Scottish Medicines Consortium

fondaparinux sodium, 2.5mg/0.5ml solution for injection, pre-filled syringe (Arixtra®) No. (420/07)

GlaxoSmithKline

09 November 2007

The Scottish Medicines Consortium has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

fondaparinux (Arixtra®) is accepted for use within NHS Scotland for the treatment of unstable angina or non-ST segment elevation myocardial infarction in patients for whom urgent (<120minutes) invasive management (Percutaneous Coronary Intervention) is not indicated.

Fondaparinux was shown to be non-inferior to a low molecular weight heparin in preventing death, myocardial infarction or refractory ischaemia in the nine days following onset of symptoms. Fondaparinux also had a significantly lower major bleeding event rate than a low molecular weight heparin.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

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

Dosing information

2.5mg once daily by subcutaneous injection, initiated as soon as possible after diagnosis and continued for up to 8 days or until hospital discharge if that occurs earlier.

Product availability date

6 September 2007

Summary of evidence on comparative efficacy

Fondaparinux is a synthetic pentasaccharide antithrombotic that selectively binds to antithrombin, which inactivates Factor Xa resulting in a strong inhibition of thrombin generation and clot formation. It does not inactivate thrombin and has no effect on platelets.

The pivotal phase III, multinational, randomised, double-blind, double-dummy trial involved 20,078 patients within 24 hours of onset of symptoms of unstable angina/non-ST elevation segment myocardial infarction acute coronary syndromes (UA/NSTEMI ACS) who met at least two of the following criteria - age $\geq$ 60 years; elevated troponin or creatine kinase MB isoenzyme; or electrocardiographic changes indicative of ischaemia. Patients were randomised equally to receive fondaparinux 2.5mg subcutaneously once daily for up to 8 days or until hospital discharge (whichever occurred first), or enoxaparin 1mg/kg body weight subcutaneously twice daily (+/- UFH) for 2 to 8 days or until the patient was in a stable condition. Follow up was for 90 to180 days.

The objective of the trial was to demonstrate the non-inferiority of fondaparinux compared to enoxaparin for the primary efficacy composite outcome of first occurrence of any component of death/myocardial infarction (MI)/refractory ischaemia (RI) up to 9 days. Secondary efficacy outcomes included the primary efficacy endpoint at 30 and 180 days; death/MI, and the individual components of the composite outcome at 9, 30 and 180 days. Data on strokes were also collected. In addition, the balance of safety and efficacy of fondaparinux relative to enoxaparin was evaluated on the basis of the proportion of subjects in each group who had an improvement in outcome, based on the composite endpoints of death/MI/RI/major bleeding up to 9, 30 and 180 days. All events were subject to blinded adjudication by committee. Analyses included all randomised patients.

Mean treatment duration was 5.4 vs 5.2 days for fondaparinux and enoxaparin groups respectively. Baseline and concomitant medications, and procedures during the trial and following hospital discharge, were similar across treatment groups except for the proportions of patients who received unfractionated heparin (UFH) in hospital: 22% vs 31% for fondaparinux and enoxaparin, respectively. In patients undergoing PCI within the first eight days after randomisation, 56% of those in the enoxaparin group and 21% in the fondaparinux group received unfractionated heparin.

The primary efficacy outcome occurred in 5.8% vs 5.7% of patients in the fondaparinux and enoxaparin groups, respectively; Hazard ratio (HR), 1.01 (95% Confidence interval (CI): 0.90 to 1.13), demonstrating the non-inferiority of fondaparinux compared to enoxaparin as the upper limit of the CI was below the pre-specified non-inferiority boundary of 1.185. At 9 days non-inferiority was also shown for the rate of death or MI: 4.1% in both treatment groups, HR, 0.99 (95% CI: 0.86 to 1.13).

Table 1: Main efficacy outcomes at 9 days

	Fondaparinux (N = 10,057)	Enoxaparin (N = 10,021)	Hazard ratio (95% CI)	p value for superiority	p value for non-inferiority
	No. of events (% of patients)				
Death, MI or RI*	579 (5.8)	573 (5.7)	1.01 (0.90 – 1.13)	0.92	0.007
Death or MI[#]	409 (4.1)	412 (4.1)	0.99 (0.86 – 1.13)	0.90	0.005
Death	177 (1.8)	186 (1.9)	0.95 (0.77 – 1.17)	0.61	
MI	263 (2.6)	264 (2.7)	0.99 (0.84 – 1.18)	0.94	
RI*	194 (1.9)	188 (1.9)	1.03 (0.84 – 1.26)	0.82	
Death, MI, RI* or major bleeding	737 (7.3)	905 (9.0)	0.81 (0.73 – 0.89)	< 0.001	
Stroke	37 (0.4)	45 (0.5)	0.82 (0.53 – 1.27)	0.37	

* RI = refractory ischaemia

[#]The non-inferiority criterion was based on the primary outcome, but the secondary outcome of death or MI also satisfied this criterion

There were significant improvements for fondaparinux compared to enoxaparin in relation to death at 30 days: 2.9% vs 3.5% (HR, 0.83; 95% CI, 0.71 to 0.97), and 180 days: 5.8% vs 6.5% (HR, 0.89; 95% CI, 0.80 to 1.00); and in the composite outcome of death/MI/RI/ major bleeding at 9 days: 7.3% vs 9.0% (HR, 0.81; 95% CI, 0.73 to 0.89), 30 days: 10% vs 12% (HR, 0.82; 95% CI, 0.75 to 0.89), and 180 days: 15% vs 17% (HR, 0.86; 95% CI, 0.81 to 0.93).

Post-hoc analyses were performed on a subset (93%) of the trial population that was deemed to reflect the licensed population for whom urgent (<120 minutes) percutaneous coronary intervention (PCI) is not indicated. Although the baseline characteristics of the licensed population were similar across the treatment groups, the proportion of patients who received UFH in hospital was substantially lower in this subset compared to the trial population, (17% vs 22% for fondaparinux and 16% vs 31% for enoxaparin respectively). There was no significant difference in the primary efficacy outcome: 5.8% vs 5.6% (HR, 1.03; 95% CI, 0.91 to 1.16) for fondaparinux and enoxaparin licensed population groups, respectively.

Summary of evidence on comparative safety

In the pivotal trial, the primary safety objective was to determine whether fondaparinux was superior to enoxaparin in the prevention of major bleeding at 9 days. Fondaparinux was associated with significantly less major bleeding at 9 days: 2.2% vs 4.1% (HR, 0.52; 95% CI, 0.44 to 0.6 - corresponding to an absolute risk reduction of 1.9% and a relative risk reduction of 48%); 30 days: 3.1% vs 5.0% (HR, 0.62; 95% CI, 0.54 to 0.72), and 180 days: 4.3% vs 5.8% (HR 0.72; 95% CI, 0.64 to 0.82). Rates of total bleeding were also substantially lower with fondaparinux compared to enoxaparin: 3.3% vs. 7.3 % (HR, 0.44; 95% CI 0.39 - 0.50). The results for the primary safety outcomes in the licensed subset were similar to those in the trial population.

An analysis of the difference in the number of deaths between treatment groups at the end of the study, showed that fewer patients in the fondaparinux group died after major bleeding (38 vs. 79 respectively) and after minor bleeding (13 vs. 33 respectively). Most of the difference in mortality between the groups at the end of the study could be attributed to the lower rate of bleeding with fondaparinux.

The rates of bleeding were consistently lower with fondaparinux, regardless of UFH administration.

The profile of adverse events other than bleeding was similar for both treatment groups.

Summary of clinical effectiveness issues

In the pivotal study, fondaparinux was shown to be as effective as enoxaparin in preventing death, MI or RI, but with a reduced risk of bleeding that is reflected in lower short term (30 day) and long term (6 months) mortality. The subset in the study that represented the licensed population showed similar outcomes to the whole study population, although there was a difference in the in-hospital use of UFH in this subset of patients. Some of this difference may be attributed to the exclusion of the patients undergoing early PCI, as these patients are more likely to be treated with UFH.

Fondaparinux is administered subcutaneously once daily and does not require dose adjustment for patient weight.

Fondaparinux cannot be used as the sole anticoagulant during PCI procedures.

Summary of comparative health economic evidence

The manufacturer presented a cost utility analysis comparing fondaparinux to enoxaparin for the treatment of UA/NSTEMI. This comparator was appropriate. The economic model used data from the 180 days follow up of the key clinical trial and also extrapolated the results to include a lifetime perspective for the evaluation. The analysis used clinical outcomes and resource use from all patients in the clinical trial, rather than only from patients in the licensed subset. The base case results indicated that fondaparinux was the dominant treatment, both at 180 days and over a lifetime, as it was cheaper and more effective than enoxaparin. Probabilistic sensitivity analysis indicated a very high likelihood that fondaparinux would be considered cost effective by conventional standards.

The manufacturer provided a cost-utility analysis that focused on a population wider than the licensed trial population (93% of the original trial participants). In the licensed subset of the trial, some of the trial outcomes were no longer statistically significant in favour of enoxaparin. The manufacturer justified their approach by indicating that the hazard ratios used in the model were similar between the two populations and that the lack of a statistically significant result was likely to be due to a loss of statistical power, and therefore the results would be comparable if the licensed population had been used. A further point to note is that the manufacturer used a regression model to estimate costs for the various events in the model. Their regression found that fondaparinux was associated with a small additional cost of £235 after controlling for other variables in the model. This cost was not included in the base case as this variable was not statistically significant, but sensitivity analysis investigated the impact of including this cost. The result was that fondaparinux was no longer dominant; instead it was associated with a positive incremental cost per QALY of £4429.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network National Clinical Guideline 93: "Acute coronary syndromes" published in February 2007 states that in the presence of ischaemic electrocardiographic changes or elevation of cardiac markers, patients with an acute coronary syndrome should be treated immediately with low molecular weight heparin (LMWH) or fondaparinux for 8 days or until hospital discharge or coronary revascularisation.

The European Society of Cardiology "Guidelines for diagnosis and treatment of non-ST segment elevation acute coronary syndromes" published in 2007 state that in a non-urgent situation, as long as a decision between an early invasive or conservative strategy is pending fondaparinux is recommended on the basis of the most favourable efficacy and safety profile.

Additional information: comparators

The low molecular weight heparins enoxaparin and dalteparin are licensed for this indication.

Cost of relevant comparators

Drug	Dose regimen	Cost per course (£)
fondaparinux	**2.5mg by subcutaneous injection daily**	**33 - 53**
enoxaparin	1mg/kg by subcutaneous injection twice daily	48 - 86
dalteparin	120 iu/kg by subcutaneous injection twice daily	42 - 90

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 24.8.07. Costs for enoxaparin and dalteparin are based on body weight range 60 – 80 kg and 5 – 8 days treatment course; costs for fondaparinux are based on 5-8 days treatment course.

Additional information: budget impact

The manufacturer provided budget impact estimates based on a treatment course of five days for fondaparinux and its comparator. On the basis of 14700 patients presenting for treatment in year one (10% of the total UA/NSTEMI ACS population in Scotland that fall within the licence) the gross drug cost of fondaparinux was estimated at £492k, with an estimated saving of £209k arising from displaced comparator drug. By year five, the manufacturer estimated that 50% of the eligible population would receive fondaparinux (95000 patients) at a gross cost of £3.2m, with an estimated saving of £1.3m arising from displaced comparator drug. As nationally agreed contract prices may apply, these savings may not be fully realised. Information from clinical experts suggests that the patient numbers may be overestimated in the company submission.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

This assessment is based on data submitted by the applicant company up to and including 12 October 2007.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.

The undernoted reference was supplied with the submission.

Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, et al. (2006) The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) Investigators. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N.Engl.J.Med. 354(14): 1464-1476.