HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

11 June 2008

ARIXTRA 2.5 mg/0.5 m, solution for injection in pre-filled syringe
Pack of 10 (CIP: 563 619-7)

Applicant: GlaxoSmithKline

Fondaparinux sodium
ATC code: B01AX05

List I

Date of initial marketing authorisation (MA): 21 March 2002

(centralised European registration procedure)

MA variation of the extension of indication: 29 August 2007

Reason for request: Inclusion on the list of medicines approved for use by hospitals and various public services in the extension of indication: "**Treatment of ST segment elevation myocardial infarction (STEMI) in patients who:**

- **are managed with thrombolytics or**
- **initially are to receive no other form of reperfusion therapy"**.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1 Active ingredient

Fondaparinux sodium[1]

1.2. Indications

"- Prevention of venous thromboembolic events in patients undergoing major orthopaedic surgery of the lower limbs such as hip fracture, major knee surgery or hip replacement surgery.
- 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 (see section 5.1).
- Prevention of venous thromboembolic events (VTE) in 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 patients for whom urgent (< 120 min) invasive management (percutaneous coronary intervention: PCI) is not indicated" (see sections 4.4 and 5.1).
- Treatment of ST segment elevation myocardial infarction (STEMI) in patients who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy".

1.3. Dosage in the treatment of ST segment elevation myocardial infarction (STEMI)

- The recommended dose of fondaparinux is 2.5 mg once daily.
The first dose of fondaparinux is administered intravenously and the following doses subcutaneously.
Treatment should be initiated as soon as possible following diagnosis and continued for up to a maximum of 8 days or until hospital discharge if that occurs earlier.

Administration of fondaparinux in specific populations/situations
- Concomitant treatment with other agents likely to increase bleeding risk, such as GPIIb/IIIa receptor antagonists or thrombolytics for the treatment of UA/NSTEMI and STEMI: fondaparinux must be used with precaution (increased risk of bleeding).

- <u>Renal impairment</u>:
    - Fondaparinux is mainly eliminated by the kidney. Fondaparinux should not be used in patients with a creatinine clearance <20 ml/min. No dosage reduction is required for

1 At the 2.5 mg dose, Arixtra does not affect routine coagulation tests such as activated partial thromboplastin time (aPTT), activated clotting time (ACT) or prothrombin time (PT)/International Normalised Ratio (INR) tests in plasma, or bleeding time or fibrinolytic activity. Fondaparinux does not cross-react with sera from patients with heparin-induced thrombocytopenia.

patients with creatinine clearance > 20 ml/min when the product is administered for the treatment of acute coronary syndrome.

- Patients whose creatinine clearance is < 50 ml/min have an increased risk of bleeding and should be treated with caution.
- There are limited clinical data available on the use of fondaparinux 2.5 mg once daily for treatment of UA/INSTEMI and STEMI in patients with a creatinine clearance between 20 and 30 ml/min. Therefore the physician should determine if the benefit of treatment outweighs the risk.

- Elderly patients and/or low-weight subjects
  - The elderly population is at increased risk of bleeding. As renal function is generally decreasing with age, elderly patients may show reduced elimination and increased plasma fondaparinux concentrations. Fondaparinux should be used with caution in these patients.
  - Patients with a body weight < 50 kg are at increased risk of bleeding. Elimination of fondaparinux decreases with weight. Fondaparinux should be used with caution in these patients.

2. SIMILAR MEDICINAL PRODUCTS

2.1 ATC Classification (2007):

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

2.2 Medicines in the same therapeutic category

- Low molecular weight heparins (LMWH): enoxaparin (LOVENOX).
- Unfractionated heparins (UFH): CALCIPARIN and Heparin sodium CHOAY.

2.3 Medicines with a similar therapeutic aim

Adjuvant treatments for reperfusion (by fibrinolytic therapy or primary coronary angioplasty) to be instituted for ST segment elevation acute coronary syndrome:

- Medicines used to prevent the extension of a coronary thrombus that has already formed or an excessive thrombotic reaction induced by pre-hospital thrombolysis or coronary angioplasty: aspirin +/- clopidogrel.
- *"Glycoprotein IIb/IIIa antagonists[2] should not be used either as monotherapy, as they lack efficacy, or in combination with fibrinolysis, due to increased risk of bleeding (grade B). Their use during the acute phase of STEMI should only be attempted before primary angioplasty. Their benefit/risk ratio during the pre-hospitalisation phase, in combination with clopidogrel, is not known. The recommended molecule is abciximab at the dosage of 250 µg/kg intravenously (IV) followed by continuous IV infusion of 0.125 µg/kg/min up to a maximum of 10 µg/min".*

NB:
- The indication of ANGIOX (bivalirudin) is: "Anticoagulant in patients undergoing percutaneous coronary intervention (PCI)".
- Fibrinolytics:
  - *Fibrin-specific fibrinolytics: ACTILYSE[3] (alteplase), RAPILYSIN (reteplase)*
  - *Non-fibrin specific fibrinolytics: STREPTASE (streptokinase), ACTOSOLV UROKINASE (urokinase).*

[2] Consensus Conference. Management of Acute Myocardial Infarction outside Cardiology Departments. French Emergency Medical Services (SAMU) with the methodological partnership and financial assistance of the HAS (National Health Authority); 6 February 2007

[3] ACTILYSE indication: "Thrombolytic treatment in acute myocardial infarction. An "accelerated" dose regimen (90 minutes) is intended for patients in whom treatment can be started within 6 h of the onset of symptoms. A "3 h" dose regimen is intended for patients in whom treatment can be started 6 - 12 h after the onset of symptoms provided that the diagnosis has been clearly confirmed. Alteplase makes it possible to reduce the mortality rate 30 days after a myocardial infarction". In a study (GUSTO) including more than 40,000 patients with acute myocardial infarction, the administration of 100 mg alteplase over 90 minutes, with concomitant IV heparin infusion, led to a lower mortality after 30 days (6.3 %) compared to the administration of streptokinase (1.5 million U over 60 minutes) and SC or IV heparin (7.3 %). Actilyse-treated patients showed higher infarct related vessel patency rates at 60 and 90 minutes after thrombolysis than the streptokinase-treated patients. No differences in patency rates were noted at 180 minutes or longer. Thirty-day mortality is reduced compared to patients not undergoing thrombolytic therapy. The release of alpha-hydroxybutyrate-dehydrogenase (HBDH) is reduced. The impairment of global ventricular function and regional wall motion is lower than in patients not receiving thrombolytic therapy. In addition, a placebo controlled trial with 100 mg alteplase administered over 3 hours (LATE) showed a reduction of 30-day mortality compared to placebo for patients treated 6-12 hours after symptom onset. In cases in which clear signs of myocardial infarction are present, treatment initiated up to 24 hours after symptom onset may still be beneficial.

3. ANALYSIS OF AVAILABLE DATA

Introduction

ARIXTRA 2.5 mg (fondaparinux) was granted an MA for use during the acute phase of myocardial infarction (MI: ST+ ACS) mainly on the basis of results obtained during a single comparative clinical study ("OASIS-6"). The registration file[4] also comprised a dose-finding study (PENTALYSE study) and two phase II studies (ASPIRE and ACT2445), which evaluated the tolerance of an IV bolus dose of fondaparinux as adjuvant therapy for percutaneous coronary intervention (or coronary angioplasty). The dosage of ARIXTRA in OASIS-6 was 2.5 mg once daily; the PENTALYSE study did not evaluate this dosage in this indication.

3.1 Summary of the OASIS 6 study

Objective of the OASIS-6 study: to show the superiority of ARIXTRA 2.5 mg for preventing death or reinfarction at 30 days in comparison with a control treatment. The control treatment was either unfractionated heparin (UFH) anticoagulation or a placebo (UFH/placebo control group).

Design

Patients were managed according to the investigator's usual practices: reperfusion therapy by angioplasty or thrombolysis or no reperfusion in the case of contraindication and/or ineligibility.

Inclusion criteria: adults with characteristic ECG signs and symptoms[5] of STEMI. Patients were randomised within 12 hours, instead of 24 hours, following an amendment to the protocol.
Insulin-dependent diabetes mellitus and severe renal insufficiency (serum creatinine concentrations > 3 mg/dL or > 265 µmol/L) were exclusion criteria.

Primary endpoint: composite endpoint[6] of death and reinfarction at 30 days.

Several secondary endpoints, including:
- Efficacy endpoints at D9, D30, D90 and D180: all-cause death, cardiovascular death, reinfarction, stroke and several composite endpoints associating death +/- reinfarction +/- stroke +/- refractory ischaemia were evaluated.
- Tolerance endpoints: in particular incidence of severe and minor bleeding events[7] at different times: D9, D30, D90 and D180.

4 See on the EMEA (European drug agency) website: "Scientific Discussion no. ARIXTRA-H-403-II-24".
5 Electrocardiographic signs: persistent ST-segment elevation of at least 2 mm in two contiguous precordial leads, or at least 1 mm in two standard leads or *de novo* left bundle branch block, or electrocardiographic changes showing a posterior infarct and capable of being randomised within 12 hours of the onset of symptoms (*within 24 hours of the start of the OASIS-6 study* [22 August 2003] in amendment no. 4 [16 December 2004]).
6 The following assumptions were made for the sample size calculation: a composite endpoint frequency at D30 of 12% in the control group, extrapolated from the results of the ASSENT-3 (The Assent-3 investigators, 2001) and CREATE (The CREATE Trial Group Investigators, 2005) studies; a risk reduction of 15% in the ARIXTRA group and a power of 84% (alpha risk of 0.05).
7 Definition of bleeding events: a major bleeding event was defined by at least one of the following characteristics: fatal bleeding or clinically significant intracranial bleeding or pericardial tamponade with a drop in haemoglobin of at least 5 g/dl (according to the modified TIMI definition Cannon, 2001) or retroperitoneal bleeding or intraocular bleeding (associated with a significant loss of vision) requiring surgery or associated with a fall in blood haemoglobin requiring a blood transfusion of more than 3 g/dL or with a transfusion of more than two units of blood.

Study design/protocol: double-blind, double-placebo, comparative study in two parallel groups evaluating fondaparinux versus UFH or placebo (Strata 1 and 2).

The investigator assigned the patients to the two Strata based on the following:
- whether or not they were treated with a thrombolytic;
- how their treatment was being managed (choice of fibrinolytic treatment, no reperfusion, choice of reperfusion technique). The study was stratified at the discretion of the investigator choice.

Stratum 1 or 2 at the investigator's discretion [8] (indication for UFH optional):
- patients not undergoing reperfusion (because seen too late or absolute contraindication)
- patients being treated with a non-fibrin specific thrombolytic (streptokinase, urokinase) before randomisation or requiring treatment with a non-fibrin specific thrombolytic.

Stratum 2:
- patients being treated with a fibrin-specific thrombolytic (alteplase, reteplase, tenecteplase) before randomisation or requiring treatment with a fibrin-specific thrombolytic
- patients undergoing a primary coronary intervention (PCI).

The comparator was different in the two Strata:
- In Stratum 1: fondaparinux was compared with a placebo.
- In Stratum 2: fondaparinux was compared with an anticoagulant (UFH).

All patients had to receive aspirin.

Dosage of evaluated treatments:
- Fondaparinux 2.5 mg IV and then SC. The duration of treatment was up to 8 days.
- UFH in a slow IV bolus dose adjusted according to activated cephalin time (target ACT 1.5 to 2[9]). The duration of treatment was 1 to 2 days.

- In the case of primary angioplasty (PCI) (vascular access site determined at the investigator's discretion):
The bolus doses of fondaparinux 2.5 mg or 5 mg and UFH (65 or 100 UI/kg) were adjusted based on GP IIb/IIIa inhibitor use and, depending on whether or not the patient had received UFH (dose < 5.000 U) before randomisation, based on the ACT.
- In the case of rescue PCI:
Study treatments were discontinued before the procedure. PCIs were performed according to local practice with open-label UFH use. The use of GP IIb/IIIa inhibitors was determined at the investigator's discretion. If rescue PCI was conducted less than 24 hours after the last injection of fondaparinux/placebo or less than three hours after the discontinuation of UFH/placebo infusion, the patient had to be unblinded.
- In the case of elective PCI after randomisation:

- A bleeding event was considered to be minor if it was associated with a fall in blood haemoglobin concentration > 3.0 g/dL and ≤ 5.0 g/dL (according to the modified TIMI definition) or if it required discontinuation of the study treatment for at least 24 hours or transfusion of one unit of blood.

[8] GSK specified that the investigator's choice depended on his/her estimation of the lack of the need for UFH treatment (on the basis of management strategies recommended by international European and North-American consensuses in force at the time of the OASIS-6 study design (van of Werf, 2003; Antman, 2004). The patients for whom the investigator considered the prescription of UFH to be necessary were in stratum 2.

[9] UFH dose: 60 IU/kg (maximum 4 000 IU), followed by a continuous infusion with the dose adjusted according to changes in activated cephalin time.

The procedure was delayed, if possible, until 24 hours after the last injection of fondaparinux/placebo and 3 hours after discontinuation of the UFH/placebo infusion. Open-label administration of UFH and GP IIb/IIIa inhibitors took place according to local practice.

Results

Patients were monitored for 90 to 180 days.

OASIS-6 is an international (42 countries) multicentre study.

Remarks: Russia (16.7%), China (12.4%) and India (11.7%) were the countries that contributed most to patient recruitment and 47.5% of patients came from Eastern Europe. This geographical criterion must be taken into account insofar as the availability and organisation of healthcare may vary considerably from country to country (with respect to access to angioplasty and time to treatment after onset of first symptoms).

Evaluated populations

- A total of 12,092 patients received treatment assigned by randomisation:
  - 6,036 received ARIXTRA (Stratum 1: 2,823 and Stratum 2: 3,213)
  - 6,056 received the comparator **(**Stratum 1 [placebo])**:** 2,835 and Stratum 2 [UFH anticoagulant]: 3,221).
- The two treatment groups were similar at baseline.
- More than half (53%) of the patients were included in Stratum 2 (ARIXTRA versus UFH).
- 40% of Stratum 1 patients and 68% of Stratum 2 patients received a thienopyridine (clopidogrel) during their hospital stay.

Management procedures

Distribution of patients according to choice of reperfusion strategy* in OASIS-6:

	Total population 12,092 patients	**Stratum 1 (placebo)** 5,658 patients 47% of included patients	**Stratum 2 (UFH)** 6,434 patients, 53% of included patients
Primary angioplasty	3,798 patients 31%	17 patients 0.3%	3,781 patients 59%
Thrombolysis Type of thrombolytic: - Fibrin-specific: - Non-fibrin specific**:**	**5,437 patients** **45%**	**4,415 patients** **78%** - 99,6%	**1,022 patients** **16%** - 83,4%
No reperfusion	**2,857 patients** **24%**	**1,226 patients** **22%**	**1,631 patients** **25%**

* Data provided by GSK.

Primary endpoint:
- Fondaparinux reduced the risk of occurrence of an event of the composite endpoint of death/reinfarction at D30 by 14% compared to the UFH/placebo control group.

Results for the primary endpoint at 30 days in the total population

	Fondaparinux (6,036 patients)	UFH or placebo (6,056 patients)
Death/reinfarction at D30	584 (9.7%)	675 (11.1%)
	RR: 0.86 CI_{95}: 0.77 to 0.96 p = 0.008 14% reduction of RR	

- The results per Stratum were as follows:

Results for the primary endpoint at 30 days in Stratum 1

	fondaparinux (2,823 patients)	**placebo** (2,835 patients)
Death/reinfarction at D30	318 (11.3%)	396 (14.0%)
	RR: 0.80 CI_{95}: 0.69 to 0.93 p = 0.003 20% reduction of RR	

Results for the primary endpoint at 30 days in Stratum 2

	fondaparinux (3,213 patients)	**UFH** (3,221 patients)
Death/reinfarction at D30	266 (8.3%)	279 (8.7%)
	RR: 0.94 CI_{95}: 0.79 to **1.11** **no reduction of RR**	

- It should be underlined that the median duration of fondaparinux treatment was 7 days and that of UFH treatment was 2 days.

Overall, ARIXTRA 2.5 mg was more effective than the placebo in preventing death and reinfarction up to D30. However, no difference was demonstrated versus UFH.
ARIXTRA 2.5 mg obtained an indication in two OASIS-6 trial sub-populations: patients managed with thrombolytics and those not receiving emergency reperfusion therapy.
Remarks: it should be noted that no difference was demonstrated between fondaparinux and UFH in the thrombolysis sub-group of Stratum 2 patients and that thrombolysis was mainly performed in Stratum 1 patients, where fondaparinux was compared with a placebo.

Secondary endpoints (for information purposes)
Of the multiple measurements made (at D9, D30, D90 and D180), it should be noted that mortality was reduced with fondaparinux when compared with the placebo (Stratum 1)

except at D180 in the UFH/placebo control group. However, no difference was demonstrated with UFH (Stratum 2). The multiplicity of measures and the fact that this was a secondary endpoint make it difficult to interpret these results.

3.2 Tolerance

The tolerance of fondaparinux 2.5 mg was evaluated in 6,036 patients (and in 10,057 patients treated for UA or non-ST segment elevation acute coronary syndrome [Non-ST ACS]).

Bleeding risk
The incidence of major bleeding events appeared to be similar in patients of the ARIXTRA 2.5 mg group and in those of the control group (from D9 to D180).
- The incidence of bleeding events considered to be severe according to the modified TIMI criteria was 1.1% with fondaparinux 2.5 mg and 1.4% with UFH or placebo up to and including D9.
In Stratum 1, this incidence was 1% in the ARIXTRA 2.5 mg group and 1.6% in the placebo group (safety population). In Stratum 2, this incidence was 1.1% in the ARIXTRA 2.5 mg group and 1.2% in the UFH group (tolerance population).
- In patients who underwent non-primary PCI 6-24 hours after the last injection of fondaparinux, the median dose of UFH was 8,000 IU and the incidence of major bleeding was 2% (2/98).
- In patients who underwent PCI < 6 hours after the last dose of fondaparinux, the median dose of UFH was 5,000 IU and the incidence of major bleeding was 4.1% (2/49).
In both cases, this PCIs were performed as rescue procedures after thrombolysis failure.

Risk of guiding catheter thrombus
- Clinical studies demonstrated a low but increased risk of guiding catheter thrombus in patients receiving fondaparinux as an anticoagulant during primary PCI when compared with the control group.

In STEMI patients undergoing primary PCI, the use of fondaparinux prior to and during PCI is not recommended.
In STEMI patients undergoing non-primary PCI, the use of fondaparinux as single anticoagulant during PCI is not recommended. There is limited data on the use of UFH during non-primary PCI in patients treated with fondaparinux. Consequently, UFH should be used according to local medical practices.

NB: For non-primary PCI in UA/NSTEMI patients, the incidences were 1.0% vs. 0.3% respectively (fondaparinux vs. enoxaparin), whereas they were 1.2% vs. 0% respectively (fondaparinux vs. control group) for primary PCI in STEMI patients.

3.3 Remarks on the results of the OASIS-6 study:

Interpretation of the endpoint
The sample size was not calculated to establish the superiority of fondaparinux 2.5 mg in each Stratum. Given the difference in the control group comparators (an anticoagulant or a placebo), the homogeneity of the therapeutic effect between the two Strata is conceptually open to question. The results of the homogeneity test between Strata 1 and 2 should be interpreted with caution (lack of power). It should be noted that mortality in OASIS-6 was higher among Stratum 1 patients than among Stratum 2 patients.

Treatment modalities and choice of comparators
- Management without immediate reperfusion is a possible therapeutic alternative in certain patients at high risk of complications (e.g., diabetics and very elderly subjects) and in whom treatment with aspirin and clopidogrel, without early reperfusion, is acceptable (see results of the ISIS-2 and COMMIT studies). However, care must be appropriately organised to attempt to reduce as much as possible the number of the patients who are “seen too late”.
- The proportion of patients not undergoing immediate reperfusion was comparable between the two Strata (approximately 1 in 4). In patients who were not reperfused, the choice of placebo as comparator rather than fondaparinux is questionable. Moreover, some of these patients (those seen more than 3 hours after the symptom onset) could have undergone primary angioplasty rather than have had no reperfusion, in accordance with practices in Western Europe in general, and France in particular.

Transposability of the OASIS-6 results to clinical practice
- The issue of the transposability of the OASIS-6 results mainly concerns the population of patients in whom treatment is given earliest. For this population, angioplasty is performed more frequently and more often using the radial approach (which reduces the risk of bleeding), and fibrin-specific thrombolytic therapy is recommended (HAS, or French National Health Authority, 2005) and largely prescribed (as it reduces the risk of bleeding compared to streptokinase).
In OASIS-6:
- Only 53% of patients received an UFH (compared to 85% in the European registry: see EPAR).
- Thrombolytic therapy was used in less than one out of every two patients. It was mainly used in patients in Stratum 1, where fondaparinux was compared with placebo.
- Streptokinase (non-fibrin specific) was the thrombolytic agent prescribed most often (in 72% of thrombolysis patients). Moreover, the type of thrombolytic agent differed for Stratum 1 and Stratum 2 patients: “non-fibrin specific” in Stratum 1 patients and “fibrin-specific” in Stratum 2 patients. The extent of the thrombolytic effect varied depending on the type of thrombolytic used.
- Thrombolysis was carried out beyond the first 3 hours in more than half the patients, but its efficacy was optimal during these first 3 hours.
- Only 1/3 of patients underwent emergency primary angioplasty. Nearly all the patients managed with primary angioplasty were included in Stratum 2 (99.6%).

3.4 Conclusion

According to the results of the OASIS-6 study conducted in 12,092 patients in the acute phase of ST segment elevation myocardial infarction (STEMI) treated with emergency reperfusion by angioplasty or thrombolysis, or without emergency reperfusion therapy, ARIXTRA at a dosage of 2.5 mg/day prescribed for a median duration of 7 days was more effective than an unfractionated heparin (UFH) control prescribed for a median duration of 2 days or a placebo in reducing the occurrence of a first event (death or reinfarction) in the 30 days after inclusion.

The extent of this effect was moderate with a 14% reduction in relative risk and an absolute benefit of less than 2%. This benefit was related to a relative reduction in mortality of 13% and reinfarction of 19% at 30 days.

The occurrence of major bleeding events was similar in patients treated with fondaparinux 2.5 mg/day or UFH at a dosage complying with current practice. Compared to placebo (Stratum 1), fondaparinux was associated with fewer severe bleeding events.

According to several exploratory sub-group analyses, the effect in favour of fondaparinux was not demonstrated, in particular at 30 days, in patients:

- undergoing immediate angioplasty (the optimum management for eligible patients) and
- who received an UFH in the case of thrombolysis.

The study was not powerful enough to allow conclusions to be drawn on the efficacy of ARIXTRA 2.5 mg compared to an UFH in the case of thrombolysis (Stratum 2 patients). The comparison between these two anticoagulants in thrombolysed patients in the two Strata is unsound, in particular given the wide variations in the implemented treatments and the differences in sample sizes (most thrombolysis patients were included in Stratum 1).
Concerning the patients not undergoing reperfusion therapy, the same reservations regarding the interpretation of the results apply.
In addition, the choice of comparators poorly reflects current cardiology practices.

Concordant efficacy and tolerance results were obtained in predefined sub-groups such as elderly subjects, patients with renal impairment, and patients receiving concomitant treatment with platelet aggregation inhibitors (aspirin, thienopyridine).

Since the publication of the results of the CLARITY[10] and COMMIT[11] studies validating the use of clopidogrel in combination with aspirin[12], the benefit of combining aspirin, clopidogrel and ARIXTRA with fibrinolysis has not been established (NB: the proportion of patients treated with this combination represented nearly 40% in Stratum 1 and nearly 67% in Stratum 2).

Overall, the results of the OASIS-6 study established that ARIXTRA 2.5 mg was more effective in reducing the incidence of ischaemic complications than a placebo in patients thrombolysed with a nonspecific fibrinolytic and that an anticoagulant (UFH or fondaparinux) could be prescribed in the case of non-reperfusion**.** However questions may be raised about the transposability and clinical interpretation of the OASIS-6 results:

1- The transposability of these results to a French setting may be questioned in particular since the speed of treatment implementation, which depends on healthcare organisation, strongly affects the expected reduction in mortality.

2- The thrombolytic prescribed in OASIS-6 was a non-fibrin specific agent. However, in France, specific thrombolytic agents are recommended and preferentially prescribed.

3- The validity of the assessment of the clinical benefit of ARIXTRA for the total population is questionable since the clinical results for patients receiving different treatments - an active comparator (UFH) or a placebo - were grouped together. This is especially so since the superiority of ARIXTRA in comparison with an UFH (Stratum 2) was not demonstrated after 30 days on the primary endpoint in the total population (because of the unfavourable result in the sub-group of patients who underwent angioplasty) or in the population of the patients treated by thrombolysis alone.

10 Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med* 2005; 352:1179-89

11 COMMIT collaborative group. Addition of clopidogrel to aspirin in 45 852 patients with acute myocardial infarction: randomised placebo-controled trial. *Lancet* 2005; 366:1607-21

12 See the Transparency Commission's opinion of 6 June 2007 on PLAVIX (clopidogrel) in this indication.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

In the extension of indication to include “treatment of ST segment elevation myocardial infarction (STEMI) in patients who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy”:

4.1 Actual Benefit

All acute coronary syndromes require emergency management by a specialised team. An electrocardiogram (ECG) must be performed in order to identify myocardial infarction requiring emergency reperfusion therapy to restore patency to the coronary artery. ARIXTRA 2.5 mg is indicated in the acute phase of ST-segment elevation myocardial infarction: these infarcts, known as STEMIs, are associated with the total occlusion of a coronary artery. These patients must therefore undergo emergency reperfusion in order to reduce the risk of death or reinfarction in particular. Coronary reperfusion is obtained by angioplasty (“mechanical” cardiological interventions or percutaneous coronary interventions - PCI) or by fibrinolysis (medical treatment; IV thrombolysis). These serious clinical conditions are life-threatening.

ARIXTRA 2.5 mg is indicated in the acute phase of STEMI:
- Either as adjunctive therapy to fibrinolysis (the aim of this treatment is to prevent the re-occlusion of the coronary artery after fibrinolysis and to prevent a worsening of the infarction)
- Or in patients not undergoing early coronary reperfusion.
It is then the drug of first choice.

What are the alternative medications?
- In case of thrombolysis, enoxaparin (LOVENOX) is recommended by the HAS (2006) in subjects under 75 years of age who have no renal impairment, or an unfractionated heparin (alternative therapy) is recommended in other settings.
- In the case of primary angioplasty, the prescription of a UFH is recommended.
- A UFH may be prescribed in patients not undergoing early reperfusion.

Public health benefit:
Ischaemic heart disease is a major public health burden. The burden of STEMI eligible for thrombolytic treatment or in patients not able to receive other reperfusion therapy can be considered less substantial because of the smaller number of patients concerned.
The improvement of secondary MI prevention still constitutes a public health need.
A review of the available data (and of the results of the OASIS 6 study in particular) shows that no additional impact in terms of morbidity and mortality is expected with this proprietary medicine compared to the existing therapies (UFH, LOVENOX).
Furthermore, there is no guarantee that the results of the OASIS 6 study can be extrapolated to real-life practice for the following reasons:
- This study does not make it possible to assess the impact of ARIXTRA on STEMI patients thrombolysed with a specific fibrinolytic agent, whereas these patients will certainly be treated with ARIXTRA more frequently in real life than in the OASIS 6 study. This doubt about the representativeness of the patients in this study is even more pronounced when we consider that this was an international study (global data) that does not necessarily reflect French practices (in terms of patient profiles, emergency healthcare and time to treatment initiation).

- There are unknown factors regarding how thrombolysed patients undergoing secondary angioplasty (clinical situation requiring a complex anticoagulant strategy) tolerate this product.

The ARIXTRA proprietary drug therefore will not provide an additional response to an identified public health need.

Consequently, given the current state of knowledge and the other therapies available at this time, the ARIXTRA proprietary drug has no expected public health benefit in this indication.

Efficacy/tolerance ratio

- In thrombolysed patients: the efficacy/tolerance ratio of ARIXTRA 2.5 mg is high on the basis of a comparison with placebo in patients thrombolysed with a non-specific fibrinolytic (OASIS-6).

NB: This ratio is not clearly established in comparison with a UFH and has not been evaluated in comparison with enoxaparin (LOVENOX) under the clinical conditions in which its prescription as first-line therapy is recommended.

- In patients not undergoing reperfusion therapy, the efficacy/tolerance ratio of fondaparinux 2.5 mg is high.

Conclusion: given the seriousness of acute coronary syndromes, the importance of having pharmacological alternatives and the demonstrated efficacy versus placebo, the actual benefit of ARIXTRA 2.5 mg in STEMI is substantial.

4.2. Improvement in actual benefit

Given the available clinical data, the committee considers ARIXTRA 2.5 mg to be an additional means of therapy that offers no improvement in actual benefit (IAB V) over the current management of ST segment elevation acute coronary syndromes. The clinical interpretation of the OASIS-6 results and their transposability to French practice raise unanswered questions.

4.3. Therapeutic use

According to a recent French consensus conference[13], the restoration of coronary patency during the acute phase of STEMI helps improve patient prognosis. Deciding on which of the two available techniques (angioplasty or fibrinolysis) will be used takes place after considering the clinical situation, particularly in light of the time lapsed since the onset of symptoms. Fibrinolysis is recommended if the time between first medical contact and admission to the interventional cardiology department is estimated to be more than 45 minutes. After fibrinolysis, the patient must be referred to a centre with a diagnostic and interventional catheterisation laboratory. Otherwise, the reperfusion strategy depends on the time of onset of symptoms and fibrinolysis remains possible when the attack started less than three hours before arriving to the emergency department.

Concerning the use of antithrombotics:

- The main purpose of instituting antithrombotic therapy is to prevent the extension of pre-existing coronary thrombi or an excessive thrombotic reaction induced by pre-hospital thrombolysis or primary angioplasty, and therefore prevent arterial reocclusion.
- The use of clopidogrel (PLAVIX) is recommended during the early phase of ST-segment elevation acute coronary syndromes either in combination with aspirin or as single agent if

13 Consensus Conference. Management of Acute Myocardial Infarction outside Cardiology Departments. French Emergency Medical Services (SAMU) with the methodological partnership and financial assistance of the Haute Autorité de Santé; 6 February 2007

aspirin is contraindicated. The recommended oral starting dose (loading dose) is 300 mg in patients under 75 years of age and 75 mg in patients over 75 years of age.
- The use of heparins is considered to be beneficial in the management of ST segment elevation acute coronary syndromes:

- In the case of fibrinolysis, enoxaparin is superior to unfractionated heparin (UFH) in patients under 75 years of age with normal renal function (level B). The recommended low molecular weight heparin (LMWH) is enoxaparin given in an initial IV bolus dose of 30 mg, followed by subcutaneous injections of 1 mg/kg every 12 hours.

NB: Since the publication of the CLARITY study results, which validated the use of clopidogrel in combination with aspirin, the benefit of combining aspirin, clopidogrel and enoxaparin or UFH with fibrinolysis remains to be determined.

- *In the case of angioplasty, there is no evidence in favour of LMWH versus UFH, which remains, in this case, the reference treatment.*
- *In subjects over 75 years of age and subjects with impaired renal function, the recommended heparin is UFH (grade B). The UFH dose is 60 IU/kg for the initial bolus dose by direct IV injection (not to exceed 4,000 IU) with a maintenance dose of 12 IU/kg/h (maximum 1,000 IU/h).*

Therapeutic use of ARIXTRA 2.5 mg in the management of STEMI patients
On the basis of the OASIS-6 study results, when angioplasty cannot be used, ARIXTRA 2.5 mg represents an alternative to UFH:
-> in thrombolysed patients, especially when the fibrinolytic agent prescribed is streptokinase or another nonspecific fibrinolytic;
-> in patients not undergoing immediate reperfusion therapy by thrombolysis or angioplasty.

When rescue angioplasty must be performed after thrombolysis, the prescription of fondaparinux (ARIXTRA 2.5 mg) is not recommended (see the SPC).

Choice of technique for restoring coronary patency
Given that:
- During the first three hours after the onset of symptoms, it has been shown (grade B) that primary angioplasty and fibrinolysis are equally effective in reducing mortality at 30 days, provided that this strategy can be implemented with a “first-medical-contact-to-balloon” time of under 90 minutes. There is a lower incidence of haemorrhagic stroke with primary angioplasty than with fibrinolysis.
- After 3 hours, the benefit of fibrinolysis diminishes and primary angioplasty gives better results. Primary angioplasty should therefore be used at this time, bearing in mind that the speed of implementing a reperfusion technique continues to impact prognosis (*N.B., in particular by reducing mortality*). Primary angioplasty must therefore be carried out within 90 minutes; if angioplasty cannot be performed within 90 minutes, fibrinolysis should be performed, assuming there are no contraindications.
- After 12 hours, urgent reperfusion is no longer considered to reduce mortality or morbidity in STEMI. However, late reperfusion may be considered in certain situations (cardiogenic shock or persistent chest pain). Angioplasty should be the preferred reperfusion technique.

Given these items, the jury of the Consensus conference recommends the following initial strategy:

- If the "door to cardio"[14] time is greater than 45 minutes, the probability that the total "first-medical-contact-to-balloon" time is greater than 90 minutes is too high and justifies fibrinolysis for any patient in the 12 hours following the onset of symptoms. The strategy is identical for under and over 3 hours.
- if the "door-to-cardio" time is less than 45 minutes and the sum of this time and the "door to-balloon"[15] time is less than 90 minutes, the strategy depends on the time of symptom onset:

- if this time is under than 3 hours, the patient's physician can suggest either fibrinolysis or primary angioplasty, depending on written and evaluated procedures. These procedures, which are used by cardiologists and emergency physicians alike, must take into account the informed patient's choice and certain clinical characteristics (in particular age, the area anterior to the necrosis, and time to treatment of less than 1 hour);
- If the time since symptom onset is 3 to 12 hours, primary angioplasty should be preferred.

4.4 Target population

The ARIXTRA 2.5 mg target population proposed by GSK was estimated using:
- an analysis of public and private PMSI (French Medicalised Information System Programme) 2006 databases to evaluate the annual number of patients with acute coronary syndrome; according to the PMSI 2006 database, 64,720 hospital stays were due to a diagnosis (primary or associated) of Q-wave myocardial infarction (now grouped together under the term "non-ST elevation acute coronary syndrome (ACS)" or "UA/NSTEMI")
- an analysis of the current management of patients with acute coronary syndrome in France using data from the FAST-MI registry: 36.1% of patients do not undergo reperfusion, 18.8% receive pre-hospital thrombolysis, 10.4% receive hospital thrombolysis and 34.8% undergo primary angioplasty.

The following distribution is obtained by applying these percentages to the PMSI data and the management strategy recommended by HAS:

- 23,300 patients do not undergo reperfusion
- 12,200 patients receive pre-hospital thrombolysis (prehosp TL)
- 6,700 patients receive hospital thrombolysis (TL)
- 22,500 patients undergo primary angioplasty (PPCI).

Of these groups, only patients not undergoing reperfusion or receiving pre-hospital or hospital thrombolysis are concerned by the ARIXTRA 2.5 mg MA indication, i.e., a total of 42,200 patients, more than half of whom are non-reperfused patients.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines approved for use by hospitals and various public services in the extension of indication *"treatment of ST segment elevation myocardial infarction (STEMI) in patients who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy*".

14 The "door to cardio time" must be determined by the admitting physician according to the estimated duration of preparation time, stretcher time and transport time of the patient to the Cardiac Catheterisation Lab (CCL). This is transmitted to the physician coordinator.
15 The "cardio-to-balloon" time must be estimated by the physician coordinator based on the time a table and and angioplasty team becomes available; this time is obtained by calling the CCL. It may also be estimated by using data in shared registries. This time must be subject to a contractual agreement between the teams. If this "cardio-to-balloon" time cannot be estimated (uncertainty regarding the availability of the CCL), it must be considered to be over 45 minutes.