HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

15 May 2013

ARIXTRA 2.5 mg/0.5 ml, solution for injection in pre-filled syringe

B/10 (CIP: 34009 563 619 7 7)

Applicant: GlaxoSmithKline

INN	fondaparinux sodium
ATC Code (2012)	B01AX05 (Antithrombotic agent). Selective indirect factor Xa inhibitor
Reason for the review	**Re-assessment of the Actual Benefit and Improvement in Actual Benefit at the request of the Committee (pursuant to Article R 163-21 of the French Social Security Code) following questions raised by the Afssaps (French Health Products Safety Agency) on 28 December 2011**
List concerned	**Hospital use** (French Public Health Code L.5123-2)
Indications concerned	**"- Treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in patients for whom an urgent (<120 min) invasive treatment (percutaneous coronary intervention: PCI) is not indicated.** **- Treatment of ST segment elevation myocardial infarction (STEMI) in adults who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy."**

Actual Benefit (AB)	**Substantial**
Improvement in Actual Benefit (IAB)	**In the treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in patients for whom an urgent (<120 min) invasive treatment strategy (percutaneous coronary intervention: PCI) is not indicated, the Committee confirms the absence of an improvement in actual benefit (IAB V, non-existent) with ARIXTRA 2.5 mg compared with current treatment in non-ST segment elevation acute coronary syndromes.** **In the treatment of ST segment elevation myocardial infarction (STEMI) in adults who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy, the Committee confirms the absence of an improvement in actual benefit (IAB V, non-existent) with ARIXTRA 2.5 mg in the treatment of ST segment elevation acute coronary syndromes.**
Therapeutic use	**First-line treatment**
Recommendations	

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Initial date (European centralised procedure): 21 March 2002 Extensions of the indications in acute coronary syndromes: 29 August 2007
Prescribing and dispensing conditions / special status	List I ARIXTRA has a European Risk Management Plan (RMP) and, since January 2007, has had national pharmacovigilance monitoring.

02 BACKGROUND

In its 28 December 2011 letter to the HAS alerting them to the serious haemorrhagic accidents observed with ARIXTRA 2.5 mg in at-risk patients (the elderly, patients with low body weight or with renal impairment), the Afssaps questioned the HAS about the possibility of re-assessing the 1.5 mg dose, suggesting that it may be of benefit to these patients. The Committee decided to re-assess the actual benefit of ARIXTRA (all dosages with a Marketing Authorisation) in all of its indications.
In this Opinion, only treatment for the acute coronary syndrome indications will be re-assessed.

03 INDICATIONS

"Treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in adults for whom urgent (< 120 min) invasive management (PCI) is not indicated.

- Treatment of ST segment elevation myocardial infarction (STEMI) in adults who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy."

"- Prevention of Venous Thromboembolic Events (VTE) in adults undergoing major orthopaedic surgery of the lower limbs such as hip fracture, major knee surgery or hip replacement surgery
- Prevention of Venous Thromboembolic Events (VTE) in adults undergoing abdominal surgery who are judged to be at high risk of thromboembolic complications, such as patients undergoing abdominal cancer surgery (see Pharmacodynamics)
- - Prevention of Venous Thromboembolic Events (VTE) in adult medical patients who are judged to be at high risk for VTE and who are immobilised due to acute illness such as cardiac insufficiency and/or acute respiratory disorders and/or acute infectious or inflammatory disease
- Treatment of adults with acute symptomatic spontaneous superficial-vein thrombosis of the lower limbs without concomitant deep-vein thrombosis."

04 DOSAGE

"**Treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI):** the recommended dose of fondaparinux is 2.5 mg once daily, administered by subcutaneous injection. 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. If a patient is to undergo percutaneous coronary intervention (PCI), unfractionated heparin (UFH), as per standard practice, should be administered during PCI, taking into account the patient's potential risk of bleeding, including the time since the last dose of fondaparinux. The timing of restarting subcutaneous fondaparinux after sheath removal should be based on clinical judgement. In the pivotal UA/NSTEMI clinical trial, treatment with fondaparinux was restarted no earlier than 2 hours after sheath removal.

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 subsequent doses are administered by subcutaneous injection. 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. If a patient is to undergo non-primary PCI, unfractionated heparin (UFH) as per standard practice should be administered during PCI, taking into account the patient's potential risk of bleeding, including the time since the last dose of fondaparinux. The timing of restarting subcutaneous fondaparinux after sheath removal should be based on clinical judgement. In the pivotal STEMI clinical trial, treatment with fondaparinux was restarted no earlier than 3 hours after sheath removal.
Patients who are to undergo coronary artery bypass graft (CABG) surgery: in STEMI or UA/NSTEMI patients who are to undergo coronary artery bypass graft (CABG) surgery, fondaparinux where possible, should not be given during the 24 hours before surgery and may be restarted 48 hours post-operatively.

Special populations and situations:

Elderly patients: elderly patients are at an increased risk of bleeding. A reduction in renal function generally occurs with age; elderly patients may present with a reduction in the elimination and an increase in plasma fondaparinux concentrations. In the elderly, fondaparinux is to be used with caution.

Renal impairment: fondaparinux should not be used in patients with creatinine clearance <20 ml/min. No dosage reduction is required for patients with creatinine clearance > 20 ml/min. In patients with creatinine clearance in the range of 20 to 30 ml/min, available data on the use of fondaparinux at the dose of 2.5 mg once daily in the treatment of UA/NSTEMI and STEMI are limited. Consequently, it is the doctor's responsibility to determine whether or not the expected benefits of treatment are greater than the risks that may be encountered.

Hepatic impairment: no dosing adjustment is necessary in patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, fondaparinux should be used with care as this patient group has not been studied.

Low body weight: patients with a body weight below 50 kg are at an increased risk of bleeding. Fondaparinux elimination decreases with weight. Fondaparinux should be used with caution in these patients.

Percutaneous coronary intervention (PCI) and risk of guiding catheter thrombus:

- In STEMI patients undergoing primary PCI, the use of fondaparinux prior to and during PCI is not recommended. Similarly, in UA/NSTEMI patients with life-threatening conditions that require urgent revascularisation, the use of fondaparinux prior to and during PCI is not recommended. These are patients are those with refractory or recurrent angina associated with dynamic ST segment deviation, heart failure, life-threatening arrhythmias or haemodynamic instability.
- In UA/NSTEMI and STEMI patients undergoing non-primary PCI, the use of fondaparinux as the sole anticoagulant during PCI is not recommended due to an increased risk of guiding catheter thrombus (see Pharmacodynamics: clinical studies section). Therefore adjunctive UFH should be used during non-primary PCI according to standard practice."

05 CLINICALLY RELEVANT COMPARATORS

05.1 Medicinal products

Relevant comparator medicines are indirect thrombin and factor Xa inhibitors:

- LMWHs administered via SC injection:

Proprietary medicinal products	INN	Indication	AB (Opinion)
FRAGMIN	Dalteparin sodium	Treatment of unstable angina and acute non-Q wave myocardial infarction, administered concurrently with aspirin	Substantial (19/12/07)
FRAXIPARIN	Nadroparin calcium		Substantial (18/10/06)
LOVENOX	Enoxaparin sodium		Substantial (02/12/09)

Of the LMWHs, only enoxaparin (LOVENOX) administered via SC injection has a Marketing Authorisation in the indication of ST segment elevation acute coronary syndromes.

- UFH administered via SC injection (CALCIPARIN) or intravenously (HEPARIN CHOAY):

Products	INN	Indication	AB (Opinion)
CALCIPARIN	Heparin calcium	Treatment of acute Q-wave or non-Q wave myocardial infarction and unstable angina.	Substantial (23/01/08)
HEPARIN CHOAY	Heparin sodium		Substantial (03/09/08)

ANGIOX (bivalirudine) is not a relevant comparator medicine to the extent that it is indicated as an anticoagulant in adult patients with ST segment elevation myocardial infarction (STEMI) undergoing a percutaneous coronary intervention (PCI), in particular if it is a primary PCI, and in cases of unstable angina/non-ST segment elevation myocardial infarction (UA/NSTEMI) in which the patient is having a emergency or early procedure.

06 SUMMARY OF PREVIOUS ASSESSMENTS

Date of Opinion (Inclusion on the list for hospital use)	11 June 2008
Indication	Treatment of unstable angina or non-ST segment elevation myocardial infarction (NSTEMI) in patients for whom urgent (< 120 min) invasive management (PCI) is not indicated.
Actual Benefit (AB)	Substantial in patients not treated with angioplasty, i.e., when treatment is medical or when the decision between an invasive or non-invasive strategy has not yet been made, i.e., while angioplasty has not yet been carried out.
Improvement in Actual Benefit (IAB)	"ARIXTRA 2.5 mg does not provide an improvement in actual benefit (IAB level V) in the treatment of non-ST segment elevation acute coronary syndromes (NSTEACS) compared with current treatment. The non-inferiority of fondaparinux (ARIXTRA 2.5 mg) compared with enoxaparin was not revealed in patients who mainly received invasive treatment."
Studies requested	Not applicable

Date of Opinion (Inclusion on the list for hospital use)	11 June 2008
Indication	Treatment of ST segment elevation myocardial infarction (STEMI) in adults who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy.
Actual Benefit (AB) (wording)	"Given the serious nature of acute coronary syndromes, the importance of having access to alternative medication, and the demonstrated efficacy versus placebo, the actual benefit of ARIXTRA 2.5 mg is substantial in ST segment elevation acute coronary syndromes."
Improvement in Actual Benefit (IAB) (wording)	"Given the clinical data available, the Committee considers that ARIXTRA 2.5 mg is an additional treatment method that does not provide an improvement in actual benefit (IAB level V) in the current treatment of ST segment elevation acute coronary syndromes. The clinical interpretation of the OASIS-6 results and their transposability to French medical practice raises questions that are yet to be resolved."
Studies requested	Not applicable

07 ANALYSIS OF NEW CLINICAL DATA

07.1 Efficacy

The applicant has not presented any new clinical efficacy data.

07.2 Safety

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

08 USAGE DATA

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

The applicant extracted the breakdown of prescriptions per dosage and the mean treatment durations for the various dosages were taken from data from the Thalès database. In order to estimate the breakdown of prescriptions by whether they were curative or preventive, a prescription for the 2.5 mg dosage was assumed to be preventive while the other dosages were assumed to be curative (see Table 1). This overestimates the number of preventive prescriptions.

Table 1. Distribution of ARIXTRA prescriptions per dosage (source Thalès)

	Period: January to March 2012	
	Number	**Percentage**
PREVENTIVE ARIXTRA 2.5 mg	**19,440**	**31.6%**
CURATIVE	**42,120**	**68.4 %**
ARIXTRA 5 mg	8,370	13.6%
ARIXTRA 7.5 mg	30,510	49.6%
ARIXTRA 10 mg	3,240	5.3%
TOTAL ARIXTRA Prescriptions	**61,560**	**100.0%**

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

OnPAAR study

The applicant presented the results of a study planned by the European RMP for the correct use of the medication in cases of acute coronary syndrome with a PCI[1].
The primary purpose of this study was to verify that the prescribers were correctly using an additional anticoagulant during the PCI. The secondary purposes were to verify prescriber compliance with SPC information on admission diagnosis (UA, NSTEMI or STEMI), on the type of anticoagulant administered and the non-use of ARIXTRA before or during primary PCI in STEMI cases.
This International observational study was conducted from November 2008 to November 2010. It included 1,056 patients in 6 countries (165 of the patients were from France). It was run as a retrospective study based on the analysis of medical files of patient who had undergone PCI and had been treated with ARIXTRA.

Results: the mean number of ARIXTRA doses administered was 3.1 per patient (2.8 in France); in 98.5% of cases, ARIXTRA 2.5 mg had been administered (99.8% of cases in France). Only 35 patients (only one in France) had received more than 8 doses of ARIXTRA. An additional anticoagulant had been used in 98.9% of the cases (99.4% of the cases in France). In 87.3% of cases (97.0% of the cases in France), this additional anticoagulant was UFH.
Table 2 summarises how anticoagulants were prescribed during PCI for OnPAAR study patients diagnosed with ACS and treated with ARIXTRA.

Table 2: Main results of the OnPAAR study

	Total (n=1,056)	France (n=165)
Additional anticoagulant during PCI	1,044 (98.9%)	164 (99.4%)
UFH	911	159
Bivalirudine	107	4
Other	26	1
Fondaparinux	3	0
None	9	1
Additional anticoagulant during PCI in patients with an initial UA/NSTEMI diagnosis	814/819 (99.4%)	108/109 (99.1%)
UFH	706	108
Additional anticoagulant during PCI in patients with an initial STEMI diagnosis	219/226 (96.9%)	52/52 (100.0%)
UFH	195	47
Additional anticoagulant during PCI in patients with an “other” initial diagnosis	11/11 (100.0%)	4/4 (100.0%)
UFH	10	4

Of the 226 patients with an initial STEMI diagnosis, 159 underwent a primary PCI and 107 (67.3%) of these patients did not receive ARIXTRA prior to or during the PCI. In France, 43 of the 47 patients with a STEMI diagnosis underwent a primary PCI and 36 (83.7%) did not receive ARIXTRA before or during the PCI.

Conclusions: the OnPAAR study demonstrated a high level of compliance with the SPC in prescribing ARIXTRA 2.5 mg to patients with ACS undergoing PCI. This was particularly true in France.

[1] OnPAAR Study Report, 2011.

09 STUDY PROGRAMMES

The risk management plan (CHMP validation: August 2010) stipulates that the collection of spontaneous reports continue with an ongoing periodic review of data. Heightened monitoring of spontaneous cases of haemorrhage and off-label use is in progress.

010 THERAPEUTIC USE

In the treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in patients for whom urgent (< 120 min) invasive management (PCI) is not indicated

The treatment strategy for these patients is based on evaluating the level of individual ischaemic risk for the patient on admission. Three clinical situations can be identified:

- A life-threatening prognosis is issued immediately: action with an immediate (within 120 minutes) emergency invasive strategy is therefore justified.
- A life-threatening prognosis is not issued immediately despite an acute risk of complications: in this situation, an invasive strategy (coronary angiography and perhaps a reperfusion procedure) may be deferred until 72 hours after this diagnosis.
- The clinical condition of the patient does not require an invasive strategy.

The aim of antithrombotic treatment (platelet aggregation inhibitors + anticoagulant) is to prevent the progression of an intracoronary thrombus and to promote stability of the atheromatous plaque, thus reducing myocardial ischaemia and preventing complications such as death or MI. Several anticoagulants may be prescribed: LMWHs, UFHs or fondaparinux (ARIXTRA 2.5 mg).

The use of fondaparinux (ARIXTRA 2.5 mg) in NSTEACS cases:

Given the clinical results available from the OASIS-5 study, and the wording of the Marketing Authorisation, the prescription of ARIXTRA 2.5 mg can be considered within the context of a non-urgent situation for as long it takes to make the decision between an early invasive strategy and a non-invasive strategy.

The question of whether there is a clinical benefit in using fondaparinux (ARIXTRA 2.5 mg) for patients receiving delayed coronary reperfusion (up to 24, 48 or 72 hours after presenting, depending on the guidelines) is relevant as the arguments in favour of using fondaparinux in cases of angioplasty (primary or secondary) are limited: its efficacy versus a different anticoagulant is questionable, coronary complications and catheter-related thrombi are possible and UFH may need to be added.

The Committee notes that compared with enoxaparin at a curative dose instead of another anticoagulant (UFH, bivalirudine), ARIXTRA at a preventive dose (2.5 mg), by causing fewer serious haemorrhages, could reduce haemorrhage-related mortality until the decision on whether or not to perform coronary angiography (and subsequent angioplasty) has been made. However, the OASIS-5 study does not document this point very clearly (See Opinion of 11 June 2008).

Establishing the therapeutic use and benefit of fondaparinux (ARIXTRA 2.5 mg) in the treatment of non-ST segment elevation ACS varies depending on whether referring to the European or the American 2007 guidelines. The European Society of Cardiology guidelines on the management of patients were updated in 2011: the anticoagulant should be selected based on the ischaemic and haemorrhagic risk and the risk-benefit relationship of the agent chosen.

These guidelines now clearly state that ARIXTRA 2.5 mg is not indicated in patients requiring urgent (< 120 min) invasive management (PCI). In other situations, ARIXTRA 2.5 mg is considered as first-line treatment (Grade I-A); LMWHs (enoxaparin) and UFHs are only recommended when ARIXTRA 2.5 mg is not available.

In summary, ARIXTRA 2.5 mg remains a first line treatment for the initial management of NSTEACS when urgent (< 120 min) invasive management (PCI) is not required.

In the treatment of ST segment elevation myocardial infarction (STEMI) in adults who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy

According to the French consensus conference[2], early removal of coronary artery obstruction in the acute phase of STEMI improves patient prognosis. The decision of which of the two available techniques (angioplasty or fibrinolysis) should be used is made based on the clinical situation, and primarily the time lapsed since the onset of symptoms. Fibrinolysis is recommended if the time lapsed between initial medical attention and arrival to the interventional cardiology unit is estimated to be greater than 45 minutes. After receiving fibrinolysis, a patient must be referred to a centre with a diagnostic and interventional coronary angiography suite. In other circumstances, the reperfusion strategy used depends on the time of symptom onset, since fibrinolysis can only be considered if the episode began less than 3 hours prior to arrival to the emergency department.

Regarding the use of antithrombotics:

The main aim of antithrombotic treatment is to prevent the expansion of a pre-formed intracoronary thrombus or to prevent an excessive thrombotic reaction brought on by prehospital thrombolysis or primary angioplasty, and to thus to prevent arterial re-blockage.

The use of heparins is considered beneficial in the management of ST segment elevation acute coronary syndromes:

- In cases of fibrinolysis, enoxaparin is superior to unfractionated heparin (UFH) in patients under the age of 75 with normal renal function (grade B). The recommended low molecular weight heparin (LMWH) is enoxaparin given as an initial IV bolus of 30 mg and followed by subcutaneous injections of 1 mg/kg every 12 hours.
- In cases of angioplasty, there is no argument in favour of the use of LMWHs over UFHs, which remain the standard treatment in this situation.
- In patients over the age of 75 and in patients with renal impairment, UFH is the recommended heparin (grade B). The dose of UFH is 60 IU/kg for the initial IV bolus (not to exceed 4,000 IU) with a maintenance dose of 12 IU/kg/h (maximum 1,000 IU/h).

The use of ARIXTRA 2.5 mg in the management of STEACS patients

Based on the results of the OASIS-6 study, when angioplasty cannot be implemented, ARIXTRA 2.5 mg represents an alternative to UFHs:

- in thrombolysis patients, particularly when the fibrinolytic prescribed is streptokinase or another non-specific fibrinolytic
- in patients who are not immediately reperfused by thrombolysis or angioplasty.

When rescue angioplasty must be carried out after thrombolysis, the prescription of fondaparinux (ARIXTRA 2.5 mg) is not recommended (see SPC and Committee Opinion of 11 June 2008).

Since the previous Committee Opinion, the European Society of Cardiology guidelines regarding the management of patients with STEACS have been updated (2011). They state that:

ARIXTRA 2.5 mg is not recommended in patients revascularised following a primary PCI.

For other patients, ARIXTRA 2.5 mg is considered as:

- a first-line treatment with a non fibrin-specific thrombolytic agent (Grade IIa-B), just like UFH (Grade IIa-B) and enoxaparin (Grade IIa-B).
- a first-line treatment for patients initially receiving no other form of reperfusion (Grade I-B); enoxaparin and UFH are only recommended when ARIXTRA 2.5 mg is not available (Grade I-B).

[2] Consensus Conference. *Prise en charge de l'infarctus du myocarde à la phase aigue en dehors des services de cardiologie* (Management of acute-phase myocardial infarction outside cardiology units). French SAMU (emergency medical services) with methodological and financial assistance from the Haute Autorité de Santé; 6 February 2007.

In summary, ARIXTRA 2.5 mg remains a first-line treatment for the initial management of patients with STEACS when revascularisation via PCI cannot be performed and in patients who cannot be reperfused.

Consideration of the risk of haemorrhage in cases of acute coronary syndrome:

According to the SPC:

Renal impairment: “Fondaparinux should not be used in patients with creatinine clearance <20 ml/min. No dosage reduction is required for patients with creatinine clearance > 20 ml/min.”

Weight < 50 kg: according to the SPC, fondaparinux should be used with caution in these patients.

75 years and older: according to the SPC, fondaparinux should be used with caution in these patients.

In patients with renal impairment and a creatinine clearance < 20 ml/min, ARIXTRA should not be used at a once-daily 2.5 mg dose.
In patients with a body weight < 50 kg and/or aged 75 years and older, the use of fondaparinux should only be considered with great care given the risk of haemorrhage and the absence of a possible dose adjustment.

011 TRANSPARENCY COMMITTEE CONCLUSIONS

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

011.1 Re-assessment of the Actual Benefit

11.1.1 In the treatment of unstable angina or non-ST segment elevation myocardial infarction (NSTEMI) in patients for whom urgent (< 120 min) invasive management (PCI) is not indicated:

The immediate seriousness of non-ST segment elevation coronary syndromes (unstable angina, non-ST elevation myocardial infarction) depends on the clinical situation, i.e., whether the situation is stable or unstable or whether the condition is immediately life threatening, as well as on risk factors. The level of seriousness will influence patient management. However, all acute coronary syndromes (ST-elevation and non-ST elevation) require management by a specialised team. Two treatment approaches are possible: entirely medical treatment or, in certain patients, an invasive strategy involving coronary angiography and revascularisation using angioplasty (PCI) or coronary artery bypass graft (CABG). The invasive strategy is performed within 120 minutes (a relatively rare situation) or within 24 to 72 hours because, although there is an acute risk of complications, the situation is not usually immediately life threatening.

Anticoagulants are recommended in combination with platelet aggregation inhibitors for these patients. Several anticoagulants have been assessed: unfractionated heparin (UFH), enoxaparin (LOVENOX), bivalirudine (ANGIOX) and fondaparinux (ARIXTRA 2.5 mg).
ARIXTRA 2.5 mg is indicated in patients for whom urgent (<120 minutes) invasive management (percutaneous coronary intervention: PCI) is not indicated. This medicinal product is therefore a first-line treatment.

Public health benefit
Ischaemic heart disease is a major public health burden. The burden of non-ST segment elevation acute coronary syndromes (unstable angina or non-ST elevation myocardial infarction) not eligible for invasive treatment (PCI) is considered substantial. Improvement in the secondary prevention of MI and unstable angina (from these clinical situations) is also a public health need.
There is no new data enabling the conclusions on the public health benefit of ARIXTRA in the previous Committee opinion (Opinion of June 2008) to be changed. Consequently, ARIXTRA 2.5 mg does not provide a public health benefit in this indication.

The efficacy/adverse events ratio for fondaparinux (ARIXTRA 2.5 mg) remains high for patients not treated with angioplasty, i.e., when treatment is medical or when the decision between an invasive or non-invasive strategy has not yet been made, i.e., while angioplasty is still to be carried out.

As a result, the actual benefit of ARIXTRA 2.5 mg remains substantial in patients with NSTEACS for whom urgent (<120 minutes) invasive management (percutaneous coronary intervention: PCI) is not indicated.

11.1.2 In the treatment of ST segment elevation myocardial infarction (STEMI) in adults who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy:

In the acute phase of an ST segment elevation coronary syndrome (myocardial infarction, STEACS), it is extremely urgent for the coronary artery to be unblocked to reduce the risk of death or MI recurrence. Coronary reperfusion is achieved through angioplasty (percutaneous coronary intervention - PCI) or fibrinolysis (medical treatment; IV thrombolysis). These serious clinical situations are life-threatening.

ARIXTRA 2.5 mg is indicated in the acute phase of STEMI as an additional treatment for fibrinolysis or in cases of early coronary non-reperfusion. This product is a first line treatment in these situations.

Public health benefit

Ischaemic heart disease is a major public health burden. The burden of ST-segment elevation myocardial infarction (MI) eligible for thrombolytic treatment or receiving no other form of reperfusion therapy may be considered moderate due to the limited number of patients concerned. Improvement in secondary prevention of MI is thus a public health need.

There are no new data enabling the conclusions from the previous Committee opinion (Opinion of June 2008) to be changed regarding the public health benefit.

ARIXTRA 2.5 mg does not provide a public health benefit in this indication.

In STEACS cases, the efficacy/adverse events ratio of fondaparinux remains high in patients not receiving reperfusion and in patients undergoing thrombolysis with a placebo-controlled non-specific fibrinolytic. However, this ratio has not been clearly established in comparison with a UFH and has not been evaluated in comparison with enoxaparin (LOVENOX) in these clinical situations, where its first-line prescription is recommended.
The Committee states that no dose adjustment is recommended for patients weighing less than 50 kg, in cases of moderate to severe renal impairment (creatinine clearance above 20 ml/min) and in patients aged 75 or older. Yet, these patients are at an increased risk of haemorrhage.

Alternative medicinal products exist:
- Enoxaparin (LOVENOX) prescription is recommended (HAS 2006) for thrombolysis in patients under the age of 75 and in the absence of renal impairment; a UFH is recommended in other situations.
- In cases of primary angioplasty, the prescription of a UFH is recommended.
- In cases that have not received early reperfusion, prescription of a UFH is possible.

***As a result, the actual benefit of ARIXTRA 2.5 mg remains substantial* for patients with STEACS who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy.**

The Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in the indications and at the dosages in the Marketing Authorisation.

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

In the treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in patients for whom an urgent (<120 min) invasive treatment strategy (percutaneous coronary intervention: PCI) is not indicated, and in the 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, the Committee confirms the absence of an improvement in actual benefit of ARIXTRA 2.5 mg (IAB V, non-existent) in the treatment of non-ST elevation acute coronary syndromes compared with current treatment.

APPENDIX

Summary of available results from previous assessment (Opinion of 11 June 2008)

In the treatment of unstable angina or non-ST elevation myocardial infarction (NSTEMI) in patients for whom an urgent (<120 min) invasive treatment strategy (percutaneous coronary intervention: PCI) is not indicated.

The OASIS-5 study is a randomised, double blind non-inferiority study on nearly 20,000 patients with unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI). This study investigated the non-inferiority of two anticoagulants: fondaparinux 2.5 mg x 1/day administered via SC injection compared with enoxaparin 1 mg/kg administered x 2/day via SC injection. The mean patient age was 67 years and approximately 60% of the patients were under the age of 65. Approximately 40% and 17% of patients had mild renal impairment (50 ml/min < creatinine clearance < 80 ml/min) or moderate renal impairment (30 ml/min < creatinine clearance < 50 ml/min) respectively. For these patients, the dosage of enoxaparin was reduced, while that of fondaparinux 2.5 mg was unchanged. The OASIS-5 study population was therefore a population at moderate to high risk of ischaemic complications eligible for early invasive treatment (within 72 hours). For cases of angioplasty, patients received additional treatment, which was either IV fondaparinux or IV UFH (enoxaparin patients). Following an amendment to the protocol, some patients in the fondaparinux group received a UFH instead of fondaparinux due to the unexpected occurrence of thrombotic complications; this unvalidated strategy was evaluated after the Marketing Authorisation was granted. The evaluation criterion was a composite endpoint combining death from any cause, myocardial infarction (MI) and refractory ischaemia in the 9 days following randomisation.

Of the patients in the fondaparinux group, 5.8% had experienced an event by the 9th day compared with 5.7% of those treated with enoxaparin (relative risk 1.01; 95% CI: 0.90 - 1.13, p value - unilateral non-inferiority = 0.003). The non-inferiority of ARIXTRA 2.5 mg compared with enoxaparin (LOVENOX) was established. The results of the study do not enable any conclusions to be drawn regarding the impact of fondaparinux on mortality (secondary endpoint). The incidence of MI and refractory ischaemia were not statistically different between the fondaparinux and enoxaparin treatment groups. The incidence of major bleeding at the 9th day was 2.1% with fondaparinux and 4.1% with enoxaparin (relative risk: 0.52; 95% CI: 0.44 - 0.61; p < 0.001). The risk of haemorrhage varied depending on whether an invasive or non-invasive strategy was followed and depending on the artery used in angioplasty.

In the sub-group of patients treated with either fondaparinux or enoxaparin and who underwent angioplasty (nearly 1/3 of the patients evaluated in the OASIS-5 study), 8.8% and 8.2% either died or had an MI or experienced refractory ischaemia in the 9 days following randomisation (relative risk: 1.08; 95% CI: 0.92 - 1.27). The incidence of major bleeding was 2.2% with fondaparinux and 5.0% with enoxaparin on the 9th day (relative risk: 0.43; 95% CI: 0.33 - 0.57). The interpretation of these results in this sub-group led the authorities to exclude patients treated with angioplasty within 120 minutes from the scope of the ARIXTRA 2.5 mg indication. This exclusion only pertained to patients who had had an emergency reperfusion procedure so as to refrain from excluding the possibility of prescribing ARIXTRA 2.5 mg to patients having a reperfusion procedure within 72 hours prior to undergoing this procedure in a catheterisation facility (see “scientific discussion”, EPAR).
Questions have been raised regarding the transposability of the OASIS-5 study results to a target population in France. According to the Marketing Authorisation for ARIXTRA 2.5 mg, only patients not eligible for immediate angioplasty, i.e., those at low risk, could be considered (through extrapolation) as likely to receive ARIXTRA. However, in this specific population, the non-inferiority of ARIXTRA versus enoxaparin was not clearly established. This population is difficult to identify in the OASIS-5 study after the fact since the majority of patients included were moderately severe or severe. Yet, the population should be able to be identified in daily practice.

In conclusion, and despite the questions raised by the analysis of the results from the OASIS-5 study, fondaparinux (ARIXTRA 2.5 mg) can be considered an alternative to enoxaparin in patients treated for a non-ST segment elevation acute coronary syndrome who are not receiving invasive treatment. For these patients, the possible loss of efficacy (since superiority was not established compared with enoxaparin) could be offset by the reduced risk of haemorrhage, including in patients with mild to moderate renal impairment. Given the results of the OASIS-6 study of myocardial infarction (STEACS) patients, the Committee is questioning the benefit of fondaparinux 2.5 mg as a first-line treatment for patients who are more seriously affected.

In the 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

According to the results of the OASIS-6 study conducted on 12,092 acute ST segment elevation myocardial infarction (STEMI) patients who received emergency reperfusion via angioplasty or via a thrombolytic agent or who were not urgently reperfused, ARIXTRA at a dosage of 2.5 mg/day prescribed for a median duration of 7 days was more effective than the control unfractionated heparin (UFH) treatment prescribed for a median duration of 2 days or placebo in reducing the first event (death or myocardial infarction relapse) in the 30 days following inclusion. The level of this effect was modest, resulting in a 14% reduction in relative risk and an absolute benefit of less than 2%. This benefit is linked to a 13% relative reduction in mortality and 19% reduction in myocardial infarction at 30 days. The occurrence of major haemorrhage was comparable whether patients were treated with fondaparinux 2.5 mg/day or with UFH at a dose that reflected current medical practice. Compared with placebo (stratum 1), fondaparinux was associated with fewer severe haemorrhages.
According to several sub-group exploratory analyses, it appeared that no effects in favour of fondaparinux were highlighted, especially after 30 days for patients who received immediate angioplasty (best treatment if feasible and if patient is eligible) and for patients who received a UFH is cases of thrombolysis. The study lacked the power to make a conclusion about a comparison of the efficacy of ARIXTRA 2.5 mg with that of a UFH in thrombolysis cases (patients in stratum 2). The comparison of these two anticoagulants in patients who received thrombolysis in the two strata is uncertain, especially given the significant differences in the treatments used and the imbalance in the number of participants (the majority of the patients receiving thrombolysis were included in stratum 1). The same reservations regarding the interpretation of the results apply to patients who did not undergo reperfusion. Furthermore, the choice of comparator medicine poorly reflects current cardiology practices.
In conclusion, the results of the OASIS-6 study established that ARIXTRA 2.5 mg was more effective than placebo at reducing the occurrence of ischaemic complications in patients receiving thrombolysis in the form of a non-specific fibrinolytic, and that an anticoagulant (UFH or fondaparinux) can be prescribed in cases of non-reperfusion. However, the transposability and clinical interpretation of the results of the OASIS-6 study raise the following questions:

1- The transposability of the results to French medical practice is questionable, especially since the speed of treatment initiation, which depends on the organisation of care, strongly influences the expected impact on the reduction in mortality.
2- The thrombolytic prescribed in OASIS-6 was usually not fibrino-specific. Yet, in France, specific thrombolytics are recommended and preferentially prescribed.
3- Assessing the clinical benefit of ARIXTRA for the overall population is problematic as it combines the clinical results of patients who were treated differently, i.e., with an active comparator (UFH) or with a placebo. Furthermore, the superiority of ARIXTRA over a UFH (stratum 2) after 30 days was not revealed for the primary endpoint or in the overall population (due to the unfavourable result in the sub-group of angioplasty patients) or in the population of patients receiving thrombolysis only.