HAUTE AUTORITÉ DE SANTÉ

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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 (2012)	B01AX05 (Antithrombotic agent). Selective indirect factor Xa inhibitor
Reason for the review	**Re-assessment of the 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)
Indication concerned	**"Treatment of adults with acute symptomatic spontaneous superficial vein thrombosis of the lower limbs without concomitant deep-vein thrombosis."**

Actual Benefit (AB)	**Moderate in the treatment of adults with acute symptomatic spontaneous superficial vein thrombosis of the lower limbs without concomitant deep-vein thrombosis**
Improvement in Actual Benefit (IAB)	**The Committee confirms the absence of an IAB (level V, non-existent) in the treatment strategy given the uncertainty of the clinical benefit of extending the treatment duration to 45 days in the heterogeneous population of patients with an isolated SVT.**
Therapeutic use	**This product is a first-line treatment**
Recommendations	**It should be reiterated that a re-assessment of this opinion will take place once the results of the ongoing post-inclusion study requested on 20 June 2011 are presented.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Initial date (European centralised procedure): 21 March 2002 Extension of the indication for SVT: 31 August 2010.
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.

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 indication in the treatment of superficial vein thrombosis will be re-assessed.

03 INDICATIONS

"**Treatment of adults with acute symptomatic spontaneous superficial vein thrombosis of the lower limbs without concomitant deep-vein thrombosis (see Dosage and Method of administration and Pharmacodynamics sections)"**

- 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 mins) invasive management (PCI) is not indicated (see Special warnings and precautions for use and Pharmacodynamics sections)
- 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."

04 DOSAGE

“Treatment of superficial vein thrombosis: the recommended dose of fondaparinux is 2.5 mg once daily, administered by subcutaneous injection. Patients eligible for fondaparinux 2.5 mg treatment should have acute, symptomatic, isolated, spontaneous superficial vein thrombosis of the lower limbs, at least 5 cm long and documented by ultrasonographic investigation or other objective methods. Treatment should be initiated as soon as possible following diagnosis and after exclusion of concomitant DVT or superficial vein thrombosis within 3 cm of the saphenofemoral junction. Treatment should be continued for a minimum of 30 days and up to a maximum of 45 days in patients at high risk of thromboembolic complications (see Special warnings and precautions for use and Pharmacodynamics sections). Patients could be recommended to self-inject the product when they are judged willing and able to do so. Physicians should provide clear instructions for self-injection.

Patients who are to undergo surgery or other invasive procedures: in superficial vein thrombosis patients who are to undergo surgery or other invasive procedures, fondaparinux, where possible, should not be given in the 24 hours before surgery. Fondaparinux may not be restarted until at least 6 hours post-operatively, and only if haemostasis has been achieved.

Special populations:

The elderly: no dosing adjustment is necessary. In patients 75 years and older, fondaparinux should be used with care, as renal function decreases with age.

Renal impairment: Fondaparinux should not be used in patients with creatinine clearance below 20 ml/min (see Contraindications section). 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 Pharmacokinetics sections). 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 (see Special warnings and precautions for use section).

Hepatic impairment: The safety and efficacy of fondaparinux in patients with severe hepatic impairment has not been studied, therefore fondaparinux is not recommended for use in these patients (see Special warnings and precautions for use section).

Low body weight: The safety and efficacy of fondaparinux in patients with body weight less than 50 kg has not been studied, therefore fondaparinux is not recommended for use in these patients (see Special warnings and precautions for use section).”

05 CLINICALLY RELEVANT COMPARATORS

05.1 Medicinal products

No other medicinal product has a Marketing Authorisation in this indication.
According to the Afssaps November 2009 guidelines[1] for the treatment of superficial vein thrombosis (SVT), administering prophylactic LMWH doses (Grade C) for venous thromboembolic disease (VTED) could prevent the risk of thromboembolic complications.

05.2 Other health technologies

According to Afssaps November 2009 guidelines[1] in the treatment of SVT, venous compression is recommended in the acute phase of superficial vein thrombosis of a limb, unless it is contraindicated (Professional Agreement).
Surgery is not recommended (Grade C) except for SVT extending towards the saphenofemoral junction (Professional agreement).

[1] *PREVENTION ET TRAITEMENT DE LA MALADIE THROMBOEMBOLIQUE EN MEDICINE. GOOD PRACTICE GUIDELINES* (PREVENTION AND TREATMENT OF VENOUS THROMBOEMBOLIC DISEASE IN MEDICINE. GOOD PRACTICE GUIDELINES) French Health Products Safety Agency (Afssaps), December 2009.

06 SUMMARY OF PREVIOUS ASSESSMENTS

Date of Opinion (Inclusion on the list of medicines reimbursed through National Insurance and approved for use by hospitals)	22 June 2011
Indication	Treatment of adults with acute symptomatic spontaneous superficial vein thrombosis of the lower limbs without concomitant deep-vein thrombosis.
Actual Benefit (AB)	moderate
Improvement in Actual Benefit (IAB)	The Committee considers that ARIXTRA 2.5 mg does not provide an improvement in actual benefit (IAB V) in the treatment strategy, given the uncertainty of the clinical benefit of 45 days of treatment in the heterogeneous population of patients with an isolated SVT
Studies requested	The Committee's recommendation that ARIXTRA is reimbursed in the treatment of SVT was conditional upon conducting a study among physicians in private practice (general or vascular medicine) within 2 years so that the following could be understood: - the characteristics of patients treated for SVT and in particular those of patients treated with ARIXTRA 2.5 mg, enabling a comparison of patient profile by treatment to be performed - the prescribed treatments (including ARIXTRA) and their true conditions of use - the impact on mortality and morbidity (especially in terms of the occurrence of VTE and major haemorrhage) of these treatment strategies (in particular, treatment with ARIXTRA), with a comparative analysis of this impact by observed SVT treatment strategy - the impact on the organisation of healthcare overall and by SVT treatment strategy.

07 ANALYSIS OF NEW CLINICAL DATA

07.1 Efficacy

The applicant has not presented any new clinical efficacy data.

An update of the Cochrane review on SVT was carried out in March 2012[2]. This update took into account the results of the CALISTO study.
In this review, randomised, controlled studies evaluating topical medications (e.g., NSAID-based preparations), medicinal products or surgical procedures for patients with SVT of the lower limbs were investigated up to 29 November 2011.
Twenty-six (26) studies on a total of 5,521 patients were taken into consideration. The methodological quality of the majority of these studies was deemed poor. The medicinal products evaluated were fondaparinux, LMWHs, UFHs and NSAIDs.
The only study based on fondaparinux is the CALISTO study (included in the Committee Opinion of 22 June 2011). This was a placebo-controlled study of 3,000 patients. Fondaparinux reduced symptomatic VTE (RR = 0.15; 95% CI [0.04 to 0.50]), the spread of the thrombosis (RR = 0.08; 95% CI: [0.03 to 0.22]) and recurrence (RR = 0.21; 95% CI [0.08 to 0.54]). The risk of major bleeding with ARIXTRA 2.5 mg was no different than with placebo (RR = 0.99; 95% CI: [0.06 to 15.86])[3].
This review also provides the following information, albeit with limited evidence: with LMWHs used at prophylactic doses, the spread of the thrombosis and its recurrence were reduced compared with placebo (RR = 0.40; 95% CI: [0.22 to 0.72]). At curative doses, this reduction (RR) was 0.42; 95% CI: [0.23 to 0.75]. NSAIDs (with no details of administration route) also reduced this risk: RR = 0.41; 95% CI: [0.23 to 0.75]. There was no difference in effect between LMWHs (curative and preventive doses) and NSAIDs versus placebo for symptomatic VTE and the risk of major bleeding.
Overall, topical medication improved localised symptoms, but there was no data for assessing their effect on the occurrence of VTE and the spread of the thrombosis.
Surgical procedures combined with mechanical compression (elastic stockings) also reduced the occurrence of VTE and the spread of SVT more than mechanical compression alone.

07.2 Adverse effects

See Safety the section of the ARIXTRA 2.5 mg re-assessment opinion in its thromboprophylaxis indications.

08 USAGE DATA

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

[2] Di Nisio M, Wichers IM, Middeldorp S. Treatment for superficial thrombophlebitis of the leg. Cochrane Database Syst Rev. 2012 Mar14; 3: CD004982.doi: 10.1002/14651858.CD004982.pub4.
[3] Decousus H, Prandoni P, Mismetti P, Bauersachs RM, Boda Z, Brenner B, et al. CALISTO Study Group. Fondaparinux for the treatment of superficial vein thrombosis in the legs. NEJM 2010;363(13):1222–32.

Table 1. 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%**

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

09 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.

A usage study should be carried out within the context of the European RMP to evaluate compliance with the SPC in prescribing ARIXTRA for SVT, and in particular to verify whether or not the dosage has been respected in this indication.

010 THERAPEUTIC USE

In its 22 June 2011 Opinion, the Committee considered that:
The aim of treatment for acute symptomatic superficial vein thrombosis is to relieve pain, to prevent the spread of the thrombosis into the deep tissue and to prevent subsequent pulmonary embolism.
According to the Afssaps November 2009 guidelines, in cases of SVT (drafted before the results of the CALISTO study):

- Venous compression, preferably with elastic or non-elastic compression methods (depending on the physician practices and preferences) is recommended in the acute phase of superficial vein thrombosis of a limb (Professional agreement).
- NSAIDs are not recommended (Grade C).
- Curative VTED anticoagulant doses are not recommended (Grade C), except for SVT that extend towards the saphenofemoral junction, which may justify an anticoagulant at a curative dose. LMWHs (Grade C) and fondaparinux (Professional Agreement) at a prophylactic dose for VTED may reduce the risk of thromboembolic complications. If one of these treatments is started, treatment should continue for 7 to 30 days (Professional Agreement).
- Surgery is not recommended (Grade C). However it may be discussed for SVT extending towards the saphenofemoral junction (Professional agreement).

When an anticoagulant is considered for the treatment of SVT, the product with the best evaluation is fondaparinux sodium 2.5 mg/day via SC injection.
Adult patients likely to receive fondaparinux sodium should have a spontaneous, acute, symptomatic, isolated SVT of the lower limbs, at least 5 cm in length, confirmed by ultrasound. Treatment should be started as quickly as possible after diagnosis and after ruling out concomitant

deep vein thrombosis (DVT) or a superficial vein thrombosis at least 3 cm from the saphenofemoral junction. Fondaparinux should not be administered in the 24 hours preceding a surgical procedure. Treatment with fondaparinux may be restarted until at least 6 hours post-operatively and only if haemostasis has been achieved.
The Committee reiterates that fondaparinux 2.5 mg/day is contraindicated in cases of severe renal impairment, defined as creatinine clearance below 50 ml/min. The Committee has highlighted that the 1.5 mg/day dose of fondaparinux has not been evaluated in this clinical situation.
The Committee notes that treatment requiring a daily subcutaneous injection for 45 days is restrictive for the patient and that the benefit of this treatment duration has only been established for patients with the same profile as those included in the CALISTO study and provided that the protocol is followed correctly.

Since this Opinion, several expert guidelines have been published:
- The French Society of Vascular Medicine (SFMV) recommends the use of ARIXTRA 2.5 mg for 30 to 45 days (Marketing Authorisation) for the treatment of isolated acute spontaneous SVT of the lower limbs[4] .
- In the North American guidelines published in 2012[5], updating those produced in 2008[6], recommend ARIXTRA 2.5 mg and, by extrapolation, LMWHs, as first-line treatment for a duration of 45 days in the treatment of SVT (Grade 2B). ARIXTRA 2.5 mg is preferred to LMWHs (Grade 2C).
- According to the Cochrane review[7], fondaparinux administered over 6 weeks at a dose of 2.5 mg/day appears to be a valid treatment option for patients with an isolated lower limb SVT.

<u>Consideration of the risk of haemorrhage</u>
According to the Marketing Authorisation:
- Renal impairment: Fondaparinux should not be used in patients with creatinine clearance below 20 ml/min. The dose should be reduced to 1.5 mg once daily in patients with creatinine clearance in the range of 20 to 50 ml/min. No dosage reduction is required for patients with mild renal impairment (creatinine clearance >50 ml/min). The SPC states that the efficacy and safety of the use of a 1.5 mg dose has not been studied in this indication.
- Weight < 50 kg: “The safety and efficacy of fondaparinux in patients with body weight less than 50 kg has not been studied, therefore fondaparinux is not recommended for use in these patients.”
- Patients 75 years and above: in the elderly, fondaparinux is to be used with caution.

ARIXTRA should not be used at a 2.5 mg dose once daily in patients with renal impairment (creatinine clearance < 50 ml/min).
In patients with a body weight < 50 kg and/or aged 75 years and above, the use of fondaparinux should only be considered with great care given the risk of haemorrhage and the absence of a possible dose adjustment.

[4] Laroche JP. Thrombose Veineuse Superficielle (Superficial Vein Thrombosis) - Actualités 2011. http://www.sfmv.fr/file_tmp/4f9244bc933e6.pdf.
[5] Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141 (suppl): e419S-e494S
[6] Kearon C, Raskob GE, Comerota AJ, Kahn SR, Agnelli G, Goldhaber S. Antithrombotic Therapy for Venous Thromboembolic Disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:454-545.
[7] Di Nisio M, Wichers IM, Middeldorp S. Treatment for superficial thrombophlebitis of the leg. Cochrane Database Syst Rev. 2012 Mar14; 3: CD004982.doi: 10.1002/14651858.CD004982.pub4.

011 TRANSPARENCY COMMITTEE CONCLUSIONS

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

011.1 Re-assessment of the Actual Benefit

SVT, which generally is not serious, can be a complication of venous thromboembolic disease (symptomatic DVT or PE), can be life-threatening (potentially fatal pulmonary embolism) or can lead to significant sequelae (post-thrombotic syndrome). In acute symptomatic spontaneous superficial vein thrombosis of the lower limbs with no concomitant deep vein thrombosis, ARIXTRA at a dosage of 2.5 mg/day aims to eliminate the occurrence of thromboembolic complications. However, this complication is rare (1.5% of symptomatic events in the placebo group of the CALISTO study).
ARIXTRA 2.5 mg is intended as curative therapy.
In the CALISTO study, patients were at low risk of thrombosis and haemorrhage and the difference observed for clinically relevant complications (symptomatic DVT and PE) was modest; fondaparinux has a moderate efficacy/adverse events ratio. In addition, the benefit of a 45-day treatment period (protocol compliance, moderate expected clinical benefit) was not clearly established.
There are no alternative medicinal products with a Marketing Authorisation in this indication. The therapeutic benefit of LMWHs, used off-label in this indication, is poorly established.
ARIXTRA is a first-line treatment.

Public health benefit
The public health burden of venous thromboembolic disease (VTED) is substantial. The burden of isolated superficial vein thrombosis (SVT) is considered low since it is not particularly serious (limited incidence of complications [DVT, PE]) and the number of patients affected is limited. Access to SVT treatment with an anticoagulant that has demonstrated efficacy for thromboembolic complications and is guaranteed safe to use is a therapeutic need. However, improvement in the management of isolated SVT is not explicitly identified as a public health need since the indicator used in the appendix of French Public Health Law no. 69 refers to reducing mortality.
In the absence of new data to clarify the uncertainties regarding the impact of ARIXTRA 2.5 mg in current medical practice on morbidity and mortality in this indication, and given the pharmacovigilance monitoring data for ARIXTRA 2.5 mg (all indications combined) highlighting the increased risk of haemorrhage and misuse, the impact of this medicinal product can no longer be considered low.
Thus, ARIXTRA 2.5 mg does not have an impact on morbidity and mortality. Furthermore, no new data is available about its impact on the organisation of healthcare.
Consequently, in the current state of knowledge and while awaiting the results of the ongoing post-inclusion study requested by the Committee, ARIXTRA 2.5 mg does not offer a public health benefit in this indication.

Consequently, the Committee considers that the actual benefit of ARIXTRA 2.5 mg remains moderate in the treatment of adults with acute symptomatic spontaneous superficial vein thrombosis of the lower limbs without concomitant deep-vein thrombosis.

◗ Proposed reimbursement rate: 30%.

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

The Committee confirms the absence of an IAB (level V, non-existent) in the treatment strategy given the uncertainty of the clinical benefit of extending the treatment duration to 45 days in the heterogeneous population of patients with an isolated SVT.

012 TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Committee recommends the continued inclusion of ARIXTRA 2.5 mg on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the "treatment of adults with acute symptomatic spontaneous superficial vein thrombosis of the lower limbs without concomitant deep-vein thrombosis".

It should be noted that a re-assessment of this opinion based on the results of an ongoing post-inclusion study requested on 20 June 2011 will be presented.

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