All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report:

Fondaparinux Sodium (Arixtra®) for the treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI)

GlaxoSmithKline

Advice No: 0608

Recommendation of AWMSG

Fondaparinux (Arixtra®) should be recommended as an option for use in the treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in patients for whom urgent (less than 120 minutes) invasive management (percutaneous coronary intervention [PCI]) is not indicated.

Treatment with fondaparinux (Arixtra®) and its monitoring/supervision should be retained under secondary care.

AWMSG is of the opinion that fondaparinux (Arixtra®) would not be suitable for shared care within NHS Wales.

This report should be cited as:

1.0 RECOMMENDATION OF AWMSG

The AWMSG recommendation is based on: the Preliminary Appraisal Report, the Company Response to this, the Form B submission, medical expert opinion and discussions at the AWMSG meeting.

Date: Wednesday, 16th April 2008

The recommendation of AWMSG is:

Fondaparinux (Arixtra®) should be recommended as an option for use in the treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in patients for whom urgent (less than 120 minutes) invasive management (percutaneous coronary intervention [PCI]) is not indicated.

Treatment with fondaparinux (Arixtra®) and its monitoring/supervision should be retained under secondary care.

AWMSG is of the opinion that fondaparinux (Arixtra®) would not be suitable for shared care within NHS Wales.

Additional note:

- AWMSG is of the view that formalised early risk assessment is good practice to determine which patients are likely to undergo early, invasive intervention. Fondaparinux would not be suitable for these patients.

- Consensus in approach to management in this treatment area would be welcomed in Wales.

2.0 PRODUCT DETAILS:

2.1 Licensed indication[1]:

Fondaparinux is licensed in the treatment of unstable angina or non-ST segment elevation myocardial infarction (UA/NSTEMI) in patients for whom urgent (less than 120 minutes) invasive management (percutaneous coronary intervention [PCI]) is not indicated.

Fondaparinux is also licensed for other indications, a full list of which can be found in the Summary of Product Characteristics (SPC) [1].

2.2 Dosing[1]:

For the treatment of 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 eight days or until hospital discharge if that occurs earlier.

2.3 Market authorisation date: 29th August 2007[2]

2.4 UK Launch date: September 2007[3]

3.0 DECISION CONTEXT

Acute coronary syndrome (ACS) comprises a range of unstable coronary disease, which includes unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI) or ST segment elevation myocardial infarction (STEMI) [4]. This appraisal focuses on the use of fondaparinux in the treatment of UA/NSTEMI ACS. Its use in the treatment of STEMI is the subject of AWMSG appraisal number 0508.

A key element of the management of ACS is the determination of the presence or absence of ST segment elevation using an electrocardiogram. The initial strategy for patients with acute chest pain but without persistent ST- segment elevation, is to alleviate ischaemia and symptoms, to undertake serial ECG monitoring, and repeat measurements of markers of myocardial necrosis [4]. The working diagnosis of non-ST-segment elevation acute coronary syndrome, based on measurements of troponins, can then be further qualified into NSTEMI or UA [4].

The company, in their submission, estimate the prevalence of UA/NSTEMI ACS patients in Wales in 2008 to be 87,629; with an estimated incidence of 8,935 [5]. Furthermore, approximately 114,000 hospital admissions annually in the UK are due to this condition [6]. Notably, such patients are at an increased risk of death, with the increased risk extending up to and beyond six months. In a cohort of UA/NSTEMI ACS patients the overall mortality at a maximum of 45 months was 22%, and the majority of these deaths were cardiovascular in nature [7]. This poor prognosis for patients with ACS is recognised by the European Society of Cardiology (ESC) guidelines [4].

In contrast to STEMI, where most events occur before or shortly after presentation, in NSTEMI/UA these events continue over days and weeks. This implies that treatment strategies need to address the requirements of the acute phase as well as longer-term treatment [4]. Acute treatment involves: anti-ischaemic agents, anticoagulants, antiplatelets, and coronary revascularisation (PCI). The therapeutic approach is based on whether the patient is to be only medically treated, or in addition referred for angiography and revascularisation [4].

Notably, bleeding is reported to be associated with an increased risk of adverse outcomes such as MI, and death [8-10]. Anticoagulants, such as the low molecular weight heparins (LMWH) have been shown to reduce ischaemic coronary events, however they are associated with an increased risk of bleeding [11,12]. The risk of bleeding with LMWH is dose-related and is increased with higher age, female gender, lower body weight, reduced renal function, and interventional procedures [4,13].

Fondaparinux is a synthetic pentasaccaride that is structurally related to the antithrombin-binding site of heparin and LMWH. In contrast to heparin, however, fondaparinux selectively binds to antithrombin and causes rapid inhibition of activated Factor X [14]. It has no significant influence on the usual variables that monitor anticoagulant activity, such as aPTT, activated clotting times, prothrombin, and thrombin times[4]. Consequently, fondaparinux might also be an alternative to LMWH in the treatment of UA/NSTEMI ACS.

4.0 EXECUTIVE SUMMARY:

4.1 Review of the evidence on clinical effectiveness

Evidence included in the company submission for the use of fondaparinux in the treatment of UA/NSTEMI ACS is derived from the OASIS-5 trial and a randomised dose finding study. Data from the pivotal trial (OASIS-5), which included a total of 20,078 patients, demonstrates in the short term (at nine days), that fondaparinux and the LMWH, enoxaparin, have similar efficacy in the prevention of death, myocardial infarction, or recurrent ischaemia in those presenting within 24 hours with symptoms of UA/NSTEMI. Fondaparinux also demonstrated a reduced risk of bleeding, which was associated with lower, long-term mortality (up to 180 days). Post ad hoc analysis of the licensed population showed similar outcomes to that of the study population as a whole. Enoxaparin was considered to be a valid comparator based on its common usage in the management of UA/NSTEMI and also its general recommendation in the ESC guidelines.

4.2 Review of the evidence on cost-effectiveness

The company submitted an economic model that compares fondaparinux with the LMWH enoxaparin in patients with UA/NSTEMI who are ineligible for urgent (<120 minutes) invasive management (PCI).

The initial 180-day efficacy data used in the model relates to the whole population of the OASIS-5 trial; 7.2% of which do not meet the licensed indication for fondaparinux. A key outcome in the model would appear to be stroke, which is estimated to be associated with the greatest decrement in utility and the greatest risk of death out of the outcomes considered in the model. As with the other individual events included in the model, the OASIS-5 trial was not powered for stroke outcome. Other uncertainties include the resource use, and the handling of utility values in the long term, which may to a degree bias the model in favour of fondaparinux.

In the base-case analysis, fondaparinux is less expensive than enoxaparin (-£52 [95% CI: -£173 to +£106]) and is associated with a gain of 0.043 QALYs (95% CI: 0.005 to 0.093). Therefore, fondaparinux dominates enoxaparin in the primary analysis. Sensitivity analysis indicates this is sensitive to the assumption of conditional independence of costs (i.e. the assumption that differences in costs, other than study drug, result only from differential event rates). Removing this assumption results in fondaparinux no longer being dominant over enoxaparin, with an incremental cost per QALY gained of £4,429.

5.0 LIMITATIONS OF DECISION CONTEXT:

- Exclusions criteria from OASIS-5 trial include poor renal function. There is limited clinical data available on the use of fondaparinux in patients with creatinine clearance between 20 and 30ml/min.
- Clinical and safety data are limited in children; fondaparinux is therefore not recommended in patients below 17 years of age.

6.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

6.1 Clinical efficacy:

Evidence included in the company submission for the use of fondaparinux in the treatment of UA/NSTEMI ACS patients is derived from the pivotal OASIS-5 trial and a randomised dose finding trial, both of which compare fondaparinux to the low molecular weight heparin, enoxaparin [14-16].

6.1.1 The Fifth Organisation to Assess Strategies in Acute Ischaemic Syndromes Investigators (OASIS-5) Trial[15]

This study was a Phase III multinational, randomised, double blind, double dummy trial in which fondaparinux was compared to enoxaparin in 20,078 patients within 24 hours of the onset of symptoms of UA/NSTEMI. Patients were eligible if they met at least two of the three following criteria: an age of at least 60 years; an elevated troponin or creatine kinase MB isoenzyme; or electrocardiographic changes indicative of ischaemia. Patients were excluded if there was a contraindication to LMWH, they had had a recent haemorrhagic stroke, there were indications for anticoagulation other than ACS or they had a serum creatinine level of ≥ 3 mg/dL. Participants were then randomised equally to receive fondaparinux 2.5mg subcutaneously plus placebo enoxaparin twice daily by subcutaneous injection, or enoxaparin at a dose of 1 mg/kg of body weight twice daily plus placebo fondaparinux once daily by subcutaneous injection. Fondaparinux could be given until hospital discharge or for up to eight days (whichever occurred first), and enoxaparin for two to eight days or until the patient was in a stable condition. Patients undergoing PCI within the first eight days of randomisation also received unfractionated heparin. Follow up was for 90 to180 days.

The objective of the primary efficacy composite outcome (first occurrence of any component of death, myocardial infarction [MI], or refractory ischaemia [RI]) was to demonstrate the non-inferiority of fondaparinux compared to enoxaparin at nine days. Secondary efficacy outcomes included the following: death or MI; death, MI or RI; and the individual components of the composite outcomes at 30 days and at the end of the study (up to180 days). Information on strokes was also collected.

Safety data collected in order to determine whether fondaparinux was superior to enoxaparin in preventing major bleeding is discussed under Section 6.2, as well as an assessment of the balance of benefit and risk of fondaparinux relative to enoxaparin.

Results:

The analyses included all patients who underwent randomisation. Baseline and concomitant medications, and interventions 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 (31.2% versus 22% for enoxaparin and fondaparinux, respectively) [5].

The primary efficacy outcome (first occurrence of death, MI or refractory ischaemia at nine days) occurred in 5.8% (579/10,057) of patients randomised to fondaparinux and in 5.7% (573/10,021) of patients randomised to enoxaparin. The hazard ratio (HR) for this outcome was 1.01 (95% confidence interval [CI]: 0.90 to 1.13). These results demonstrate the non-inferiority of fondaparinux compared to enoxaparin with the upper confidence limit within the set boundary of 1.185 (p = 0.007 for non-inferiority). Non-inferiority was also reported for rates of death or MI at nine days (4.1% in both groups; HR 0.99; 95% CI: 0.86 to1.13; p = 0.005).

At 30 days, the composite of death, MI, or RI showed a trend towards a lower rate with fondaparinux than with enoxaparin (8.0% versus 8.6%; HR 0.93; 95% CI: 0.84 to1.02) and so did the composite of death or MI (6.2% versus 6.8%; HR 0.9; 95% CI: 0.81 to 1.01). These differences were considered by Yusuf and colleagues to be due to a significant reduction in mortality with fondaparinux compared to enoxaparin at 30 days (2.9% versus 3.5%, respectively; HR 0.83; 95% CI: 0.71 to 0.97; p=0.02), and 180 days (5.8% versus 6.5%; HR 0.89; 95% CI: 0.80 to 1.00). These differences in the composite endpoint persisted until the end of follow-up; death, MI or RI for fondaparinux compared to enoxaparin at 30 days: 8.0% versus 8.6%; HR 0.93; 95% CI: 0.84 to 1.02; p=0.13, and 180 days: 12.3% versus 13.2%; HR 0.93; 95% CI: 0.86 to 1.00; p=0.06.

The event rates for all adjudicated strokes were low at all time points, with the incidence of stroke numerically lower in the fondaparinux group. The composite secondary endpoint death, MI, or stroke was reduced by 11% at Day 180 (p=0.007)[17].The results for the composite endpoint of death, MI, refractory ischaemia, or major bleeding are reported under Section 6.2.

6.1.2 Post Ad Hoc analysis[5]

A small proportion of the OASIS-5 trial population, 7.2% (1,442 patients) underwent angiography within two hours of randomisation. Post ad-hoc analyses were therefore performed on the subgroup of the trial population that was deemed to reflect the licensed population for fondaparinux (those not indicated for urgent PCI). This analysis was undertaken on the working hypothesis that the clinical effectiveness of fondaparinux in the licensed population was at least as equivalent to that in the total trial population. The results demonstrated that the licensed population was similar to the total OASIS-5 trial population.

Points to note from the study (Sections 6.1.1 and 6.1.2):

- The low molecular weight heparin, enoxaparin, was considered to be a valid comparator based on its common usage in the management of UA/NSTEMI and also its general recommendation in the ESC guidelines [4,17].
- Mean treatment duration was 5.4 versus 5.2 days for fondaparinux and enoxaparin groups, respectively. The general recommendation in the ESC guidelines, which recommends if fondaparinux is the chosen anticoagulant, it should be administered for up to five days or until hospital discharge is based on the findings of this trial[4].
- Fondaparinux demonstrated a reduced risk of bleeding, which was associated with lower, long-term mortality (up to 180 days).
- Approximately 40% of patients underwent PCI and 15% had a by-pass graft.
- The composite of death, MI, stroke was not a pre-specified outcome.

- The Committee of Medicinal Products for Human Use (CHMP) comment that, the observed efficacy and safety profile of fondaparinux 2.5mg for acute treatment of ACS raises the question whether the lower VTE prevention doses of LMWHs might also be effective and better tolerated. Unlike those conducted with fondaparinux, however, the Phase II ACS studies for LMWHs did not evaluate the wide dose range that included the lower VTE prevention doses [17].
- The trial committee adjudicated all events in a blinded fashion; this was maintained for all patients undergoing PCI.
- The company have confirmed that patients with a creatinine clearance between 20 ml/min and 30 ml/min received a dose reduction of enoxaparin subcutaneous injection to 1 mg/kg once a day. This was true for 2.4% (241) patients in the fondaparinux group and 2.4% (242) patients in the enoxaparin group of the trial.

6.1.3 Pentasaccaride in Unstable Angina (PENTUA) Trial [14]

The PENTUA study was a randomised dose finding trial, which compared fondaparinux with the LMWH, enoxaparin for the treatment of UA/NSTEMI patients. The study involved 1,138 patients with ACS without persistent STEMI who were randomised to receive one of four doses of fondaparinux (2.5, 4, 8 or 12 mg once daily) or enoxaparin 1mg per kg twice daily, for three to seven days with the first doses given intravenously. The dosage range for fondaparinux could vary however depending on whether the patient was less than 50kg or more than 100kg in weight. In addition all patients received 75 to 160mg of daily aspirin, preceded by a loading dose if necessary. Of the total trial population, 929 patients had complete follow up information. The primary efficacy outcome measure was the composite endpoint of death (from any cause except bleeding), MI or recurrent ischaemia up to and including day nine. To support this primary efficacy analysis, the incidence of the composite endpoint was also assessed up to and including day 30 [17]. The primary safety analysis is discussed under Section 6.2.

Results:
There was no linear dose response relationship between the incidence of the primary endpoint and any of the tested fondaparinux doses. There was a significant reduction in the composite endpoint at day nine in the 2.5mg fondaparinux group (30.0%) compared to the 4mg (43.5%, p=0.011), 8mg (41%, p=0.036) and the enoxaparin (40.2%, p=0.047) groups; all other differences were not statistically significant [17]. At Day 30 there was also a statistically significant reduction in the composite endpoint between the fondaparinux 2.5mg (33.8%) and the 4mg (44.9%, p=0.032) groups; all other differences were not significant [17].

6.2 Safety [15]:

In the Oasis-5 trial, in order to determine whether fondaparinux was superior to enoxaparin in preventing major bleeding, the primary safety outcome was major bleeding at nine days. In addition, the balance of benefit and risk of fondaparinux relative to enoxaparin was assessed on the basis of the combination of the primary efficacy and safety outcomes (i.e. composite endpoints of death/MI/RI/major bleeding up to 9, 30 and 180 days).

The rate of major bleeding at nine days was lower in the fondaparinux group than the enoxaparin group (2.2% versus 4.1% HR 0.52; 95% CI: 0.44 to 0.61; p<0.001). This difference persisted during the longer-term follow-up (refer to Table 1; Appendix 1).

The composite endpoint of death, MI, refractory ischaemia, or major bleeding was reported as significantly lower in the fondaparinux group compared with the enoxaparin group at nine days (7.3% versus 9.0% respectively; HR 0.81; 95% CI: 0.73 to 0.89; p<0.001), 30 days: 10.2% versus 12.4% (HR 0.82; 95% CI: 0.75 to 0.89; p<0.001), and 180 days: 15% versus 17.1% (HR 0.86; 95% CI: 0.81 to 0.93; p<0.001)The results for the primary safety outcomes in the licensed population were found to be similar to those of the trial population.

The number of patients with intracranial bleeding was the same in each group, however, the numbers of patients with major bleeding requiring surgical intervention, retroperitoneal bleeding, transfusions, and bleeding associated with death at the end of the study were significantly lower with fondaparinux than with enoxaparin (p<0.001 for all comparisons). The rate of major bleeding was also significantly lower with fondaparinux than with enoxaparin among patients with poor renal function (refer to Table 2; Appendix 1) The rate of total bleeding was significantly lower with fondaparinux than with enoxaparin (3.3 versus 7.3%; HR 0.44; 95%CI: 0.39 to 0.50). The rates of bleeding were consistently lower with fondaparinux, regardless of UFH use.

When analysing the difference between the two treatment groups in the number of deaths at the end of the study, 41 fewer patients in the fondaparinux group than in the enoxaparin group died after major bleeding (38 versus 79) and 20 fewer patients in the fondaparinux group died after minor bleeding (13 versus 33).

The composite of death, MI, RI, or major bleeding occurred in 7.3% of the patients in the fondaparinux group, as compared with 9% of the patients in the enoxaparin group (HR 0.81; 95% CI: 0.73 to 0.89; p<0.001) at nine days. This difference persisted until the end of the study.

A total of 1.6% (163/ 9979) serious adverse events (other than death) that occurred in the fondaparinux group and 2.8% (285/9969) in the enoxaparin group were considered drug-related [17]. The profile of adverse events (other than bleeding), were similar in both groups. PCI-related coronary complications such as catheter thrombus formation were observed in both groups. This was at a significantly higher rate with fondaparinux than with enoxaparin (0.9% versus 0.4%, Relative Risk [RR] 3.59, 95% CI: 1.64 to 7.84, p=0.001) [15].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES:

7.1 Comparator medications:

- Enoxaparin
- Dalteparin

7.2 Comparative effectiveness:

- There are currently no ongoing studies of fondaparinux in the treatment of NSTEMI patients or updated analyses of the trials described in Section 6.1 [5].
- Of the total Oasis-5 trial population (refer to Sections 6.1.1 and 6.1.2), 93% (18,631/20,078) of patients were eligible for treatment of UA/NSTEMI ACS within the licensed indication for fondaparinux [5].
- Enoxaparin is administered by subcutaneous injection twice daily at a dose of 1mg/kg body weight. Fondaparinux is also administered subcutaneously, but only once daily and does not require dose adjustment for patient weight, although there is a precaution in the SPC for those with a low body weight (less than 50kg)[1].
- On the basis of the unexpected AE related to catheter thrombus formation during PCI in the pivotal trial [15], the ESC guidelines state that if fondaparinux is chosen as the anticoagulant therapy then it cannot be used as the sole anticoagulant during PCI procedures [4].
- CHMP concluded that the PCI subgroup from the OASIS-5 trial showed no significant advantage for fondaparinux over enoxaparin, and there were clear safety concerns regarding the higher incidence of coronary complications observed during the PCI procedure. Hence, in order to maintain a positive risk: benefit balance in the UA/NSTEMI population, the indication has been restricted to patients for whom urgent (less than 120 minutes) invasive management (PCI) is not indicated.
- Following discussion with the company, AWMSG agreed that enoxaparin was the most appropriate comparator as this is the most commonly used LMWH for UA/NSTEMI within NHS Wales. It should be noted that there is an alternative LMWH, dalteparin, which is also licensed for this condition. There is, however, no comparative data with fondaparinux currently available.

8.0 SUMMARY OF HEALTH ECONOMIC EVIDENCE:

8.1 Overview of the key economic issues for the AWMSG to consider

The key economic issue for the AWMSG to consider is whether any additional benefits offered by the use of fondaparinux in its licensed indication for the treatment of patients with UA/NSTEMI justify any associated increase in costs over relevant comparators.

8.2 Review of published evidence on cost-effectiveness

Standard searches conducted by WMP have not identified any other published economic studies of the use of fondaparinux in the treatment of UA/NSTEMI.

8.3 Review of the company's submission on cost-effectiveness

8.3.1 Description and critique of the company's submission

The company's submission[5] describes a cost-utility analysis of fondaparinux compared with the LMWH enoxaparin in patients with UA/NSTEMI who are ineligible for urgent (<120 minutes) invasive management (PCI). An event-based decision model has been created, with risk equations fitted to data from the OASIS-5 trial to estimate the probabilities of events occurring by 180 days. These risk equations are Weibull functions in which the hazard of the event is estimated as a function of randomised treatment and other covariates, as judged relevant by an expert clinician. Patients may fall into one of five mutually exclusive model states at 180 days: dead (fatal cardiovascular event or other cause of death), alive having experienced a non-fatal MI, alive having experienced a non-fatal stroke, alive having experienced both non-fatal events and alive having experienced neither event. This is in contrast to the submission made for the STEMI indication, which does not consider stroke. Relative risks (RRs) of mortality compared with the general population have then been attached to these model states to determine the prognosis over the remainder of the patients' lives using a Markov model run over what appears to be 85 years[5].

The model assumes that the effectiveness of treatment in the first 180 days influences prognosis over the remaining lifetime of patients, which is compounded by assumed constant relative risks of mortality derived from NSTEMI patients. The efficacy data used in the model relates to the whole population of the OASIS-5 trial, 7.2% of which do not meet the licensed indication for fondaparinux in the treatment of UA/NSTEMI. Utility weights for the model were derived from age-specific UK population norms, with decrements for non-fatal MI, non-fatal stroke and ACS based on published EQ-5D survey data from US patients, rather than from patients in trials of fondaparinux. Resource use beyond 180 days has been taken from a published review of clopidogrel in NSTEMI[5]. These are sources of uncertainty in the model. The model has been provided.

8.3.2 Population

The OASIS-5 study [15], on which the 180-day efficacy data for the model is based, was conducted in 20,078 patients with UA/NSTEMI presenting within 24 hours of the onset of symptoms. Those with a high risk of bleeding, or those receiving anticoagulants, were excluded from the trial. Patients were randomised to receive fondaparinux or enoxaparin. 7.2% of the trial population were referred for angiography, suggesting they were candidates for urgent PCI. These patients do not meet the licensed indication for fondaparinux [1]. The economic model however, uses data based on the entire trial population. This has been justified on the basis that post hoc analyses indicate the baseline characteristics and outcomes are very similar for the entire trial population and

for the subpopulation that meets the licensed indication for fondaparinux in UA/NSTEMI (see Section 8.3.5 below).

8.3.3 Perspective and time horizon

The model considers direct health-related costs from the perspective of NHS Wales[5]. A lifetime time horizon has been used in the base case analysis [5], which would seem appropriate for this disease area.

8.3.4 Comparator

The model compares fondaparinux 2.5mg subcutaneously daily against enoxaparin 1mg/kg subcutaneously twice daily. This would seem appropriate for this indication[18].

8.3.5 Clinical inputs

8.3.5.1 Efficacy data

The probabilities of clinical events occurring by 180 days are based on risk equations derived from the entire OASIS-5 trial population data. A *post hoc* analysis of the OASIS-5 data restricted to those patients meeting the licensed indication for fondaparinux suggests that the baseline characteristics and outcomes achieved were numerically similar to those of the entire OASIS-5 trial population[19]. On this basis, the company submission states that the use of the entire OASIS-5 population data in the model is justified, and preserves the randomisation of the trial participants[5]. The data for the licensed indication could also have been used in sensitivity analysis to explore any differences in the model outputs; however this has not been done. There are some small differences in the event hazard ratios that favour fondaparinux in the OASIS-5 population compared with the licensed population. The cumulative impact on the model outputs of these apparently small differences is unclear.

The hazard ratio for stroke at 180 days in the OASIS-5 trial (fondaparinux versus enoxaparin, 0.78 [95%CI: 0.62–0.99]) is substantially lower than that for any of the other outcomes considered in the model and would be expected to be a significant driver of the model outputs, especially as the data used in the model indicates that stroke is also associated with the greatest decrement in utility values and the greatest RR of mortality in the longer term (see below). It should be noted that the outcome of stroke is not included in the model for the STEMI submission. As with the other individual events included in the model, the OASIS-5 trial was not powered for stroke outcome, and only in the entire trial population at 180 days was a p-value of <0.05 achieved (p=0.04). The significant contribution that this outcome appears to make to the model should be interpreted accordingly.

For each of the five risk equations, the choice of covariates was based on the judgement of trial steering group clinicians, guided by those variables (which were available in OASIS-5), used in the TIMI and GRACE risk scoring systems for non ST-segment elevation ACS, and regardless of each covariates' statistical significance. These covariates were treatment, age, gender (male), heart failure at entry, history of diabetes, history of hypertension, ST-depression at study entry, and creatinine clearance[5].

Long-term mortality rates are apparently based on Government Actuary Department age and sex-specific life tables for Scotland, which may marginally underestimate life expectancy for the Welsh population. These have been adjusted by the RR of mortality compared with the general population for patients with no further events, those with recurrent non-fatal MI, or stroke (with or without a recurrent non-fatal MI) in the initial 180-day period. A Markov model, which appears to run over 85 years, has been used to model the long-term outcomes and costs[5].

The RRs of mortality are reported to have been obtained from a secondary analysis of the PRAIS study, which followed a cohort of 490 UK patients with NSTEMI for mortality and causes of death for 45 months [7]. An exponential model was fitted to data relating to those who survived at least six months following the acute event, with adjustments for age, history of MI on the previous year and any history of stroke. Based on the fitted model, probabilities of dying within one year were estimated for patients who had a history of MI and for patients who had a history of stroke. The probability of dying for any reason was estimated from UK life tables and the RRs were then estimated by taking the ratio between the probability of dying given a NSTEMI episode and the probability of dying for any reason. Patients who experienced both an MI and stroke had their mortality adjusted on the basis of the more severe event (considered to be stroke in this case) [Personal communication, GSK, February 2008]. The model assumes the same RR of mortality for patients with UA as for those with NSTEMI.

8.3.5.2 Adverse events

Major and minor haemorrhages are the adverse events considered in the model[3]. Risk equations for these events include the same covariates as above.

8.3.5.3 Utility weights

Utility weights for the model were derived from age-specific UK population norms, with decrements applied for non-fatal MI, non-fatal stroke and ACS [20]. The decrements are based on published EQ-5D data collected in 2000–02 from US patients and relate to ICD 9 definitions of acute MI (decrement of 0.0409, n=244), cerebrovascular accident (decrement of 0.0524, n=340) and other chronic ischaemic heart conditions (decrement of 0.0336, n=183), respectively [21]. The extent to which these decrements reflect those that would be experienced by patients in Wales is unclear. No data are presented for patients who experience both non-fatal events over time. In addition, the decrements associated with the acute events of stroke and MI are assumed to persist in the long term. Whilst it may be reasonable to assume that the decrement in utility related to ACS will persist throughout life, the decrement associated with the acute events of MI or stroke may reasonably be expected to change over time.

8.3.6 Healthcare resource utilisation and cost

Resource use in the first 180 days has been taken from the OASIS-5 trial. Unit costs, derived from published sources and inflated to 2006 prices, have been applied to the resource use associated with these events and regression modelling has then been used to estimate the mean costs of patients with and without events[5]. These data from OASIS-5 cover resource use categories including general inpatient days in hospital; days in intensive care/coronary care units, major therapeutic and diagnostic procedures, concomitant medications and blood transfusions[22]. Details, however of only selected procedures and concomitant drugs are provided [22].

Only around a quarter of the trial population were recruited from North West Europe and only 1.5% from the UK[5]. There is no indication in the submission that the assumed resource use has been verified by Welsh clinicians, and in the base case analysis the cost regression was based on all trial participants with a dummy variable used to indicate whether a patient was treated in the UK. Those patients not experiencing any further events in the initial 180-day period, and who were treated in the UK, attracted lower costs than those treated elsewhere. Resource use, based on patients from North West Europe, is also explored in the model [22].

In the period beyond 180 days, resource use data has been derived from a health technology assessment of clopidogrel in NSTEMI[23]. This assumes that no subsequent events beyond 180 days attract additional costs to those of event free ACS.

8.3.7 Discounting

All costs and outcomes were discounted at 3.5% in the base case analysis[5], which is the preferred discount rate. Sensitivity analysis explores discount rates of 0% and 6%.

8.3.8 Results

In the base-case analysis, fondaparinux dominates enoxaparin on the basis of lower costs
(-£52 [95% CI: -£173 to +£106]) and a gain of 0.043 QALYs (95% CI: 0.005 to 0.093).

8.3.9 Sensitivity analysis

8.3.9.1 One-way sensitivity analyses

One-way sensitivity analyses have explored the impact of restricting the time horizon to within the trial period of 180 days, replacing the UK population data in the cost regression with the North West Europe population, and incorporating a fondaparinux treatment coefficient into the cost regression (which removes the assumption of conditional independence of costs, i.e. the assumption that differences in costs, other than study drug, result only from differential event rates). In the first two scenarios, fondaparinux still dominates enoxaparin. In the latter scenario, fondaparinux costs increased by £186, resulting in the incremental cost per QALY gained with fondaparinux over enoxaparin being £4,429 (incremental costs of £186 and a gain of 0.042 QALYs)[22]. Heterogeneity of patient risk has been explored by ranking patients in terms of their net benefits and applying risk factors associated with the 2.5th, 25th, 50th, 75th and 97.5th percentiles of net benefit. When the fondaparinux treatment coefficient of the cost regression is excluded (as in the base case), fondaparinux dominates enoxaparin across all percentiles of net benefit. Inclusion of the coefficient results in an expected incremental cost per QALY of £826 for the highest 2.5th percentile of net benefit, and £11,460 for the 97.5th percentile[3].

Other uncertain aspects of the parameters used in the model have not been explored (e.g. efficacy data in the licensed population, long term resource use).

8.3.9.2 Probabilistic sensitivity analysis

Appropriate distributions appear to have been fitted to the parameters of the model and Monte Carlo simulation was performed (1000 simulations appear to have been run in the model). Cost-effectiveness acceptability curves were generated from the results[5].

The probability of fondaparinux being cost-effective vs. enoxaparin at a willingness to pay (WTP) threshold of £10,000 per QALY gained is stated as 100%[3].

Analyses of the 2.5th, 25th, 50th, 75th and 97.5th percentiles of net benefit have been conducted, and also indicate that the probability of fondaparinux being cost effective versus enoxaparin approaches 100% in all cases at a WTP threshold of £10,000 per QALY[5].

8.4 Review of evidence on budget impact:

8.4.1 Description and critique of the company's submission

The company's submission considers the impact of the use of fondaparinux in its licensed indication in UA/NSTEMI (patients with UA/NSTEMI in who urgent invasive management is not indicated) [5]. The analysis uses an number of assumptions, which are subject to a degree of uncertainty.

In the absence of Welsh national data specifically in relation to the number of patients experiencing STEMIs and NSTEMIs, it is assumed that the proportions of these in a global registry study of ACS are representative of those in Wales. These data have been applied to the estimated number of CHD cases each year, which is made up of a constant percentage of the population, plus incident cases. The incident cases are estimated based on trends observed in a study of GP database records, which have been observed to change over time. The model also assumes that the proportion of patients undergoing urgent invasive management in the OASIS-5 trial (7.2%[2]) is representative of the situation in Wales, and that the remainder (92.8%) are eligible for treatment with fondaparinux[5].

8.4.2 Perspective and time horizon

The perspective adopted by the budget impact analysis is that of NHS Wales, with a five-year time horizon[5].

8.4.3 Data sources

8.4.3.1 Incident cases

Based on a study of UK general practice database records between 1996 and 2005, the age-standardised incidence of coronary heart disease (CHD) decreased by 2% per year to 4.84 per 1000 population in 2005. This study also indicated that the average annual mortality rate decreased by 3.35%, such that in 2005 the mortality rate was 2.65%[24]. Based on population estimates for Wales in 2008, incident cases of CHD would be 14,182. Based on a global registry study of patients with ACS[25], it has been estimated that around 25% of patients with CHD have NSTEMI and 38% have UA[3] (however, the figures from the registry study suggest these are 28% and 40%, respectively[25]). On this basis, the company submission claims there would be 8935 incident cases of UA/NSTEMI in 2008, rising to 9135 in 2012[5]. These estimates however, would be higher if the figures of 28% and 40% are used.

8.4.3.2 Prevalent cases

Based on Quality and Outcomes Framework data described by the British Heart Foundation, the prevalence of CHD in Wales has been taken to be 4.3%[5]. This is assumed to remain constant. Taking account of the CHD mortality rates above (stated to be 2.65% and to be decreasing each year by 3.35%), the company submission states that in 2008 this would yield 128,567 prevalent CHD cases plus the incident cases of 14,182 calculated above, equivalent to 139,093 people with CHD in 2008. Based on the assumption that 63% of these cases are due to UA/NSTEMI (25% NSTEMI and 38% UA as assumed in the company submission), the model estimates that there would be 87,629 cases of UA/NSTEMI in 2008, rising to 89,599 in 2012[3].

There appears, however, to be errors in the calculation of CHD mortality each year and in the incidence of CHD. The figures presented indicate a CHD mortality rate of 2.84% has been used consistently, rather than 2.65% decreasing by 3.35% each year. The CHD incidence rate of 4.84 per 1000 has been reduced by 2% in 2009, but not further reduced in subsequent years. The quoted figures for the number of patients eligible for fondaparinux in each year are therefore not consistent with the stated assumptions used for their calculation. These uncertainties are potentially further compounded by the assumed proportions of ACS patients with UA and NSTEMI and the assumption that the proportion of these undergoing urgent PCI is the same as in the OASIS-5 trial.

8.4.3.3 Rates of adoption

Two scenarios of uptake are described: an uptake of 5% in 2008 followed by an increase of 5% each year, and an uptake of 10% in 2008 followed by an increase of 10% each year[3].

8.4.3.4 Costs and resource use

The direct costs of treatment with fondaparinux 2.5mg daily or enoxaparin 1mg/kg twice daily are based on mean treatment durations in the OASIS-5 trial (approximately five days for each). Drug costs have been applied to the quantities of drug used, with two scenarios presented: one with average patient weight of 60kg and one of 70kg[5].

Fondaparinux 2.5mg daily costs £6.66. Enoxaparin 1mg/kg twice daily costs £9.50 in a 60kg patient (based on two Clexane® 60mg pre-filled syringes). Enoxaparin 1mg/kg twice daily costs £10.80 in a 70kg patient (based on two Clexane® 80mg pre-filled syringes) [26].

8.4.4 Results

Only the direct costs of drug treatment are considered. The figures below relate to the stated estimates of eligible patients in the company submission, which do not appear to have been computed from the stated assumptions. As fondaparinux treatment is less expensive than enoxaparin on a daily basis, the use of fondaparinux instead of enoxaparin is estimated to result in net cost savings.

8.4.4.1 Scenario 1: 5% initial uptake in 2008, rising to 25% in 2012

	Net savings in 2008	Net savings in 2012
60kg patient	£57,533	£294,135
70kg patient	£83,962	£429,251

8.4.4.2 Scenario 2: 10% initial uptake, rising to 50% in 2012

	Net savings in 2008	Net savings in 2012
60kg patient	£115,067	£588,271
70kg patient	£167,924	£858,501

8.4.5 Sensitivity analysis

No sensitivity analyses have been conducted.

9.0 ADDITIONAL INFORMATION:

9.1 Guidance and audit requirements:

- The licensed indication statement for fondaparinux in patients with UA/NSTEMI ACS aligns to the recommendations in recently published ESC Guidelines for the diagnosis and treatment of UA/NSTEMI ACS 2007 [4].
- Fondaparinux would not be suitable for a shared-care agreement. Treatment, monitoring, and supervision should be retained under specialist care.

9.2 Related advice:

- The ESC Guidelines for diagnosis and treatment of non-ST-segment elevation acute coronary syndromes [4].
- Scottish Intercollegiate Guidelines Network (SIGN). Acute Coronary Syndromes. National Clinical Guidelines No.93; February 2007[18].
- Department of Health 2000. Coronary Heart Disease: National Service Framework for coronary heart diseases – modern standards and service model[27].
- Das R, Kilcullen N, Morrell C, et al. The British Cardiac Society Working Group definition of myocardial infarction: implications for practice. Heart 2006; 92(1): 21-26 [28].

9.3 Previous AWMSG/NICE advice

None.

9.4 Patient Interest Group information

A patient interest group submission was not received.

References

1. Summary of Product Characteristics. Arixtra®. GlaxoSmithKline UK. 9th October 2007. Available at: http://emc.medicines.org.uk/ (accessed December 2007)
2. European Public Assessment report: Procedural Steps Taken. Major and/or minor changes and summaries after authorisation: Fondaparinux Sodium (Arixtra®) http://www.emea.europa.eu/humandocs/PDFs/EPAR/arixtra/011502en8b.pdf (accessed December 2007).
3. Form A: Initial appraisal information. GlaxoSmithKline. August 2007.
4. Bassand J-P, Hamm CW, Addissino D et al. Task Force for Guidelines for diagnosis and treatment of non-ST-segment elevation acute coronary syndromes of the European Society of Cardiology. European Heart Journal 2007;28:1598-1660.
5. Form B: Detailed appraisal information. GlaxoSmithKline. 16th November 2007.
6. Bakhai A, Flather MD, Collinson JR, et al. National economic impact of tirofiban for unstable angina and myocardial infarction without ST elevation; example from the United Kingdom. International Journal of Cardiology 2003; 91(2-3): 163-72.
7. Taneja AK, Collinson J, Flather MD, et al. Mortality following non-ST elevation acute coronary syndrome: 4 years follow-up of the PRAIS UK Registry (Prospective Registry of Acute Ischaemic Syndromes in the UK). European Heart Journal 2004; 25(22): 2013-18.
8. Kinnaird TD, Stabile E, Mintz GS, et al. Incidence, predictors, and prognostic implications of bleeding and blood transfusion following percutaneous coronary interventions. American Journal of Cardiology 2003; 92(8): 930-35.
9. Rao SV, O'Grady K, Pieper KS, et al. Impact of bleeding severity on clinical outcomes among patients with acute coronary syndromes. American Journal of Cardiology 2005; 96(9): 1200-06.
10. Rao SV, Jollis JG, Harrington RA, et al. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. Journal of the American Medical Association 2004; 292(13): 1555-62.
11. Rao SV, Eikelboom JA, Granger CB, et al. Bleeding and blood transfusion issues in patients with non-ST-segment elevation acute coronary syndromes. European Heart Journal 2007; 28(10): 1193-204.
12. Eikelboom JW, Anand SS, Malmberg K, et al. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. Lancet 2000; 355(9219): 1936-42.
13. Hirsh J, Raschke R. Heparin and low-molecular-weight heparin: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004;126:188S–203S.
14. Simoons ML, Bobbink IW, Boland J, et al. A dose-finding study of fondaparinux in patients with non-ST-segment elevation acute coronary syndromes: The Pentasaccharide in Unstable Angina (PENTUA) Study. Journal of the Amercian College of Cardiology 2004; 43(12): 2183-90.

15. Yusuf S, Mehta SR, Chrolavicius S, et al. The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) Investigators. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. New England Journal of Medicine 2006; 354(14): 1464-76.
16. Summary of Product Characteristics. Clexane®. Sanofi-Aventis. 8th December 2006. Available at: http://emc.medicines.ork.uk/ (accessed December 2007)
17. European Public Assessment Report: Scientific Discussion Available at: http://www.emea.europa.eu/humandocs/PDFs/EPAR/arixtra/Arixtra-H-403-II-24.pdf (accessed November 2007)
18. Scottish Intercollegiate Guidelines Network (SIGN). Acute Coronary Syndromes. National Clinical Guidelines No.93; February 2007. Available at: http://www.sign.ac.uk (accessed December 2007)
19. GlaxoSmithKline. Data on File; 2007, (2).
20. Kind P, Hardman G, and Marcran S. UK population norms for EQ-5D. Working Paper 172. Centre for Health Economics, University of York, 1999.
21. Sullivan PW and Ghushchyan V. Preference-based EQ-5D index scores for chronic conditions in the United States. Medical Decision Making 2006; 26: 410–20.
22. Davies A, Stamuli E, and Sculpher M. Fondaparinux versus enoxaparin in acute coronary syndromes (OASIS-5): UK cost-effectiveness analysis. Oxford Outcomes, May 2007. [Appendix 3 of the company submission.]
23. Main C, Palmer S, Griffin S, et al. Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST segment-elevation acute coronary syndromes: a systematic review and economic evaluation. Health Technology Assessment 2004;8(40).
24. Davies A, Smeeth L, and Grundy EMD. Contribution of changes on incidence and mortality to trends in the prevalence of coronary heart disease in the UK: 1996–2005. European Heart Journal 2007; 28:2142–47.
25. Budaj A, Brieger D, Steg PG, et al. Global patterns of use of antithrombotic and antiplatelet therapies in patients with acure coronary syndromes: insights from the Global Registry of Acute Coronary Events (GRACE). American Heart Journal 2003; 146: 999–1006.
26. Martin J. (ed) British National Formulary No. 54, September 2007. Available at: http://www.bnf.org/ (accessed December 2007).
27. Department of Health 2000. Coronary Heart Disease: National Service Framework for coronary heart diseases – modern standards and service model.
28. Das R, Kilcullen N, Morrell C, et al. The British Cardiac Society Working Group definition of myocardial infarction: implications for practice. Heart 2006; 92(1): 21-6.

Appendix 1. Additional Clinical Information

OASIS-5 Trial[15]:

Following an interim statistical analysis, after the initial 4,000 patients, the inclusion criteria for the trial were amended such that patients below the age of 60 were required to have both an elevation of biomarkers and ischemic electrocardiographic changes. At this stage the sample size was increased to 20,000.

Table 1: Main safety outcomes at nine days, 30 days and 180 days in the OASIS-5 trial population [5,15]

	Fondaparinux (N = 10,057)	Enoxaparin (N = 10,021)	Hazard ratio (95% CI)	p value for superiority
	No. of events (% of patients)			
Major bleeding at nine days	217 (2.2)	412 (4.1)	0.52 (0.44 – 0.61)	< 0.001
Major bleeding at 30 days	313 (3.1)	494 (5.0)	0.62 (0.54 – 0.72)	< 0.001
Major bleeding at 180 days	417 (4.3)	569 (5.8)	0.72 (0.64 – 0.82)	< 0.001

Table 2: Major bleeding and related patient characteristics[5,15]

	Fondaparinux (N = 10,057)	Enoxaparin (N = 10,021)	p value
	No.of events		
Surgical intervention	41	77	< 0.001
Retroperitoneal bleeding	9	37	< 0.001
Transfusions	164	287	< 0.001
Associated with death at end of the study	38	79	< 0.001
	% (No of events)		
Creatinine clearance < 30 ml/min	2.4 (6/ 265)	9.9 (26/ 270)	<0.001
Creatinine clearance of at least 30 ml/min	2.2 (211/ 9,743)	4.0 (384/ 9,699)	<0.001

Appendix 2. **Additional Health Economic Information** - none

Appendix 3. Clinical Expert Summary - included as separate document(s)

Appendix 4. Patient Interest Group submission(s) - none

Appendix 5. Company Response- included as a separate document