

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

<u>OPINION</u>

18 April 2007

ARIXTRA 2.5 mg/0.5 ml, solution for injection in prefilled syringe Pack of 2 (CIP: 359 225-4) Pack of 7 (CIP: 359 226-0) Pack of 10 (CIP: 563 619-7)

Applicant: GLAXOSMITHKLINE

Fondaparinux

ATC Code: B01AX05

List I

Date of Marketing Authorisation: March 21, 2002 MA Variation of July 7, 2005 (extension of indication)

Reason for request: Change to the conditions of inclusion.

Inclusion on the list of medicines reimbursed by National Insurance (B/2 and B/7) and approved for use by hospitals (B/2. B/7 and B/10) in the extension of indication: "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".

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Fondaparinux

1.2. Indications

- Prevention of venous thromboembolic events in patients undergoing abdominal surgery who are judged to be at high risk of thromboembolic complications such as patients undergoing abdominal cancer surgery (**extension of indication**).

- Prevention of venous thromboembolic events in major orthopaedic surgery of the lower limb, such as hip fracture, hip replacement or major surgery of knee.

- Prevention of venous thromboembolic events in patients, who are judged to be at high risk of thromboembolic complications 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

Patients undergoing major orthopaedic surgery or abdominal surgery:

The recommended dosage of ARIXTRA is 2.5 mg administered once daily after surgery by subcutaneous injection.

The initial dose must be administered 6 hours after the end of the surgical procedure, 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 for 5 to 9 days after surgery.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2005)

В	Blood and haematopoietic organs
B01	Antithrombotics
B01A	Antithrombotics
B01AX	Other antithrombotic medicinal products
B01AX05	Fondaparinux

2.2. Medicines in the same therapeutic category

Comparator medicines

For initial thromboprophylaxis in patients undergoing abdominal surgery who are judged to be at high risk of thromboembolic complications such as patients undergoing abdominal cancer surgery.

Unfractionated heparins (UFH):

Low molecular weight heparins (LMWH).

INN	Medicinal Product
Dalteparin sodium	FRAGMINE
Nadroparin calcium	FRAXIPARIN
Tinzaparin sodium	INNOHEP
Enoxaparin sodium	LOVENOX

<u>For prolonged thromboprophylaxis</u> in patients undergoing abdominal surgery who are judged to be at high risk of thromboembolic complications such as patients undergoing abdominal cancer surgery, vitamin K antagonists may be prescribed to relay heparin therapy (UFH or LMWH).

2.3. Medicines with a similar therapeutic aim

None.

NB: According to the SFAR¹ guidelines (2005 SPC), elastic compression by wearing graduated compression stockings is recommended in the case of contraindications to anticoagulant treatment (grade A) and in combination with medical treatment (grade B). Intermittent pneumatic compression has not been shown to be effective for major abdominal surgery, which has a high thromboembolic risk (level 3).

¹ SFAR: French Society of Anesthesia and Critical Care Medicine.

Table 1: Wording of the MA of the four LMWH available in France for the prevention of VTED* in general surgery at high thrombogenic risk

LMWH	Dosage of LMWH for surgery at high thrombogenic risk
Fragmine	- Hip and knee surgery:
(dalteparin)	 Dosage is 5000 anti-Xa IU, with a single daily injection. The first injection is given: either 2 hours before surgery using half the dose (2500 anti-Xa IU) and repeating the same dose 12 hours later; or on the evening before surgery using a full dose (5000 anti-Xa IU); the same dose is repeated 24 hours later; Other situations: when the thromboembolic risk is raised because of the type of surgery (in
	same prophylactic dosage may be given as in high-risk orthopaedic surgery (hip, knee). In cancer surgery, dalteparin has an established efficacy at the dosage of 5000 anti-Xa IU per day, according to the same dosage schedule as in orthopaedic hip surgery.
Fraxiparin	- Hip and knee surgery
(nadroparin)	The dosage of nadroparin is adjusted to patient bodyweight and administered in a single daily injection:
	 38 anti-Xa IU/kg: pre-op: 12 hours before surgery; post-op: 12 hours after the completeion of the surgery; and then daily for three days after surgery;
	• 57 anti-Xa IU/kg: From the 4th day after surgery.
	- Other situations: When there is an increased risk of thromboembolism because of the type of surgery (in particular cancer surgery) and/or patient (in particular, past history of thromboembolic disease), a dosage of 2850 IU nadroparin (0.3 ml) is sufficient.
Innohep	- Hip and knee surgery:
(tinzaparin)	• The dosage is 4500 anti-Xa IU, with a single daily injection
	 The treatment regimen comprises a first injection of 4500 anti-Xa IU 12 hours before surgery.
	 Other situations: When there is an increased risk of thromboembolism because of the type of surgery (in particular cancer surgery) and/or patient (past history of thromboembolic disease), a dosage of 3500 anti-Xa IU of tinzaparin (0.3 ml) is required.
Lovenox	- Hip and knee surgery:
(enoxaparin)	The dosage is a single daily injection of 4000 anti-Xa IU (0.4 ml). The studied treatment regimen comprises either a first injection of 4000 anti-Xa IU (total amount) 12 hours before surgery, or a first injection of 2000 IU anti-Xa (half dose) 2 hours before surgery.
	- Other situations: when the thromboembolic risk is raised because of the type of surgery (in

- Other situations: when the thromboembolic risk is raised because of the type of surgery (in particular cancer surgery) and/or patient (in particular history of thromboembolic disease) the same prophylactic dosage may be given as in high-risk orthopaedic surgery (hip, knee).

*VTED - Venous Thromboembolic Disease

ANALYSIS OF AVAILABLE DATA 3

The efficacy and safety of fondaparinux (ARIXTRA 2.5 mg) in the prevention of venous thromboembolic disease (VTED) after abdominal surgery is mainly based² on the results of the PEGASUS study.

3.1. Efficacy

The PEGASUS study³ compared the efficacy and safety of fondaparinux administered subcutaneously at the dosage of 2.5 mg once daily with those of dalteparin administered subcutaneously at the dosage of 5,000 IU once daily in the prevention of VTED (deep vein thrombosis (DVT) and pulmonary embolism (PE)) for 10 days after high-risk abdominal surgery. The initial objective was to show the superiority of fondaparinux compared to dalteparin. As the incidence of VTEE was lower than expected, a non-inferiority analysis was also performed before unblinding. This change in the protocol, made in accordance with European recommendations was discussed by EMEA during the analysis of the registration dossier (ARIXTRA, EPAR⁴ 2005).

Design of the PEGASUS study

This was a randomised double-blind study in parallel groups.

To establish non-inferiority, the non-inferiority margin⁵ was fixed at a value of 1.70 for the odds ratio, corresponding to a value of 70% for the reduction in odds ratio.

Patients were randomised not more than 24 hours before the first injection and not later than 2 hours before the induction of anaesthesia.

To be enrolled, the patients had to be:

- undergoing high-risk abdominal surgery (under general anaesthesia) planned to last longer than 45 minutes from incision to incision closure,
- aged over 60 years with or without any other risk factor for VTE,
- or aged over 40 years and at risk of VTE

Note: obesity (body weight index greater than 30 kg/m² for men and 28.6 kg/m² for women), cancer surgery, history of DVT or EP, NYHA stage III or IV congestive heart failure, COPD or inflammatory bowel disease.

Patients undergoing urological surgery other than renal or gynaecological, laparoscopic or vascular surgery were not enrolled in the study.

The preoperative injection was not given when spinal anaesthesia was planned coupled with general anaesthesia.

² The results of randomised study APOLLO will not be discussed in this opinion. This study was conducted double-blind versus placebo, on two parallel groups of patients, all of whom received thromboprophylaxis by intermittent pneumatic compression (IPC). However, when this trial was started, the US consensus recommended IPC as an alternative to UFH and LMWH within the scope of the prevention of VTED in both moderate and high risk general surgery (Grade 1A; Geerts, 2001). This is no longer the case today (cf. 4.3.: therapeutic strategy).

³ PEGASUS Clinical Study Report, 2004; Agnelli, 2005; Clinical Responses to CHMP Day 90. 2005; ARIXTRA, EPAR 2006.

EPAR: European Public Assessment Report, accessible on the EMEA website.

⁵ The setting of this noninferiority limit was accepted by the European Registration Authorities (for a discussion of its clinical implication see the scientific discussion of the European assessment report - EPAR).

The threshold is defined by the upper limit of the 95% confidence interval (CI) of the odds ratio (OR) or the reduction in the odds ratio between fondaparinux and dalteparin.

The primary efficacy endpoint was the incidence of VTE at 10 days. This was a composite endpoint grouping the following VTEs: asymptomatic DVT detected by systematic phlebography between D5 and D10. symptomatic DVT and fatal or non-fatal PE.

Secondary efficacy endpoints were the incidence of the total DVT, proximal DVT, distal DVT, and symptomatic VTE at D10 as well as the incidence of symptomatic VTE at D32. The composite criterion "symptomatic VTE and death" on D32 was also analyzed.

The primary safety endpoint was the incidence of major bleeding between the first injection of the study medications and two days after the last injection.

Note: Bleeding was defined as major in the following cases:

- Fatal bleeding,
- Bleeding in a critical organ: retroperitoneum, brain, eye, adrenal glands, pericardium, spine,
- Bleeding requiring surgery, or

- Bleeding associated with a bleeding index of 2 or more (defined as the number of units transfused + [haemoglobin (g/dl) before bleeding - haemoglobin (g/dl) after bleeding] in 48 hours following the occurrence of the bleeding).

Results

A total of 2,927 patients were randomised: 2,858 (97.6%) received at least one dose of the study product and were therefore enrolled in the safety analysis, 2,048 (70.0%) were evaluable for the primary efficacy endpoint. The percentage of patients nonevaluable for the primary efficacy endpoint was 30%.

Approximately 97% of the patients had at least two risk factors for VTED; more than 60% of the patients had 3 or more. Surgery for cancer was performed in 67.9% of patients. More than one third of patients underwent spinal anaesthesia.

Thirty three percent of the patients in the dalteparin group did not receive a preoperative injection, mainly because loco-regional anaesthesia was performed.

<u>Table 2:</u> PEGASUS – Duration of study treatments (patients evaluable for safety)

	ARIXTRA 2.5 mg	Dalteparin
	(N=1433)	(N=1424)
Number of days of treatment*		
Median (min-max)	7 (1-10)	7 (1-10)
Mean \pm SD	6.8 ± 1.8	6.9 ± 1.8
Duration of treatment – n (%)		
< 5 days	104 (7.3)	89 (6.3)
Between 5 and 9 days	1319 (92.0)	1323 (92.9)
> 9 days	10 (0.7)	12 (0.8)

*From the first to last day of treatment and without taking into account periods of temporary discontinuation

After discontinuation of the study products, thromboprophylaxis was continued in 38% (526/1384) of patients in the ARIXTRA 2.5 mg group and 38.7% (532/1375) of those in the dalteparin group. In 91.7% of the cases, this treatment consisted of the administration of a LMWH.

The total incidence of VTE was 4.6% (47/1,027) with fondaparinux *versus* 6.1% (62/1,021) with dalteparin; this difference is not significant (p = 0.14). It is mainly due to the reduction in the incidence of asymptomatic distal DVT.

Non-inferiority analysis: the relative reduction in the odds ratio⁶ was -25.8%, 95% CI: [-49.7%, 9.5%]; the upper limit of the 95% CI of the difference between the two groups (fondaparinux *versus* dalteparin) was 9.5%, i.e. lower than the predetermined margin of 70%: demonstrating the non-inferiority of fondaparinux compared to dalteparin.

Other efficacy results:

- In the sub-group of patients operated for cancer (68% of the population), the incidence of VTE was 4.7% (33/696) in patients treated by ARIXTRA 2.5 mg and 7.7% (55/712) in dalteparin-treated patients. The relative risk reduction was 38.6%, (95% CI: 6.7 at 59.7) in favour of ARIXTRA 2.5 mg (p<0.05).

- The incidence of symptomatic DVT was similar in the two treatment groups: 6 patients (0.4%) with fondaparinux *versus* 5 patients (0.3%) with dalteparin.

3.2. Adverse effects

The incidence of major haemorrhage at the end of active treatment (D10) was 3.4% (49/1,433) in the fondaparinux group and 2.4% (34/1,425) in the dalteparin group. For the whole monitoring period, i.e. up to D30, this rate was 4.3% in the fondaparinux group and 2.7% in the dalteparin group.

Severe thrombocytopenia (less than $< 50 \times 10^9$ /l) was rare, with a similar incidence in the two treatment groups.

Platelet count	ARIXTRA 2.5 mg	Dalteparin	
	(N=1421)	(N=1410)	
<100 x 10 ⁹ /l*	49 (3.4)	50 (3.5)	
[50 – 100[x 10 ⁹ /l*	45 (3.2)	42 (3.0)	
<50 x 10 ⁹ /l**	5 (0.4)	8 (0.6)	

Table 3: PEGASUS - Patients with thrombocytopenia during treatment administration

*Patients with a baseline platelet count \geq 100 x 10⁹/l or missing data *Patients with a baseline platelet count > 50 x 10⁹/l or missing data

No heparin-induced thrombocytopenia (HIT) was observed.

⁶ The upper limit of the 95% CI of the odds ratio was 1.10; it was therefore lower than the predetermined noninferiority threshold of 1.70.

3.3. Conclusion

The extension of indication of fondaparinux (ARIXTRA) to the "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" is based on the results of a single study called the PEGASUS study.

This randomised study compared fondaparinux 2.5 mg/day with dalteparin 5.000 IU/day for not more than 10 days in patients undergoing abdominal surgery with a high-risk of venous thromboembolic events.

Efficacy was evaluated using a composite endpoint combining events of different clinical relevance (cf. scientific discussion of EPAR) and collected in only 70% of enrolled cases. Most of the observed events were radiological events (asymptomatic distal VTE).

Both a superiority and a non-inferiority analysis were performed on the study results. These analyses showed that fondaparinux was not more effective than dalteparin at the end of a maximum period of 10 days of thromboprophylaxis. On the contrary, the non-inferiority of fondaparinux compared to dalteparin was demonstrated (cf. EPAR). However, post-hoc subgroup analysis conducted on a solely exploratory basis suggested that fondaparinux may be more effective than dalteparin in the context of cancer surgery (with a particularly high risk of VTED).

Concerning safety (cf. discussion in EPAR), an increased risk of major bleeding with fondaparinux in comparison with dalteparin cannot be excluded, taking into account the incidence of this adverse reaction in the PEGASUS study.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

In the extension of indication "prevention of venous thromboembolic events in patients undergoing abdominal surgery who are judged to be at high risk of thromboembolic complications such as patients undergoing abdominal cancer surgery":

4.1. Actual benefit

Venous thromboembolic disease (deep vein thrombosis, pulmonary embolism) may be life-threatening.

Pulmonary embolism may cause death, including after implementation of anticoagulation; it may recur and cause serious and sometimes disabling complications (chronic venous insufficiency, venous ulcers).

Public Health Benefit

The public health burden of venous thromboembolic disease (VTED) is considerable. In the subpopulation of patients undergoing abdominal surgery and considered to be at high-risk of thromboembolic complications, the burden is moderate.

Thrombocytopenia is an uncommon but serious risk of treatment with unfractionated heparins and in particular low molecular weight heparins. The availability of an anti-thrombotic drug as effective as the usual treatments but not causing this adverse reaction for prophylaxis of VTEs during abdominal surgery in patients at high risk of VTED would meet a unanswered therapeutic need.

Taking into account existing treatments and according to the clinical trial data, the only expected public health benefit of ARIXTRA is a reduction in the occurrence of HIT. The absence of a need for platelet monitoring may also have a positive impact on healthcare organisation.

In practice, prolonged thromboprophylaxis (more than 10 days of treatment) should be considered in most patients concerned by this extension of indication (cf.: French and international guidelines). In the PEGASUS study, more cases of major bleeding were observed in the fondaparinux group that in the dalteparin group for the whole duration of the study. Since no evaluation was performed after prolonged thromboprophylaxis, the possibility that ARIXTRA increases the risk of bleeding cannot be ruled out. Therefore it is not expected that ARIXTRA will benefit public health in this extension of indication.

The efficacy/adverse effects ratio of fondaparinux is high

ARIXTRA is used for first-line therapy. There are alternative treatments: unfractionated heparins and low molecular weight heparins for initial thromboprophylaxis (7 to 10 days).

Conclusion: The actual benefit of ARIXTRA 2.5 mg in this extension of indication is substantial

4.2. Improvement in actual benefit

ARIXTRA 2.5 mg/0.5 ml, solution for injection in pre-filled syringes does not improve the actual benefit (IAB V) compared to dalteparin, the LMWH tested in the PEGASUS study in the indication "prevention of venous thromboembolic events in patients undergoing abdominal surgery who are judged to be at high risk of thromboembolic complications such as patients undergoing abdominal cancer surgery".

Taking into account the currently available data and its action mechanism (biological plausibility), ARIXTRA does not seem to be associated with a risk of occurrence of immunoallergic thrombocytopenia. However an increased risk of major bleeding with fondaparinux in comparison with dalteparin cannot be excluded in the PEGASUS study as the duration of thromboprophylaxis was often less than 10 days. However, thromboprophylaxis will most certainly be prescribed for more than 10 days in most of these patients, particularly in those treated for cancer.

4.3. Therapeutic use

The objective of prevention of venous thromboembolic disease is to avoid the two complications of pulmonary embolism and post-thrombotic syndrome.

What is the risk of occurrence of a venous thromboembolic event after "high-risk" abdominal surgery?

In major abdominal surgery (liver, pancreas, colon, inflammatory or neoplastic disease of the gastrointestinal tract), the incidence of thrombosis estimated by paraclinical investigations, in the absence of prevention, is evaluated to be between 20 and 40% for distal deep vein thromboses (the clinical significance of which is still controversial), and from 3 to 8% for proximal thromboses. The incidence of symptomatic pulmonary embolism is from 1.5 to 4% and that of fatal pulmonary embolism is from 0.4 to 1% (cf. SFAR⁸, ACCP⁹ guidelines). In carcinological abdominal surgery, the thromboembolic risk is even higher with an incidence of fatal embolism of 3% in patients after colorectal surgery.

Recommended prevention strategy

The international (ACCP, 2004) and national guidelines (SFAR, 2005) recommend first-line treatment with an anticoagulant at preventive doses, combined with a non-pharmacological prophylactic method.

The value of standard heparin therapy (reduction of mortality; A.N. Nicolaides; J vasc Br 2002) and LMWH is established in surgical situations with a high thrombogenic risk.

UFH and LMWH are the medicinal products currently recommended for the prevention of VTED in patients undergoing high-risk abdominal surgery.

Experts at the seventh consensus conference of the ACCP (American Board of Chest Physicians) on the use of antithrombotic treatments, recommended prophylaxis with UFH (at the dose of 5000 IU three times daily) or LMWH at doses appropriate for a high risk (level of evidence 1A for the 2 options) (Geerts, 2004).

SFAR experts recommended LMWH rather than UFH, in the absence of renal insufficiency, for reasons of efficacy, safety and ease of use (grade A) (SFAR, 2005). LMWH dosages appropriate for high risk situations are recommended in major abdominal surgery (grade A).

⁸ "Prévention de la maladie thromboembolique veineuse périopératoire et obstétricale". Clinical practice guidelines (CPG), French Society of Anesthesia and Critical Care Medicine - SFAR 2005.

^g Geerts W.H. et al. Prevention of venous thromboembolism: the seventh ACCP Conference on antithrombotic and thrombolytic therapy. Chest 2004;126:338s-400s.

Therapeutic use of fondaparinux for thromboprophylaxis

Fondaparinux (ARIXTRA 2.5 mg) represents an alternative to the prescription of dalteparin (FRAGMINE) within the scope of **initial thromboprophylaxis lasting from 7 to 10 days** in abdominal surgery at high-risk of VTED.

What is the recommended duration of thromboprophylaxis?

According to SFAR 2005 guidelines, **prolonged thromboprophylaxis** is recommended in major abdominal carcinological surgery (grade A).

Since these guidelines were published, a study¹⁰ compared the prevention of thromboembolic complications by dalteparin in patients undergoing major abdominal surgery (60% for cancer) with short-lasting prophylaxis (8 days) *versus* prolonged prophylaxis (30 days). Prolonged prophylaxis reduced the total number of thromboembolic events (16.3% *versus* 7.3%) and proximal venous thromboses (8% *versus* 1.8%), without a significant increase in bleeding.

Taking into account these data, patients will probably receive prolonged treatment in practice. However the PEGASUS study data comparing fondaparinux with dalteparin were limited to 10 days. The pertinence of prescribing fondaparinux (ARIXTRA) for 30 days may be doubted as during the PEGASUS study, the risk of bleeding was increased at D30 in comparison with dalteparin.

Strategy in the case of locoregional anaesthesia

In the case of locoregional anaesthesia, there is a risk of complications associated with the administration of an antithrombotic drug.

According to the SFAR guidelines, the medical benefit of initiating prophylaxis after the intervention has not been investigated and there is no evidence in favour of either approach.

According to expert opinion, spinal anaesthesia may be given under both ARIXTRA and LMWH (initial administration after surgery).

Other treatments

Elastic compression is recommended in the case of contraindication to anticoagulants (grade A) and in combination with medical treatment (grade B) (SFAR, 2005).

¹⁰ Rasmussen M. S. et al. Prolonged prophylaxis with dalteparin to prevent late thromboembolic complications in patients undergoing major abdominal surgery: a multicenter randomised open-label study. Journal of Thrombosis and Haemostasis 2006;4(11):2384-2390

4.4. Target population

4.4.1 Definition

The target population is defined by patients undergoing abdominal surgery and considered to be at high-risk of venous thromboembolic complications.

4.4.2 Estimation of the target population

The target population may be estimated using the data obtained from the public and private hospital medical information database in 2005.

Two approaches may be used for the calculation: according to SFAR guidelines or on the basis of the PEGASUS study inclusion criteria.

According to SFAR guidelines

The SFAR:

- considers that the risk of thromboembolism is high in the following types of surgery:

- major abdominal surgery: liver, pancreas, colon, inflammatory or neoplastic disease of the gastrointestinal tract,

- bariatric surgery.

- recommends thromboprophylaxis with moderate doses for non-major abdominal surgery (parietal surgery, appendix, noninflammatory gall bladder, proctology) when there is a patient-related risk.

Patient-related risk factors are as follows:

- Immobility, confinement to bed, paralysis of limbs,
- Cancer and cancer therapy,
- History of VTE,
- Age > 40 years,
- Oral contraception with oestrogens or hormone replacement therapy,
- Oestrogen receptor modulator treatments,
- Acute disease,
- Heart failure, respiratory failure,
- Inflammatory bowel disease,
- Nephrotic syndrome,
- Myeloproliferative syndrome,
- Nocturnal paroxysmal haemoglobinuria,
- Obesity (body mass index < 30 kg/m2),
- Smoking.
- Varicose veins,
- Central venous catheter,
- Congenital or acquired thrombophilia.

<u>Table 4:</u> Number of stays for major abdominal surgery or non-major abdominal surgery but with a risk factor according to SFAR criteria

Major abdominal surgery	91,527
Bariatric surgery	15,341
Non-major abdominal surgery with risk factor	36,183
Total	143,051

According to the inclusion criteria of the PEGASUS study

The inclusion criteria of the PEGASUS study were as follows:

High-risk abdominal surgery with a planned duration of more than 45 minutes, under general anaesthesia and the following criteria:

- Age over 60 years,
- Age over 40 years with at least:
 - $BMI > 30 \text{ kg/m}^2$,
 - Undergoing cancer surgery,
 - History of DVT or PE,
 - Grade III or IV (NYHA) congestive heart failure,
 - Chronic obstructive pulmonary disease,
 - Inflammatory bowel disease.

<u>Table 5:</u> Number of stays for major abdominal surgery with a risk factor according to the PEGASUS study inclusion criteria

Major abdominal surgery (age over 60 years)	59,098
Abdominal surgery (between 40 and 60) with risk factor	40,840
Total	99,938

<u>Overall</u>, the target population of ARIXTRA may be estimated to be between 100,000 and 143,000 stays per year in France for criteria derived from the SFAR guidelines or PEGASUS study respectively. This population is probably underestimated.

4.5. Committee Recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance (B/2 and B/7) and on the list of medicines approved for use in hospitals and various public services (B/2. B/7 and B/10) in the extension of indication "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" and at the posology in the Marketing Authorisation.

Packaging: Appropriate for the prescription conditions

Reimbursement rate: 65%