HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

10 March 2010

ARIXTRA 1.5 mg/0.3 ml, solution for injection in pre-filled syringe
Box of 2 (CIP: 363 500-6)
Box of 7 (CIP: 363 501-2)
Box of 10 (CIP: 564 989-2)

Applicant: GLAXOSMITHKLINE

Fondaparinux sodium
ATC code: B01AX05

List I

Date of European Marketing Authorisation (MA): 24 October 2003

Reason for request: inclusion on the list of medicines reimbursed by National Insurance (B/2 and B/7) and approved for hospital use (B/2, B/7 and B/10).

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Fondaparinux sodium

1.2. Indications

" - Prevention of Venous Thromboembolic Events (VTE) in patients undergoing major orthopaedic surgery of the lower limbs such as hip fracture, hip replacement or major knee 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."

1.3. Dosage of ARIXTRA for patients with renal impairment

"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. No dose reduction is required for patients with mild renal impairment (creatinine clearance > 50 ml/min).

The special warnings and precautions for use in the SPC indicate that "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 < 30 ml/min."

The pharmacokinetic properties section of the SPC states that "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 severe renal impairment."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2009)

B	Blood and blood forming organs
B01A	Antithrombotic agents
B01AX	Other antithrombotic agents
B01AX05	Fondaparinux

2.2. Medicines in the same therapeutic category

2.2.1. Indirect thrombin and factor Xa inhibitor

Unfractionated heparins:
- Heparin calcium (subcutaneous route): CALCIPARINE;
- Heparin sodium (IV route): HEPARINE NA CHOAY, HEPARINE NA PANPHARMA.

Low molecular weight heparins (LMWH):
- Dalteparin: FRAGMINE 2,500 and 5,000 IU
- Enoxaparin: LOVENOX 2,000 IU and 4,000 IU
- Nadroparin: FRAXIPARINE
- Tinzaparin: INNOHEP 2,500 IU, 3,500 IU and 4,500 IU

Others:
- Danaparoid: ORGARAN 750 IU (IV or subcutaneous route). This medicinal product can be supplied through the French "retrocession" [dispensing of drugs to outpatients by hospital pharmacies] system.

2.2.2. Direct factor Xa inhibitor
- Rivaroxaban: XARELTO 10 mg, tablets.

2.2.3. Direct thrombin inhibitor
- Dabigatran: PRADAXA 110 mg, PRADAXA 75 mg, capsules.
- Desirudin: REVASC 15 mg/0.5 ml (subcutaneous route). This medicinal product cannot be supplied through the French "retrocession" system.

2.3. Medicinal products with a similar therapeutic aim

Vitamin K antagonists
- Acenocoumarol: SINTROM 4 mg, MINISIMTROM 1 mg, tablets.
- Warfarin: COUMADINE 2 mg, COUMADINE 5 mg, tablets.
- Fluindione: PREVISCAN 20 mg, tablets.

The various indications for ARIXTRA 1.5 mg/0.5 ml and its comparators are summarised in Table 1 (page 4 of this opinion).

Table 1: Comparison of indications for ARIXTRA 1.5 mg and its comparators.

Proprietary medicinal products		Therapeutic indications					
		Prevention of VTEs in major lower limb orthepaedic surgery such as HF, THR or TKR				Prevention of VTEs in abdominal surgery for patients judged to be at high risk (abdominal surgery for cancer)	Prevention of VTEs for patients judged to be at high risk for VTE and who are immobilised due to medical illness
		Initial thromboprophylaxis	Long-term thromboprophylaxis				
			TKR	THR	HF		
ARIXTRA 1.5 mg		**+** THR, TKR, HF: 5-9 days	**–**	**–**	**+** **19-23 days**	**+**	**+**
NFH	**heparin sodium**	(off-label) Exact wording: prevention of arterial thromboembolic events in patients suffering from embolic heart disease undergoing endovascular treatment or undergoing arterial vascular surgery					**–**
	heparin calcium	**+** Exact wording: prevention of VTED in a surgical setting					**+** **(in the case of severe renal insufficiency)**
LMWH	**enoxaparin LOVENOX**	**+** (2,000 IU and 4,000 IU) Exact wording: prophylaxis of VTED in surgery in moderate- or high-risk situations: **10 days and up to 4 to 5 weeks in the case of orthopaedic hip surgery (4,000 IU)**					**+** **(4000 IU ≤ 14 days)**
	dalteparin FRAGMINE	**+** (2,500 IU and 5,000 IU) Exact wording: prophylaxis of VTED in surgery in moderate- or high-risk situations and in oncological surgery **10 days and up to 35 days in the case of orthopaedic hip surgery (5,000 IU)**					**+** **(5,000 IU < 14 days)**
	nadroparin FRAXIPARINE	**+** Exact wording: prophylaxis of VTED in surgery in moderate- or high-risk situations: **10 days**					**–**
	tinzaparin INNOHEP	**+** Exact wording: prophylaxis of VTED in surgery in moderate- or high-risk situations: **10 days**					**–**
ORGARAN For hospital use only		Exact wording: Prophylaxis of VTED in orthopaedic and oncological surgery: **7-10 days**. Or as an alternative to heparins for patients suffering from type II HIT or with a history of type II HIT					**–**
XARELTO		**+** Exact wording: Prevention of VTEs in adults undergoing scheduled surgery of the hip or knee (THR, TKR) **2 weeks (TKR) or 5 weeks (THR)**			**–**	**–**	**–**
PRADAXA		**+** Exact wording: Prevention of VTEs in adults who have undergone scheduled THR or TKR surgery **10 days (TKR) or 28 to 35 days (THR)**			**–**	**–**	**–**
REVASC For hospital use only		Exact wording: Prevention of deep vein thromboses following scheduled orthopaedic surgery (hip or knee replacement) **9-12 days.**			**–**	**–**	**–**
VKA	**acenocoumarol**	**–** Because onset of pharmacological action takes 5 days	**–**	**+** As follow up to heparins	**+** As follow up to heparins	**–**	**–**
	warfarin						
	fluindione						

VTE: venous thromboembolic event. **TKR**: total knee replacement. **THR**: total hip replacement. **HF**: hip fracture. **LMWH**: low molecular weight heparins. **VTED**: venous thromboembolic disease (phlebitis or pulmonary embolism). **DVT**: deep vein thrombosis. **HIT**: heparin-induced thrombocytopenia. **RI**: renal insufficiency

MA guidelines for the use of these medicinal products in patients with renal insufficiency:

Table: Comparison of guidelines for using various injectable anticoagulants according to creatinine clearance

<table>
<tr><th>Creatinine clearance
(mL/min)</th><th>< 20</th><th>≥ 20 and < 30</th><th>≥ 30 and < 50
(moderate renal insufficiency)</th><th>≥ 50 and < 80
(mild renal insufficiency)</th></tr>
<tr><td>NFH</td><td>Indicated</td><td>Indicated</td><td rowspan="3">Indicated (NFH, LMWH)</td><td rowspan="3">Indicated (NFH, 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 instead of 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>
<tr><td>PRADAXA</td><td>Contraindicated</td><td>Contraindicated</td><td>Indicated
but
little clinical data
use with caution
at a lower dose
(75 mg dose)</td><td>Indicated
(110 mg dose)</td></tr>
</table>

[1] ORGARAN is contraindicated for patients with severe renal insufficiency unless the patient has HIT and there is no therapeutic alternative.

3 ANALYSIS OF AVAILABLE DATA

Clinical data from the follow-up of a cohort of 450 patients with moderate renal insufficiency who were given 1.5 mg/day of fondaparinux as thromboprophylaxis after lower limb orthopaedic surgery were offered to support this new application for inclusion. Historical comparisons of symptomatic VTE and major bleeding rates with those observed in the phase III studies available for fondaparinux 2.5 mg/day and its comparators and in other cohort studies are proposed.

3.1. Efficacy

3.1.1. Post-MA observational study (PROPICE)

This was a non-comparative cohort study, whose primary objective was to assess haemorrhagic risk in patients with moderate renal insufficiency. The secondary objective was to assess the antithrombotic efficacy of ARIXTRA 1.5 mg. The patients taking part were adults receiving thromboprophylaxis after major orthopaedic surgery of the lower limb following an initial (or repeated) total hip or knee replacement (THR/TKR) or a hip fracture (HF).

Fondaparinux was administered at a dosage of 1.5 mg/day (SC route) for 5 to 10 days following TKR or THR and up to 35 days after HF, with the first injection given at least six hours after the end of the surgical procedure.
The primary endpoint was the occurrence of a major haemorrhagic incident between D0 and D10. The secondary endpoints were the occurrence a major haemorrhagic incident by 1 month ± 5 days and confirmed symptomatic thromboembolic events between D0 and D10 and by 1 month ± 5 days. An investigation of haemorrhagic and thromboembolic risk factors was conducted.

The number of subjects needed was calculated *based on the following major haemorrhagic incidence assumptions among individuals taking fondaparinux at 1.5 mg/day*:

- 2.6% (incidence observed in patients taking fondaparinux at 2.5 mg/day who had creatinine clearance values > 50 ml/min in phase III studies of orthopaedic surgery of the lower limb)
- the upper limit of the 95% CI of this incidence must not exceed 4.2% (upper limit of the 95% CI of the incidence of major bleeding observed in patients taking LMWH prescribed at prophylactic doses appropriate for major surgery, in the phase III studies).

It was estimated that 450 subjects were required.

Results:

Study population characteristics:

- 451 patients were recruited by 29 centres (80% of the patients were women)
- The analysis of the results was carried out on data from 442 patients, broken down as follows: 193 (43.7%) scheduled THR, 122 (27.6%) scheduled TKR and 127 (28.7%) HF. More than two-thirds (71.3%) of the recruited patients were scheduled to have orthopaedic surgery (THR or TKR); 13.3% of the recruited patients were scheduled to have a repeat replacement procedure.
- Most of the patients had creatinine clearance levels between 20 and 50 ml/min. Almost 40% were given preoperative antithrombotic treatment.
- The number of potentially eligible patients who were not included, and the reason for the non-inclusion, was not provided.
- This is a population at risk of thromboembolism: the average age is 81.6 +/- 6.6; 65% were over 80 and 31% were over 85. Furthermore, almost 40% had an ASA score[2] >3 and almost

[2] preoperative severity score devised by the American Society of Anesthesiology

27% had a major thromboembolic risk factor (history of cancer or VTE in particular).
- More than 50% of the patients underwent treatment with fondaparinux for a total of at least 10 days. The median duration of treatment was 8 days [2-49] for patients undergoing THR, 8 days [1-39] for those having TKR and 28 days [1-61] for those having surgery for a hip fracture; 36.6% of the patients continued to take fondaparinux after being discharged from hospital.
- 42% of the patients received their first injection within eight hours after surgery, while 4.3% had it within six hours.

N.B.: The results for the primary endpoint are presented in the section dealing with adverse effects.

Antithrombotic efficacy (secondary endpoint): three cases of symptomatic VTE (distal DVT) occurred: two between D0 and D10 (after HF) and one 17 days after discontinuing fondaparinux (after THR). This means that the incidence figures at D10 and 1 month are 0.5% and 0.7% respectively. No cases of proximal DVT or pulmonary embolism occurred.

Mortality: ten patients died. Six of these deaths occurred between D10 and 1 month ± 5 days, representing an incidence of 0.9% and 2.3% at D10 and D30 respectively. None of the deaths were attributed to fondaparinux or were due to bleeding. Seven of the deaths occurred after HF and three after THR.

3.1.2 Historical comparisons were performed and suggest that the rate of symptomatic VTE in PROPICE is:
- comparable to or lower than the rate observed in cohorts of patients not selected on the basis of renal function (ESCORTE and FOTO [LMWH] observational studies, EXPERT [fondaparinux 2.5 mg/day]);
- comparable to the rates observed in phase III studies comparing enoxaparin to fondaparinux 2.5 mg/d and to rivaroxaban.

3.2. Adverse effects

3.2.1 Haemorrhagic risk (primary endpoint)

Twenty major bleeding events (in 20 patients) occurred between D0 and D10 or within 72 hours after discontinuing treatment. Consequently, the incidence is 4.5% (95% CI: [2.79; 6.90]) whereas the expected incidence was 2.6%. One of these bleeding events did not occur at the surgical site. None of them involved a critical organ. Two surgical site haematomas required another procedure, one of which was surgery (removal of a haematoma and drainage). Four occurred after THR, 10 after TKR and 6 after HF.

Three additional major haemorrhagic incidents occurred between D10 and 1 month ± 5 days. One of these required a new procedure (removal of a haematoma at the surgical site), while the other led to a definitive discontinuation of fondaparinux (gastroduodenal ulcer).

In total, the overall incidence of major haemorrhagic events occurring between D0 and 1 month ± 5 days in the PROPICE study was 5.2% (95% CI: [3.3;7.7]).

The risk of major bleeding occurring was therefore higher than expected: 4.5% instead of 2.6% between D0 and D10; the upper limit of its 95% confidence interval was higher than that of 4.2%.

An investigation of risk factors for major bleeding at D10 was carried out: the univariate analysis demonstrated that medical history, age, weight, BMI and creatinine clearance had no detectable effect on this risk. The following factors were associated with elevated risk: gender (45% of the incidents occurred in men, though they accounted for only 20% of the study population), time of first postoperative injection (65% of the incidents occurred in patients who had had their first injection within the 8 hours following surgery), whether or not the patient had received preoperative antithrombotic medication (60% of the incidents), TKR surgery (50% of the incidents and 27% of the surgical procedures), and an ASA score > 3

(55% of the incidents). The multivariate analysis demonstrated that only the “male gender” and “ASA score > 3” combination was still significant (p=0.002).

3.3. Comments on the efficacy and tolerance results

Antithrombotic efficacy

- This was assessed on the basis of symptomatic venous thromboembolic events, since the purpose of the treatment was to prevent the occurrence of these events. It would have been useful to take into account the asymptomatic events confirmed by imaging to determine the efficacy. Indeed, the incidence of both symptomatic and asymptomatic VTEs, systematically confirmed by imaging, was the assessment criterion used in the available phase III clinical studies (in particular those carried out on fondaparinux 2.5 mg/d). Only three PROPICE study subjects (0.5%) had a symptomatic VTE.
- The lack of a control arm in PROPICE is debatable: NFHs and LMWHs represent an alternative for patients with moderate renal insufficiency. Rivaroxaban (XARELTO 10 mg), which does not require dose adjustment in the event of moderate renal insufficiency, can be prescribed, as can dabigatran etexilate if the patient is having surgery.
- As the underlying risk of VTE varies according to the indication (TKR, THR or HF) and age, interpreting historical comparisons is a delicate task.
- The hypothesis tested was comparable efficacy between ARIXTRA 1.5 mg/day in patients with moderate renal insufficiency and ARIXTRA 2.5 mg/day in patients with normal renal function. The rate of symptomatic VTE appears to be similar, but the possibility of a rate higher than that observed in other studies cannot be ruled out.

Haemorrhagic risk

- Historical comparison of observational data and of data derived from randomised trials raises the issue of patient selection differences. However, by analysing the sub-group of patients with moderate renal insufficiency, we can assume that the risk profiles of the population included in the trials and in the observational study are less divergent.
- The aim of the 1.5 mg/day dose is to reduce the haemorrhagic risk observed with the 2.5 mg/day dose of fondaparinux. This has not been clearly demonstrated (wide overlap of confidence intervals).

Bleeding events at D10 n/N (%) [95% CI] among patients with creatinine clearance <50 ml/mn

Study	Procedure	Rate of major bleeding events
PROPICE	Fondaparinux 1.5 mg/d	20 / 442 (4.5%) [2.8-6.9]
Phase III studies	Fondaparinux 2.5 mg/d If interval prior to administration > 6 hours Enoxaparin 40 mg/d	26 / 637 (4.1%) [2.7-6.0] 10 / 375 (2.7%) [1.3-4.8] 21 / 691 (3.0%) [1.9-4.6]

- The historical comparisons show no reduction in the risk of bleeding with fondaparinux 1.5 mg/d in patients with moderate renal insufficiency compared to enoxaparin 40 mg/d, dabigatran etexilate 150 mg/d and rivaroxaban 10 mg/d.

- Furthermore, the results have a low level of proof because there is no control arm and there may have been recruitment and monitoring bias. The fact that patient management changed between the initial studies and the PROPICE study gives rise to bias in the results.

3.4. Conclusion

Patients with moderate renal insufficiency, defined as creatinine clearance of 20 to 50 ml/min, are at a greater risk of potentially fatal bleeding if they take fondaparinux at a dose of 2.5 mg/d. It is suggested that these patients be given a dose of 1.5 mg/d.

The clinical assessment of this dose was initially based on pharmacokinetic studies (modelling) and four dose-finding studies, all of which were carried out in the context of major lower limb orthopaedic surgery with thrombogenic risk.

GSK has presented the results of a non-comparative cohort study in the context of thromboprophylaxis following lower limb orthopaedic surgery. The objective of this study was to assess the risk of major bleeding (primary endpoint) and antithrombotic efficacy in terms of symptomatic VTEs (secondary endpoint) in adult patients with moderate renal insufficiency being treated with s.c. fondaparinux at a dose of 1.5 mg/d. The risk of major bleeding was higher than expected: 4.5% rather than 2.6% between D0 and D10; the upper limit of its 95% confidence interval was higher than that of 4.2%. All the major bleeding events occurred after the sixth hour.
No clinical data is available for ARIXTRA 1.5 mg's two other indications (prevention in abdominal surgery and for patients with medical conditions).

Historical comparisons have been performed. They suggest that the rate of symptomatic VTE observed in the PROPICE study population taking fondaparinux at a dose of 1.5 mg is similar to that observed in patients taking fondaparinux at a dose of 2.5 mg/d and the other antithrombotics investigated in the phase III studies, and that the risk of bleeding for patients with moderate renal insufficiency taking fondaparinux at 1.5 mg/d is not higher than that expected for patients with normal renal function taking the substance at 2.5 mg/d. In contrast, the two dosages seem to expose patients with renal insufficiency to a fairly similar risk of bleeding. These indirect comparisons are purely exploratory in nature as they are open to selection bias and confusion bias.

The data presented do not allow the performance of fondaparinux at this dosage in these patients to be accurately quantified, and alternative treatments exist.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Venous thromboembolic disease (deep vein thrombosis, pulmonary embolism) can be life-threatening. Pulmonary embolism may cause death, even after implementing anticoagulation treatment; it may recur and cause serious and sometimes disabling complications (chronic venous insufficiency, venous ulcers).

Public health benefit

The public health burden represented by venous thromboembolic disease (VTED) is considerable. Having effective treatments with a low risk of bleeding that help prevent VTED in patients with renal insufficiency (a population at a greater risk of bleeding) is a public health need.

In the light of the data available on the proprietary medicinal product ARIXTRA 1.5 mg/0.3 ml in these patients, and particularly the results of the PROPICE real-life study (non-comparative cohort of patients with moderate renal failure who are also at increased risk of bleeding, the failure to achieve the statistical objective, highly dubious interpretation of results using several indirect comparisons), it is difficult to quantify the additional impact on morbidity and mortality, and particularly on the reduction in occurrence of major bleeding, that this proprietary medicinal product might be expected to have.

It is therefore difficult to ascertain whether or not the proprietary medicinal product ARIXTRA 1.5 mg/0.3 ml can offer an additional response to the identified need. Consequently, in the light of the data available, it is impossible to assess the public health benefit that the proprietary medicinal product ARIXTRA 1.5 mg/0.3 ml might be expected to have.

The efficacy/adverse effects ratio of fondaparinux at the 1.5 mg/d dosage has not been sufficiently assessed.

Practitioners wishing to prescribe thromboprophylaxis for patients with creatinine clearance of 20 to 50 ml/min can consider prescribing an NFH (CALIPARINE) or an LMWH if the patient's creatinine clearance is greater than 30 ml/min (see SPC for LMWHs), or oral dabigatran etexilate (PRADAXA) or rivaroxaban (XARELTO) (for patients who have had a total hip or knee replacement).

The actual benefit of ARIXTRA 1.5 mg must be considered inadequate in the absence of sufficient clinical data.

4.2. Therapeutic use

The objective of prevention of venous thromboembolic disease is to avoid the two complications of pulmonary embolism and post-thrombotic syndrome, while at the same time controlling the occurrence of bleeding. The following medicinal products can be prescribed for patients with moderate renal failure: NFH, LMWH and, for patients undergoing scheduled surgery of the hip or knee, dabigatran etexilate (PRADAXA) and rivaroxaban (XARELTO).

4.3. Recommendations of the Transparency Committee

The Transparency Committee does not recommend inclusion of the proprietary medicinal product 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 various public services.