in patients at risk of haemorrhage, such as those with renal impairment, those aged 75 years or older or those with a low body weight, is a public health need.
Given the available data for ARIXTRA 1.5 mg, there is no clinical information enabling us to assess the impact of this medicinal product on morbidity and mortality (on antithrombotic efficacy and on haemorrhagic risk reduction) in at-risk patients and in the indications for this dosage. Consequently, ARIXTRA 1.5 mg is not able to provide any additional response to an identified need.
As a result, ARIXTRA 1.5 mg does not provide a public health benefit in these indications.

◗ There are medicinal and non-medicinal alternatives available for patients at increased risk of haemorrhage. In cases of moderate renal impairment, the following medicinal products may be used with caution:

- oral: dabigatran etexilate (PRADAXA), rivaroxaban (XARELTO), apixaban (ELIQUIS) and vitamin K antagonists
- injectable: LMWHs and CALCIPARIN.

In cases of severe renal impairment, CALCIPARIN may be used, and XARELTO and ELIQUIS may be used with caution.

◗ The therapeutic use of ARIXTRA 1.5 mg in its registered indications in patients with renal impairment has not been demonstrated, and for patients with low body weight or who are over the age of 75 years, the use has not been assessed.

Given the aforementioned, the Committee considers that the actual benefit of ARIXTRA 1.5 mg remains insufficient to justify its reimbursement by public funding.

APPENDICES

APPENDIX I - Summary of available results from previous assessments:

Initial assessment:

The 1.5 mg dosage of fondaparinux is intended for patients with severe renal impairment. No clinical efficacy and/or safety data for the 1.5 mg fondaparinux dosage in patients with severe renal impairment is available. The benefit of this dose for patients with moderate to severe renal impairment has only been established based on a pharmacokinetic modelling study.

Second assessment

New pharmacovigilance data obtained within the context of current usage practices are available for the 2.5 mg fondaparinux (ARIXTRA) dosage. These data show that the haemorrhagic safety profile for fondaparinux in elderly patients and/or patients with renal impairment, and in particular when there non-compliance with the recommendations for use, justifies the implementation of a national risk management plan to monitor the risk of haemorrhage.

The use of fondaparinux (ARIXTRA 1.5 mg and 2.5 mg) in renally impaired patients with a creatinine clearance of 20 to 50 ml/min has not been established. The Committee reiterates that the management of these patients is based on the prescription of a UFH, in particular for cases of very severe renal impairment. When creatinine clearance is greater than 30 ml/min, an LMWH may be prescribed in compliance with the SPC for these proprietary medicinal products. The Committee notes that the determination of the degree of renal impairment according to the Cockroft-Gault formula in elderly patients is problematic (expert opinion) and that the choice of one LMWH over another is poorly documented. In patients with mild to moderate renal impairment with a creatinine clearance of 20 to 50 ml/min, a low dose of fondaparinux (ARIXTRA 1.5 mg) is proposed by GlaxoSmithKline to replace the 2.5 mg dose. However, their evaluation is only based on pharmacokinetic studies (modelling) and four dose-ranging studies, all performed within the context of major orthopaedic surgery of the lower limbs involving thromboembolic risk. The evaluation of the clinical efficacy of fondaparinux 1.5 mg is therefore very limited, especially when creatinine clearance is below 30 ml/min (see SPC) and in other clinical situations where ARIXTRA 2.5 mg may be prescribed. This dosage of ARIXTRA is contraindicated in cases of severe renal impairment (creatinine clearance of less than 20 ml/min).
Renally impaired patients receiving thromboprophylaxis may be treated with a UFH, or even an LMWH (see SPC). There are no satisfactory data enabling the use or the benefit of ARIXTRA 1.5 mg to be determined compared with these alternatives (Opinion of 5 December 2007).

Third assessment

In patients with moderate renal impairment, defined as creatinine clearance of 20 to 50 ml/min, there is an increased risk of potentially fatal haemorrhage with 2.5 mg/day of fondaparinux. A dosage of 1.5 mg is suggested in the treatment of these patients. The clinical evaluation of this dosage was initially based on pharmacokinetic studies (modelling) and four dose-ranging studies, all performed within the context of major orthopaedic surgery of the lower limbs involving thromboembolic risk. Within the scope of thromboprophylaxis after orthopaedic surgery of a lower limb, the applicant presented the results of a non-comparative follow-up cohort study (observational study) with the aim of evaluating the risk of major haemorrhage (primary efficacy endpoint) and the antithrombotic efficacy when used for symptomatic VTE (secondary endpoint) in adult patients with moderate renal impairment receiving 1.5 mg/day of fondaparinux via SC injection. The risk of a major haemorrhage occurring was higher than expected: 4.5% versus 2.6% between Day 0 and Day 10; the upper limit of the 95% confidence interval was over 4.2%. All major haemorrhages occurred after the 6th hour. There is no clinical data available in the two other ARIXTRA 1.5 mg indications (prevention in abdominal surgery patients and prevention in immobilised acute illness patients).
Historical comparisons were made. They suggest that the rate of symptomatic VTE observed in the PROPICE study population on fondaparinux 1.5 mg would be in the same order as the rate

observed with fondaparinux 2.5 mg/day and other antithrombotics in the phase III studies. They also suggest that the risk of haemorrhage on fondaparinux 1.5 mg/day in moderately renally impaired patients would be no greater than that expected on 2.5 mg/day in the absence of renal impairment. However, the two dosages appear to expose renally impaired patients to a fairly similar risk of haemorrhage. These indirect comparisons are only exploratory since they are open to selection bias and confusion.
The data presented do not enable the performance of fondaparinux in this dosage and in these patients to be precisely quantified. Furthermore, alternative treatments are available.

APPENDIX II - Summary table of the various good 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** are 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 haemorrhages 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 and symptoms 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, 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 day 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 THR post-operative day.	**1+**
Prophylaxis with **LMWHs**, **fondaparinux**, **dabigatran**, **rivaroxaban** or **apixaban** up to the 14th TKR post-operative day is recommended.	**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+**