Scottish Medicines Consortium

fondaparinux sodium 2.5mg/0.5ml pre-filled syringe for injection (Arixtra®) No. (439/08)

GlaxoSmithKline

11 January 2008

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 sodium (Arixtra®) is accepted for use within NHS Scotland for 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.

Fondaparinux significantly reduced mortality and reinfarction during the 30 days following onset of symptoms compared to placebo and was not associated with an increased risk of bleeding.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

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.

Dosing information

Fondaparinux 2.5mg once daily with the first dose administered intravenously and subsequent doses by subcutaneous injection. Treatment should be started as soon as possible following diagnosis and continued for up to a maximum of 8 days or until hospital discharge if that is earlier.

Product availability date

August 2007

Summary of evidence on comparative efficacy

Fondaparinux is a synthetic pentasaccharide that selectively inhibits activated Factor X (Xa) in the coagulation cascade.

One pivotal study supports this new licensed indication for fondaparinux. This was a double-blind, randomised trial comparing fondaparinux with control (either placebo or unfractionated heparin (UFH)) against a background of usual care in 12,092 patients with STEMI. Eligible patients were initially enrolled within 24 hours of the onset of symptoms, but this was subsequently reduced to less than 12 hours. Randomised patients were stratified according to whether the investigator considered there was an indication for using UFH (including intended use of a fibrin-specific thrombolytic, not eligible for fibrinolytic but eligible for antithrombotic, or scheduled for primary percutaneous coronary intervention (PCI)). Those patients considered to have no indication for UFH (stratum 1, n=5,658) were randomised to receive fondaparinux 2.5mg daily or matching placebo. The remaining patients who were considered to have an indication for UFH (stratum 2, n=6,434) were randomised to receive fondaparinux 2.5mg daily or UFH (bolus dose of 60IU/kg followed by an infusion of 12IU/kg/hour for 24-48 hours). In both strata, the first dose of fondaparinux was administered intravenously but continued with daily subcutaneous injections for up to eight days or until hospital discharge if earlier. The dose of UFH was adjusted to maintain activated partial thromboplastin time within the therapeutic range (1.5 to 2.0 times control). All patients received aspirin and other standard medical therapy, including nitrates, ACE inhibitors, beta-blockers and antiplatelet drugs. Low molecular weight heparin, direct thrombin inhibitors or oral anticoagulants were not allowed during the treatment period. Patients were followed up for 3 to 6 months or until death.

The primary endpoint was the composite of death (all cause mortality) or reinfarction at 30 days. Secondary endpoints included this composite assessed at day 9 and at study end. All deaths, reinfarction, strokes and severe or major bleeds were adjudicated centrally using standard definitions. The primary endpoint was analysed using a Cox proportional hazards model for the intention-to-treat population stratified by the indication for UFH.

In the overall population, the incidence of the primary endpoint was significantly reduced in the fondaparinux group at day 30: 9.7% (n=585/6036) in the fondaparinux group versus 11.2% (n=677/6056) in the control group, corresponding to an absolute difference of -1.5% and a hazard ratio (HR) of 0.86 (95% confidence intervals (CI): 0.77 to 0.96). In terms of the individual components of the composite endpoint, there were significantly fewer deaths in the

fondaparinux group at this time: 7.8% (n=470/6036) versus 8.9% (n=540/6056) respectively, corresponding to an absolute difference of -1.1% and an HR of 0.87 (95% CI: 0.77 to 0.98). The difference for the rate of reinfarction at 30 days approached statistical significance (2.5% (n=142/6036) versus 3.0% (n=175/6056) respectively: HR 0.81 (95% CI: 0.65 to 1.01), p=0.06. The composite rates of death or reinfarction also significantly favoured fondaparinux at day 9 (7.4% (n=444/6036) versus 8.9% (n=537/6056) respectively; HR 0.83 (95% CI: 0.73 to 0.94) and at the end of the study (13% (n=756/6036) versus 15% (n=857/6056) respectively; HR 0.88 (95% CI: 0.79 to 0.97).

In the individual strata, fondaparinux was significantly more effective than placebo in stratum 1 for the primary endpoint at 30 days (11% (n=317/2823) versus 14% (n=396/2835) respectively; HR 0.79 (95% CI: 0.68 to 0.92)). However in stratum 2, fondaparinux was not significantly different from UFH (8.3% (n=268/3213) versus 8.7% (n=281/3221); HR 0.96 (95% CI: 0.81 to 1.1). In the subgroup of patients who did not undergo primary PCI (i.e. the licensed population), the rate of death or reinfarction at day 30 was 11% (n=471/4147) in the fondaparinux group and 14% (n=584/4147) in the control group (HR: 0.80 (95% CI: 0.70 to 0.90).

Summary of evidence on comparative safety

There were fewer episodes of severe haemorrhage (as defined by Thrombolysis in Myocardial Infarction (TIMI) criteria) in the fondaparinux group compared to the control group but the difference was not significant (1.0% (n=61/6036) versus 1.3% (n=79/6056) respectively). When analysed by stratum, there were fewer episodes of severe haemorrhage in the fondaparinux group compared with the placebo group of stratum 1 (1.0% versus 1.6%). However in stratum 2, the incidence was 1.1% in each group.

There was a higher incidence of severe haemorrhage and serious coronary complication in the subgroup of patients undergoing PCI treated with fondaparinux.

Summary of clinical effectiveness issues

The study design was relatively complex with fondaparinux compared with control (either placebo or UFH) against a background of “usual care” which was a heterogeneous mixture of practices and although randomisation was stratified in an effort to compensate for these differences, it makes the results difficult to interpret. Fondaparinux (median duration of 7 or 8 days) was compared with no anticoagulation plus usual care or UFH (median duration of 45 hours) plus usual care. The longer period of administration of fondaparinux may in part account for the reduction in death/reinfarction. Recent guidance recommends that anticoagulant therapy should be continued for 8 days or until hospital discharge or coronary revascularisation.

A number of factors may influence the applicability of the study results to routine clinical practice in Scotland. Only 53% of patients received treatment with UFH compared to a figure of 85% from European Heart Survey data. Primary PCI within 90 minutes of diagnosis is recommended as the optimal treatment of STEMI and has been associated with improved short and long-term outcomes. Only 31% of study patients were treated with primary PCI. However, since this subgroup of patients achieved no benefit with fondaparinux, they are not included in the licensed indication. In terms of standard treatment, of the 45% of patients treated with thrombolytics, the majority received streptokinase (73%), a non-fibrin specific agent. Current guidance recommends the use of fibrin-specific agents. In addition, only 58% of the study population received clopidogrel or ticlopidine in hospital after randomisation. In Scottish clinical practice, in line with current guidance, this figure is now likely to be higher.

These factors also caused the European Medicines Agency (EMEA) to question the relevance of the study population to European Union practice. The relatively high study mortality rate raised further concern about potential differences in background therapy and treatment care compared to current European practice. However, it was felt that the results could still be applicable to European patients.

The incidence of bleeding in the fondaparinux group is low and was numerically lower than placebo in stratum 1. Since the study excluded patients likely to be at high risk of bleeding, the rates of bleeding in clinical practice may be higher.

Fondaparinux offers advantages in administration as a subcutaneous (intravenous for first dose only) injection with a single standard dose and no need for weight-based dose calculation or for monitoring and subsequent dose adjustment.

In the STEMI population, there is no direct comparison between fondaparinux and low molecular weight heparin, and markedly different study inclusion criteria make indirect comparison difficult. There is insufficient evidence to suggest that fondaparinux is superior to low molecular weight heparin.

Experts noted that the trial may not reflect clinical practice in Scotland and therefore in practice the benefits may not be as large as in the trial.

Summary of comparative health economic evidence

The manufacturer presented a cost-utility analysis comparing fondaparinux to either placebo for those patients who were not eligible for treatment with UFH or UFH for patients who were eligible to receive it. This was based on a reanalysis of the pivotal trial excluding PCI patients in line with the licensed indication, focussing on outcomes at the secondary outcome point of 180 days. This was analysed for the two strata: those with an indication for UFH and those without an indication for UFH, the former comparison being the most relevant.

In the model, during the 180 day trial period patients could have a recurrent non-fatal MI, or die of an event; they could also experience minor or major haemorrhage. Among those surviving at 180 days evidence from the literature was used to estimate their increased mortality risk relative to the general population.

Resource use per event was drawn from the multinational trial of enoxaparin and fondaparinux for non-STEMI as it was felt that resource use per event within the pivotal would be inappropriate given that the majority of patients were recruited from Eastern Europe, Asia or Africa. Quality of life values were drawn from the literature; age-standardised quality of life values being adjusted by decrements for having acute coronary syndrome and for having had an MI.

In the stratum with no indication for UFH, fondaparinux was found to save £17 per patient, yield 0.059 QALYs and therefore to be the dominant treatment. In the stratum with an indication for UFH, fondaparinux was found to cost an additional £97 per patient, yielding 0.273 QALYs and so have an incremental cost-effectiveness ratio of £355 per QALY. On the basis of the probabilistic sensitivity analysis that was provided, both cost-effectiveness estimates were considered robust.

The main concern with the analysis was the relevance of the control arms of the pivotal trial to current practice in NHS Scotland. More minor concerns related to the transparency of how the relative mortality risks were derived and the lower rates of haemorrhage contributing to some, but not all, of the cost offsets.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published "Acute coronary syndromes. A national clinical guideline" in February 2007. In patients with ST segment elevation acute coronary syndrome, this recommends the use of fondaparinux or a low molecular weight heparin at various stages and as maintenance in-hospital medication. Fondaparinux is recommended for patients with ST segment elevation acute coronary syndrome who do not receive reperfusion therapy.

Additional information: comparators

The most likely comparators are UFH or low molecular weight heparin (e.g. enoxaparin) as recommended by SIGN but not licensed for this indication.

Cost of relevant comparators

Drug	Dose regimen	Cost per course (£)
Fondaparinux	**2.5mg once daily**	**£6.67 x 8 days = £53.36**
Enoxaparin*	30mg IV bolus plus 1mg/kg SC twice daily	£22.20 plus £9.50 - £10.80 x 8 days = £98.20 - £108.60**
Unfractionated heparin	4000U IV bolus plus 1000U/h IV infusion	£0.54 plus £1.50/24 hour infusion £12.54 in 8days

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 5.11.07.
*enoxaparin is not currently licensed for this indication.
**enoxaparin cost based on 60-80 kg bodyweight

Additional information: budget impact

The manufacturer estimated a gross budget impact of between £186k and £371k in year 1, rising to between £1.3m and £1.5m by year 5. The net drug cost was estimated as being between £166k and £332k in year 1, rising to between £1.1m and £1.4m by year 5.

This was based upon an initial 5-10% market share rising by 5% annually, and an eligible population of around 80,000 in year 1, rising to 110,000 in year 5. The eligible population estimates were based upon both the incident and prevalent STEMI population in order to account for the treatment of new as well as recurrent MI.

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 December 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 references were supplied with the submission. Those shaded grey are additional to those supplied with the submission.

The OASIS-6 Trial Group. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segmment elevation myocardial infacrtion. JAMA 2006; 295: 1519-1530.

Califf RM. Fondaparinux in ST-segment elevation myocardial infarction. The drug, the strategy, the environment, or all of the above? Editorial. JAMA 2006; 295:1579-1578.

European Medicines Agency (EMEA). European public assessment report (EPAR) for fondaparinux. www.emea.eu.int