All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report:

Fondaparinux Sodium (Arixtra®) for the treatment of ST segment elevation myocardial infarction (STEMI)

GlaxoSmithKline

Advice No: 0508

Recommendation of AWMSG

Fondaparinux (Arixtra®) should be recommended as an option for use in the treatment of ST segment elevation myocardial infarction (STEMI) in patients who are managed with thrombolytics or who are initially to receive no other form of reperfusion therapy.

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

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 encourages more research into non-invasively treated patients to help inform a preferred treatment strategy.
- 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 ST segment elevation myocardial infarction (STEMI) in patients who are managed with thrombolytics or who are initially to receive no other form of reperfusion therapy.

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 STEMI, the recommended dose of fondaparinux is 2.5 mg once daily. The first dose 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 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 [2]

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) [3,4]. This appraisal focuses on the use of fondaparinux in the treatment of STEMI ACS. Its use in the treatment of UA/NSTEMI is the subject of AWMSG appraisal number 0608.

The true incidence of STEMI is difficult to establish due to a number of reasons such as silent infarctions, frequency of acute coronary deaths outside hospital and varying methods of diagnosis of the condition [3]. The company estimate in their submission that there will be a prevalence of 41,728 patients with STEMI in Wales in 2008, with 3,158 incident cases [5].

A key element of the management of ACS is the determination of the presence or absence of ST segment elevation using an electrocardiogram [5]. For patients with the clinical presentation of myocardial infarction and with persistent ST-segment elevation, early mechanical reperfusion by percutaneous coronary intervention (PCI) or pharmacological reperfusion with a thrombolytic agent should be performed unless clear contraindications are present [3,6]. The European Society of Cardiology (ESC) guidelines for the treatment of STEMI recommends primary PCI as the preferred reperfusion therapy when it can be performed within 90 minutes after the first medical contact ('call to needle time') [3]. Pharmacological reperfusion involves a variety of therapies, and includes thrombolysis (with a fibrin-specific agent such as tissue plasminogen activator or a non-fibrin specific agent such as streptokinase) [7,8]; which if performed within 12 hours of presentation, is recommended as a suitable alternative to PCI where this is not possible [3].

Heparin has been extensively used during and after fibrinolysis, especially with tissue plasminogen activator. Heparin does not improve immediate clot lysis, but coronary patency evaluated hours or days after fibrinolysis with tissue plasminogen activator appears to be better with intravenous heparin [3,9-11]. This has not been found to be the case for either subcutaneous or intravenous heparin with streptokinase [3,12]. Low molecular weight heparin (LMWH) has been studied in patients with ACS [13-17]. The potential benefits in combination with fibrinolytic agents in the treatment of STEMI has also been highlighted by the ESC task force, although no LMWH is currently licensed for use in this setting and no recommendation for use is made in the current ESC guidelines [3,6]. The important independent and additional benefit of aspirin has been demonstrated [18] and guidelines do currently recommend patients should also be treated with a combination of aspirin and clopidogrel therapy [3,19]. The use of other potent antiplatelet agents during early PCI (glycoprotein IIb/IIa receptor antagonists and thienopyridines) has also been investigated in recent years [3].

Fondaparinux is a synthetic pentasaccaride that is structurally related to the antithrombin-binding site of heparin. In contrast to heparin, however, fondaparinux selectively binds to antithrombin and causes rapid inhibition of activated Factor X [20]. It has no significant influence on the usual variables that monitor anticoagulant activity, such as aPTT, activated clotting times, prothrombin, and thrombin times[21]. Consequently, fondaparinux might be an alternative to unfractionated heparin (UFH), or best supportive care (BSC) for some patients who are not suitable to receive UFH, in the treatment of STEMI ACS.

4.0 EXECUTIVE SUMMARY:

4.1 Review of the evidence on clinical effectiveness

The OASIS-6 trial involving 12,092 patients with STEMI, demonstrates a moderate reduction in mortality and re-infarction with the use of fondaparinux versus usual care. The reduction however was most marked in those not undergoing PCI and those who were at higher risk. Post ad hoc analysis of the licensed population (patients undergoing thrombolysis or no initial reperfusion) showed a statistically significant reduction in death and re-infarction which was consistent cross both strata of the study. No increase in major bleeding or intracranial haemorrhage with the use of fondaparinux was observed during the trial. Unfractionated heparin or best supportive care, are considered to be valid comparators based on current clinical practice and European Society of Cardiology (ESC) guidelines.

4.2 Review of the evidence on cost-effectiveness

The company submitted an economic model that compares fondaparinux against UFH, or BSC where UFH is not indicated, in patients with STEMI who are managed with thrombolytics or who are to receive no other form of reperfusion therapy.

There are several uncertainties in the model. These include the short term efficacy data being derived from a post hoc subgroup analysis of an already stratified population, the possibility that the modelled short term benefits of fondaparinux are due in part to inadequate duration of anticoagulation with UFH, the unknown effect of the omission of stroke as an outcome, the long term efficacy data being derived from NSTEMI data, and assumptions around resource use and handling of utility values in the long term, which may to a degree bias the model in favour of fondaparinux. The extent to which these influence the model outputs is unknown. However, the base case analysis indicates that fondaparinux dominates BSC and has an incremental cost per QALY versus UFH of £355.

5.0 LIMITATIONS OF DECISION CONTEXT:

- Clinical and safety data are limited in children, fondaparinux is therefore not recommended in patients below 17 years of age.
- There is limited clinical data available on the use of fondaparinux 2.5mg once daily in patients with a creatinine clearance between 20 and 30ml/min.
- Fondaparinux should be used with caution in those at an increased risk of bleeding as highlighted in the Summary of Product Characteristics.

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 STEMI ACS patients is derived from the pivotal OASIS-6 trial, which set out to evaluate the impact of fondaparinux compared to standard approaches to antithrombotic therapy in a broad range of patients with STEMI ACS [22,23].

6.1.1 OASIS-6 (Organisation for the Assessment of Strategies for Ischaemic Syndromes) trial [22,23]

This was a Phase III, randomised, double blind, parallel-group, controlled trial involving 12,092 patients with STEMI, which compared the safety and efficacy of 2.5mg fondaparinux to usual care (UFH or placebo). Patients were eligible for inclusion in the trial if they presented with STEMI initially within 24 hours of onset of symptoms. Based on the results of the CREATE trial [24] and without knowledge of any interim results from the OASIS-6 trial, this was reduced to 12 hours after approximately 4,300 patients had been enrolled. Eligible patients included those with planned reperfusion therapy with one of several thrombolytics or with primary PCI, as well as patients who were not eligible for reperfusion therapy (e.g. late presentation or contraindication to reperfusion therapy). The main exclusion criteria are listed in Appendix 1.

Patients were randomised to receive fondaparinux or BSC (UFH or placebo) following stratification based on an indication for use of UFH as judged by the investigator (see Figure 1, Appendix 1).

Stratum I: no indication for UFH;
A total of 5,658 patients, intended to receive a non-fibrin specific thrombolytic (e.g. streptokinase) or no thrombolytic were enrolled to Stratum I. Treatment was fondaparinux 2.5mg intravenously or matching placebo just after randomisation, followed on subsequent days by fondaparinux 2.5mg once daily subcutaneously or placebo for up to eight days or until hospital discharge, whichever was earlier.

Stratum II: indication for UFH (refer to Table 1, Appendix 1);
A total of 6,434 patients were enrolled in Stratum II, which involved different treatment scenarios. Some patients were treated with a fibrin-specific thrombolytic (e.g.alteplase), others underwent primary PCI, and those not eligible for reperfusion therapy but were indicated, received UFH.

Patients were randomised to receive either fondaparinux 2.5mg, followed by fondaparinux 2.5mg subcutaneously for up to eight days or discharge or UFH 60 IU/kg (max 4000IU) as an intravenous bolus an infusion followed by UFH 12IU/kg/hour (max 1,000 IU/hour) for 24 to 48 hours.

Patients who were scheduled for primary PCI received bolus injections of fondaparinux (2.5mg or 5mg) or UFH 65IU/kg or 100 IU/kg as an intravenous bolus immediately before the procedure (dependent upon the upfront use or not of intravenous GPIIb/IIIa inhibitors, and on pre-randomisation use or not of UFH). Post-procedure patients received fondaparinux 2.5mg subcutaneously or matching placebo for up to eight days or until discharge (if earlier).

The primary efficacy endpoint was the first occurrence of the composite of death (all-cause mortality) or re-MI at Day 30. Secondary efficacy endpoints included additional assessments of the primary endpoint at Days 9, and the end of the study (a minimum of 90 days to a maximum of 180 days).

Post-hoc analysis of the primary endpoint (death or re-infarction) was undertaken in the proportion of the initial trial population who were managed with thrombolytics, or who initially received no other form of reperfusion therapy as an index event [5,23]. This patient group is representative of the licensed indication for fondaparinux [1].

Results:
Patients undergoing primary PCI were predominantly in Stratum II while thrombolysis was more common in Stratum I. Overall 28.9% of patients underwent primary PCI (53.2% in Stratum II and 0.2% in Stratum I). Thrombolysis was performed in 45% of patients overall (78% in Stratum I and 15.9% in Stratum II). Streptokinase was the most commonly used thrombolytic agent (72.6% of those patients receiving thrombolysis) [5]. A total of 2,867 (23.7%) patients received no reperfusion therapy for their index event and were similarly distributed across the two strata (22% in Stratum I and 25% in Stratum II) [5].

Overall the primary efficacy composite endpoint of death or re-MI at 30 days was significantly reduced from 11.2% (677/6056) patients in the control group (UFH or placebo) to 9.7% (585/6036) patients in the fondaparinux group (hazard ratio [HR] 0.86; 95% confidence interval [CI]: 0.77 to 0.96; p=0.008). The relative risk reduction was 14% at Day 30 and the absolute risk reduction at day nine was 1.5% (95% CI: 0.4% to 2.6%) lower with fondaparinux compared with the control. This difference persisted throughout the study. Consistent reductions in secondary endpoints such as both death and re-MI at each of the time points (Day 9, Day 30 or end of study [90 or 180 days) were observed (refer to Table 2, Appendix 1). The reduction in total mortality (598 versus 674) by the study end with fondaparinux compared to control was considered by the investigators to be entirely due to the reduction in cardiac deaths (492 [8.2%] versus 573 [9.5%]; HR 0.86; 95% CI: 0.77 to 0.97).

Considering the overall randomised population, fondaparinux was superior to placebo in Stratum I (UFH not indicated) in the prevention of death or re-MI at Day 30 (11.2% versus 14%, respectively; HR 0.79; 95% CI: 0.68 to 0.92). Fondaparinux however failed to demonstrate superiority over UFH for the overall population in Stratum II. Nevertheless when patients in Stratum II were subdivided into those undergoing or not undergoing primary PCI for the index event, fondaparinux appeared to benefit those in the latter group. In this group fondaparinux was superior to UFH at 30 days (154 versus 189, respectively; HR 0.80; 95% CI: 0.65 to 0.99; p=0.04) and study end (251 versus 193; HR 0.75; 95% CI: 0.62 to 0.90; p=0.002).

When further subgroup analysis was carried out based on the type of reperfusion therapy, at 30 days significant benefits in the fondaparinux group were observed in those who received no reperfusion therapy (15.1% control versus 12.2% fondaparinux; HR 0.80; 95% CI: 0.65 to 0.98; p=0.003), and in those who received a thrombolytic agent (13.6% versus 10.9%; HR 0.79; 95% CI: 0.68 to 0.92; p=0.003). There was no

significant benefit observed with fondaparinux for those undergoing primary PCI (4.9% versus 6.0%; HR 1.24; 95% CI: 0.95 to 1.63; p=0.12; p for heterogeneity= 0.04).
Post-hoc pooling of results from sub-groups undergoing thrombolysis or no initial reperfusion (i.e. the licensed population) for their index event demonstrated a statistically significant reduction in death and recurrent MI of 20% at Day 30 (HR 0.80; 95%CI: 0.70 to 0.90; p<0.001); this beneficial effect was consistent across the two strata [5]. Evaluation of fondaparinux treatment versus usual care for the sub-group receiving no reperfusion therapy also showed a reduction in the primary endpoint at 30 days (12.2% versus 15.1%, HR 0.80; 95% CI: 0.65 to 0.98, p=0.003) [22,23].

When patients were subdivided by the Global Registry of Acute Coronary Events (GRACE) risk score [26] (a pre-specified subgroup) there was a highly significant reduction in death or MI at Day 30 in patients predicted to be at high risk (GRACE score greater than or equal to 112); 18.0% versus 14.5%, HR, 0.79; 95% CI: 0.70 to 0.90; p<0.001) with no apparent benefit in low-risk patients (4.3% versus 4.6%; HR 1.07; 95% CI: 0.84 to1.36; p=0.57; p for heterogeneity=0.03). Similar patterns were observed separately for both death and MI.

Points to note from the study:

- The OASIS-6 trial demonstrates a moderate reduction in mortality and re-infarction with the use of fondaparinux versus usual care. The reduction was most marked in those not undergoing PCI and those who were at higher risk according to GRACE score.
- The results of this study are reflected in the CHMP decision to recommend the granting of market authorisation of fondaparinux in the treatment of STEMI, only in patients who are managed with thrombolytics or who initially are to receive no other form of reperfusion therapy.
- Of the total OASIS-6 trial population (refer to Sections 6.1.1), approximately 68.6% (8,294/12,092) of patients were eligible for treatment of STEMI ACS within the licensed indication for fondaparinux [5].
- A discussion on the applicability of the study population to patients in routine clinical practice in the UK is highlighted in Sections 7.2 and 8.3.6.
- Yusuf and colleagues acknowledge that little benefit from the use of fondaparinux was apparent in the 3,789 patients who underwent primary PCI .
- Patients undergoing primary PCI were at lower predicted risk (mean entry GRACE score 101) compared to those receiving thrombolytic therapy (entry GRACE score, 114) or no reperfusion therapy (GRACE score, 124).
- Subgroup analysis on the results of death or MI were not significantly different for gender, in those older or younger than the median age, in subgroups defined by the time from symptom onset to randomisation, with use of various concomitant therapies or various types of thrombolytic agents.
- The number of days of use of study antithrombotic therapy was shorter in those undergoing primary PCI (5.4 days) compared with those receiving thrombolytic therapy (6.3 days), or no reperfusion therapy (6.6 days).
- A total of 2,747 patients were randomly assigned to also receive an infusion of glucose-insulin-potassium (GIK) or usual care to evaluate the effect of GIK in preventing death or nonfatal cardiac arrest. This part of the study was discontinued after the results from another study indicated that GIK was of no benefit [27]. Adjustment for the GIK randomisation did not alter the main comparison of fondaparinux reported [22].

6.2 Safety:
Notably, bleeding is reported to be associated with an increased risk of adverse outcomes such as MI, and death in patients with ACS [28-30]. The primary safety outcome of the OASIS-6 trial was therefore severe haemorrhage at nine days [22]. Severe haemorrhage was defined using a modified Thrombolysis in Myocardial Infarction (TIMI) trials definition for major bleeding [31]. There was no significant difference noted between treatment groups for severe haemorrhage or fatal bleeds; only for cardiac tamponade (48 versus 28, respectively; p=0.02).

In patients not undergoing primary PCI, there were 29 patients with severe bleeds in the UFH group compared with 20 in the fondaparinux group. The rates of intracranial haemorrhage were similar in the both groups (10 [0.2%] versus 11 [0.2%]). In those patients receiving no reperfusion therapy, severe bleeding at Day three was no different between fondaparinux and placebo, HR 0.39; 95%CI: 0.08-2.00, or fondaparinux and UFH, HR 0.72; 95% CI: 0.30 to 1.71, p=0.51, for heterogeneity. Neither were there differences in severe bleedings at 30 days [23].

A net clinical benefit assessment, based on the combination of primary efficacy and safety outcomes, was also performed (i.e. using the composite outcome of death, re-MI, and severe bleeding at each of the study time points). The rates of death, MI and severe bleeding were significantly lower at Day nine with fondaparinux (559 versus 464; HR 0.83; 95% CI: 0.73 to 0.94; p=0.003), with similar findings throughout the study (Day 30: 701 versus 603; HR 0.86; 95% CI: 0.77 to 0.95; p=0.005; study end: 888 versus 779; HR 0.87; 95% CI: 0.79 to 0.96; p=0.005). Similarly the composite outcome of death, MI or stroke was also reduced in favour of fondaparinux at Day nine and at each of the study time points thereafter.

There was a higher rate of catheter thrombosis in the fondaparinux group compared to those who received UFH (22 versus zero; p<0.001), and patients in the fondaparinux group experienced a higher number of coronary complications (270 versus 225, p=0.04). In general, data for the 496 patients who received UFH in the trial shows the rates of PCI complications and clinical complications to be similar, with very low rates of catheter thrombosis, with similar results in those undergoing non-primary PCI (in whom many were pre-treated with UFH); confirming that UFH can be safely used during PCI in patients with ACS already treated with fondaparinux as the initial strategy as highlighted in the Summary of Product Characteristics [1].

Serious adverse events in the overall population (as determined by the investigators) were rare occurring in 1% in the fondaparinux group and in less than 1% of patients in the control group [5].

7.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES:

7.1 Comparator medications:

- Unfractionated heparin
- Best Supportive Care

7.2 Comparative effectiveness:

- There are currently no ongoing studies of fondaparinux in the treatment of STEMI patients [5].
- Approximately two thirds of the total OASIS-6 trial population (68.6% [refer to Sections 6.1.1]) were eligible for treatment of STEMI ACS within the licensed indication for fondaparinux. CHMP however expressed a concern that a large proportion (84%) of the patients undergoing thrombolysis were treated with non-fibrin selective thrombolytics (mainly streptokinase), and only 53% of the included patients were allocated to UFH treatment. In addition the Committee considered the percentage of patients within the trial that underwent PCI appeared to be low and that the mortality rate of the study population was higher than expected [25]. Nevertheless, within the EPAR, it is reported that despite the population of patients included in the OASIS-6 (notably Stratum I) not being fully representative of the target population (taking current treatment practice and guideline recommendations into account), the study results could still be applicable to European patients [25].
- In contrast to UFH, which is administered initially as an intravenous bolus and then as an infusion, fondaparinux is administered as a subcutaneous injection once daily at a standard dose (intravenously for first dose only), and does not require monitoring or weight related dose calculation; although there is a precaution in the Summary of Product Characteristics for those with a low body weight [1].
- On the basis of the unexpected adverse event related to catheter thrombus formation during trials [1], CHMP recommended that fondaparinux cannot be used as the sole anticoagulant adjunct to non-primary PCI [25].
- Following medical expert opinion, AWMSG agreed that, in the treatment of STEMI within NHS Wales, UFH or best supportive care are the most appropriate comparators.
- No LMWH is currently licensed for use in STEMI, although the potential benefit of using LMWH has been highlighted by the ESC in their guidelines [3]. These current guidelines were published in 2003 and do not recommend the use of LMWH; stating that larger studies (especially in the elderly) are needed before recommendations can be given for their use in combination with fibrinolytic agents. It should be noted, however that these guidelines are due to be updated in 2008 [32].

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 STEMI 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 STEMI.

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 describes a cost-utility analysis of fondaparinux compared with best supportive care (BSC [aspirin and clopidogrel]) or UFH in patients with STEMI who are managed with thrombolytics or who are to receive no other form of reperfusion therapy. Results are presented separately for each comparator [5].

An event-based decision model has been created, with risk equations fitted to data from the OASIS-6 trial [22] 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 three mutually exclusive model states at 180 days: dead (fatal cardiovascular event or other cause of death), alive having experienced a non-fatal recurrent MI and alive having experienced no event. 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 70 years [5].

There are several sources of uncertainty in the model. It is possible that the benefits observed with fondaparinux in the OASIS-6 trial are due in part to inadequate duration of anticoagulation therapy with UFH. The model does not consider non-fatal stroke as an outcome (in contrast to the submission in support of fonadaparinux in patients with unstable angina/non-STEMI [UA/NSTEMI]). The model assumes that the effectiveness of treatment in the first 180 days influences prognosis over the remaining lifetime of patients and uses constant relative risks of mortality that relate to NSTEMI, rather than STEMI. Utility weights for the model were derived from age-specific UK population norms, with decrements for non-fatal MI and ACS based on published EQ-5D survey data from US patients, rather than from patients in trials of fondaparinux. With the exception of drug use, resource use has been taken from a different trial (OASIS-5), which compares fondaparinux against the LMWH enoxaparin in patients with NSTEMI, and a published review of clopidogrel in NSTEMI [5]. The model has been made available by the company.

8.3.2 Population

The OASIS-6 study, on which the 180-day efficacy data for the model is based, was conducted in 12,092 patients with STEMI presenting within 24 hours (subsequently reduced to within 12 hours) of the onset of symptoms [22]. Patients were stratified in the trial on the basis of whether UFH was indicated or not. Patients were then randomised to receive fondaparinux or usual care, which was either UFH (if indicated) or placebo. Importantly, patients with a high risk of bleeding, or those receiving anticoagulants, were excluded from the trial. The efficacy data for the model are based on a subpopulation of the trial (69%), which was not scheduled to undergo primary PCI. This is in line with the licensed indication for fondaparinux in ACS[1].

8.3.3 Perspective and time horizon

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

8.3.4 Comparator

The model compares fondaparinux against UFH or against BSC (aspirin and clopidogrel) if UFH is not indicated. The company submission states that LMWH has been demonstrated to reduce MI in patients with STEMI compared with UFH but does not decrease mortality and is associated with a higher risk of bleeding. Following medical expert opinion within NHS Wales, WMP considers UFH currently to be a more appropriate comparator than LMWH for the model[4].

The Scottish Intercollegiate Guidelines Network guidance on ACS, published in February 2007, notes that LMWH has advantages over UFH in STEMI in the outcomes of MI, recurrent ischaemia, and a composite of these including death, but not all cause mortality [19]. An increased risk of bleeding has been seen particularly when using enoxaparin with alteplase and tenectaplase, and predominantly in those aged over 75 years. The SIGN guideline does not specifically preclude LMWH in favour of UFH [19]. It would seem feasible that LMWH may be used in clinical practice (unlicensed indication), and this would appear to be the case based on registry data provided by the company [33]. The potential impact of using LMWH as a comparator in the model instead of UFH is unclear, given the different acquisition costs, modes of administration and adverse event risks.

Another consideration is the duration of anticoagulation treatment received by patients. The SIGN guideline states that a strategy of using anticoagulation for 48 hours is insufficient, as there is an increased risk of MI following cessation[19]. In the OASIS-6 study, UFH was only administered for up to 48 hours (mean duration was 37.6 hours), whilst fondaparinux was administered for up to eight days or discharge from hospital, whichever occurred first (mean approximately 6.6 days) [34]. The published paper for OASIS-6 notes that the benefits observed with fondaparinux may be partly due to the more prolonged duration of antithrombotic therapy [22].

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 a subpopulation of the OASIS-6 trial that meets the licensed indication [5]. Few data are provided in the company submission on the efficacy data in relation to the outcomes considered in the model.

For each risk equation, covariates have been included based on expert opinion and those variables that were available in the OASIS-6 trial, guided by relevant risk scoring systems. The covariates for the risk of death were treatment, age, heart failure at entry, history of diabetes, creatinine clearance, baseline ECG with ST elevation greater than or equal to 0.2mV, and heart rate greater than 100. The inclusion of these covariates was not based on statistical significance in subgroups. For recurrent non-fatal MI, only treatment and age were included as predictors. The company submission states that this is due to the small number of these events in the trial and limited power to fit these covariates. The relative treatment effects of fondaparinux are held constant[5].

Patients may fall into one of three mutually exclusive model states at 180 days: dead (fatal cardiovascular event or other cause of death), alive having experienced a non-fatal MI and alive having experienced no event. The effectiveness of treatment in the first 180 days is assumed to influence the prognosis over the remaining lifetime of

patients in terms of these events [5]. Non-fatal stroke is not considered in the model (in contrast to the submission made for the UA/NSTEMI indication, where stroke outcome appears to be a significant driver of the model outputs). No data are provided for the incidence of stroke in the licensed population, and at no time point was the incidence of stroke statistically significantly different between fondaparinux and control in the full trial population. However, it is noteworthy that the incidence of stroke was numerically greater at all time points for stratum II (indicated for UFH) in the full trial population [25]. The impact of the omission of stroke from the model is unknown, especially in those with an indication for UFH.

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 for patients with no recurrent MI and recurrent MI in the first 180 days. A Markov model, run over 70 years, has been used to model the long-term outcomes and costs [5].

The RRs of mortality have been reported to be obtained from a secondary analysis of the PRAIS study, which followed a cohort of 653 UK patients with NSTEMI for mortality and causes of death for up to 45 months [35] 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 [Personal communication, GSK, February 2008].

The company submission states that NSTEMI patients have a worse prognosis than STEMI patients and claims that the RRs used in the model are likely to be conservative. However, the EPAR for fondaparinux notes that in-hospital mortality (7 to 9% for STEMI and 5 to 6% for NSTEMI) and 30-day mortality (11.1% and 7.4%, respectively) is higher for STEMI than NSTEMI based on registry data. These differences are also reflected in the results from the GUSTO-11b trial, which show a significantly higher 30-day mortality risk following STEMI compared to NSTEMI (6.1% versus 3.8%, respectively), but similar mortality rates at one year [25]. The extent to which the RR of subsequent events in NSTEMI patients represents the RR in STEMI patients, as assumed in the model, is not certain.

8.3.5.2 Adverse events

Severe and minor haemorrhages are the adverse events considered in the model [5]. Risk equations for these events include only treatment and age as covariates. The company submission states that this is due to the small number of these events in the trial and limited power to fit these covariates. These adverse events are assumed to have no influence on patients' prognoses beyond 180 days [5].

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 and ACS [36]. 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) and other chronic ischaemic heart conditions (decrement of 0.0336, n=183), respectively [36]. The extent to which these decrements reflect those that would be experienced by patients in Wales is unclear. The decrement associated with the acute event of MI is 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 event of MI may reasonably be expected to change over time." If this is held constant throughout the lifetime horizon, this may have the effect of biasing the model against the comparators of fondaparinux, in which the incidence of acute MI was greater.

8.3.6 Healthcare resource utilisation and cost

The duration of use and quantities of fondaparinux and UFH used in the model are derived from OASIS-6. However, the other resources used in the first 180 days are taken from the OASIS-5 trial, which compares fondaparinux against the LMWH enoxaparin in patients with NSTEMI [5,17]. The reasons for this are stated to be that the population mix of OASIS-6 does not lend itself well to the UK context, as the majority of patients were recruited from Eastern Europe, Africa and Asia, and only 13% of patients were recruited from Western Europe (73 patients specifically from the UK). In OASIS-5, only around a quarter of patients were recruited from North West Europe and only 301 patients (1.5% of the study population) were recruited from the UK. The company submission considers that the resource use associated with specific events in the OASIS-5 population will be similar to those in OASIS-6-type patients [5]. However, there is no indication in the submission that the assumed resource use has been verified by Welsh clinicians.

The events included in the model in the first 180 days are ACS (applied to all patients), and additional events of MI, death, severe haemorrhage and minor haemorrhage. Unit costs, derived from published sources and inflated to 2007 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 these events [5]. These data from OASIS-5 are stated to cover resource use categories including general inpatient days in hospital, days in intensive care, major therapeutic and diagnostic procedures, concomitant medications and blood transfusions. This data, however, is not presented and it is not possible to verify the costs assumed in the model.

In the period beyond 180 days, resource use data has been derived from a health technology assessment of clopidogrel in NSTEMI [38]. This assumes that no subsequent events beyond 180 days attract additional costs to those of event free ACS and that the costs of event free ACS are the same regardless of whether the patient has experienced STEMI or NSTEMI.

8.3.7 Discounting

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

8.3.8 Results

8.3.8.1 Fondaparinux versus BSC/placebo

Fondaparinux dominates BSC/placebo on the basis of reduced costs (-£17, 95% CI: -243 to +354) and a gain of 0.059 QALYs (95% CI: -0.056 to +0.182) [5].

8.3.8.2 Fondaparinux versus UFH

The incremental cost per QALY gained is estimated as £355 on the basis of incremental costs of £97 (95% CI: -462 to +1122) and a gain of 0.273 QALYs (95% CI: 0.102 to 0.46) [5].

8.3.9 Sensitivity analysis

8.3.9.1 One way sensitivity analyses

A series of one-way sensitivity analyses were conducted. These included limiting the analysis to within the 180-day trial period, varying the discount rate to 0% and 6%, reducing the RR of mortality for patients who experience a recurrent MI to 2.4 (in line with a separate estimation), and varying long term costs by ±25%. None of the estimated incremental costs per QALY gained exceeded £843, which suggests that the model is relatively insensitive to these parameters [5]. However, these do not address the uncertainty in the model due to assumed utility value decrements, resource use costs in the first 180 days, and the issue of RR of mortality used in the long term phase of the model being based on NSTEMI data.

8.3.9.2 Probabilistic sensitivity analysis

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

The probability of fondaparinux being cost-effective versus BSC/placebo at a willingness to pay (WTP) threshold of £20,000 per QALY gained is stated as 82%. Compared with UFH, the probability is stated as 100% [5, 34].

Analyses of the 2.5th, 25th, 50th, 75th and 97.5th percentiles of net benefit have been conducted, and indicate that the probability of fondaparinux being cost effective versus. BSC/placebo exceeds 80% in all cases at a WTP threshold of £20,000 per QALY gained and £30,000 per QALY gained. For fondaparinux versus UFH, the probability exceeds 99.7% in all cases [34].

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 STEMI (patients with STEMI who are managed with thrombolytics or who initially are not to receive other forms of reperfusion) [5]. The analysis uses a 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 is representative of those in Wales. These data have been applied to the estimated number of coronary heart disease (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. It is also assumed that the proportion of patients undergoing reperfusion in the OASIS-6 trial (38% including PCI and coronary artery by-pass graft (CABG) is representative of the situation in Wales, and that the remainder (approximately 62%) are eligible for treatment with fondaparinux. The model also assumes that the proportion of patients eligible for UFH in the OASIS-6 trial is the same in Wales. The model considers the additional cost of using fondaparinux instead of UFH in those in whom UFH may be indicated, and the cost of fondaparinux in addition to BSC in those patients not eligible for UFH [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 CHD decreased by 2% per year to 4.84/1000 population in 2005. This study also indicated that the mortality rate decreased by an average of 3.35% each year, to 2.65% in 2005 [39]. Based on population estimates for Wales in 2008, the company submission estimates incident cases of CHD would be 14,182. Based on data from a global registry study of patients with ACS [39], it has been assumed that around 30% of patients with CHD have STEMI[4] (STEMI accounted for 32% of patients in the global registry study [39]). On this basis, the company submission claims there would be 3,158 incident cases of STEMI in 2008, rising to 3,229 in 2012 [5]. However, these figures do not appear to compute from the stated assumptions, as they represent around 22% of the estimated incident cases of CHD, not 30%.

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 over the next five years. 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 30% of these cases are due to STEMI, the model estimates that there would be 41,728 cases of STEMI in 2008, rising to 42,666 cases of STEMI in 2012 [5]. Further, the model assumes that around 62% of these would be eligible for fondaparinux treatment, as observed in the OASIS-6 trial.

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 mortality rate of 2.84% has been used consistently, rather than 2.65% decreasing by 3.35% each year. The CHD incidence rate of 4.84/1000 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.

8.4.3.3 Rates of adoption

Two scenarios 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 5% each year [5].

8.4.3.4 Costs and resource use

The direct costs of treatment with fondaparinux and UFH are based on mean treatment durations in the OASIS-6 trial (approximately seven days for fondaparinux and 37.6 hours for UFH). Drug costs have been applied to the quantities of drug used. For those patients in whom UFH is not indicated, only the additional cost of fondaparinux is taken into account as it is assumed that all other medications making up BSC would also be given to those given fondaparinux [5].

8.4.4 Results

Only the direct costs of drug treatment are considered. The figures in 8.4.4.1 and 8.4.4.2 relate to the stated estimates of eligible patients in the company submission, which do not appear to have been computed from the stated assumptions.

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

In 2008, the additional cost of the use of fondaparinux over the use of UFH and BSC is estimated as £55,124 rising to £281,817 in 2012 [5].

8.4.4.2 Scenario 2: 10% initial uptake, rising to 30% in 2012

In 2008, the additional cost of the use of fondaparinux over the use of UFH and BSC is estimated as £110,248 rising to £338,180 in 2012 [5].

8.4.5 Sensitivity analysis

No sensitivity analysis has been conducted.

9.0 ADDITIONAL INFORMATION:

9.1 Guidance and audit requirements:

- 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 Task Force on the management of acute myocardial infarction of the European Society of Cardiology. Management of acute myocardial infarction in patients presenting with ST-segment elevation [3].
- 2007 focused update of the American College of Cardiology/American Heart Association 2004 guidelines for the mamangement of patients with ST-Elevation myocardial Infarction [41].
- Scottish Intercollegiate Guidelines Network (SIGN). Acute Coronary Syndromes. National Clinical Guidelines No.93; February 2007 [19].
- Department of Health 2000. Coronary Heart Disease: National Service Framework for coronary heart diseases – modern standards and service model[42].
- 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 [43].

9.3 Previous AWMSG/NICE advice

None.

9.4 Patient Interest Group information

A patient interest group submission was not received.

Glossary

Primary PCI: Angioplasty and/or stenting without prior or concomitant fibrinolytic therapy [3].

Rescue PCI: PCI performed on a coronary artery that remains occluded despite fibrinolytic therapy [3].

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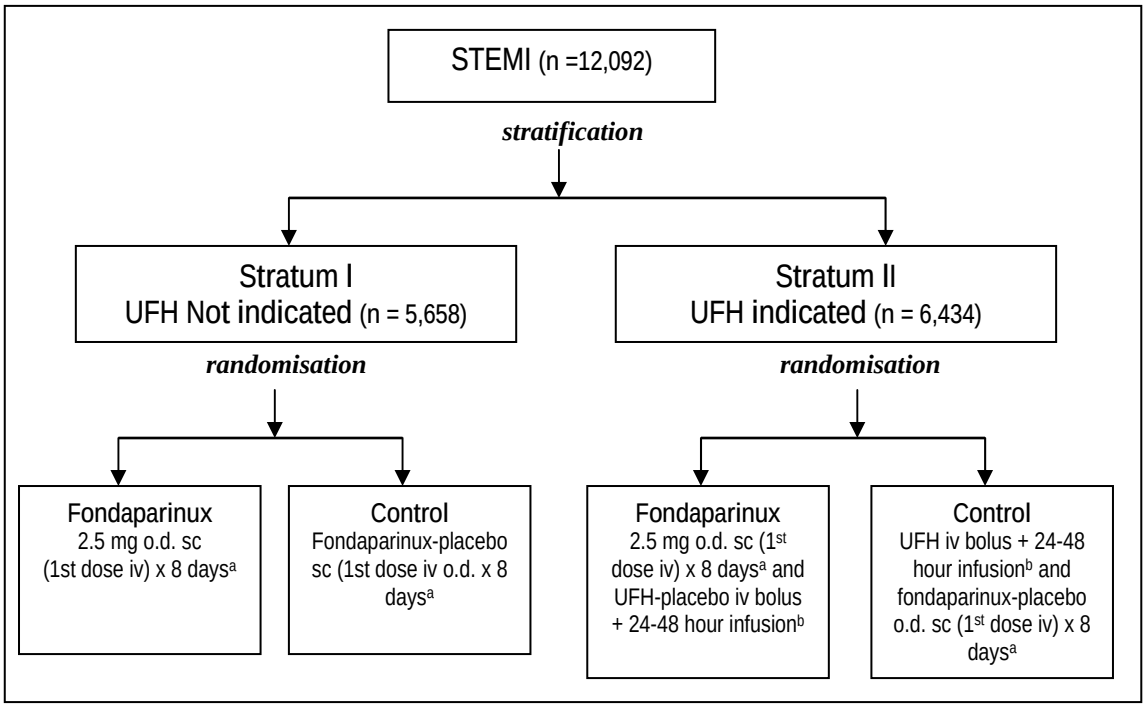
Appendix 1. Additional Clinical Information

OASIS-6 Trial [23]

Key Exclusion criteria

Severe renal insufficiency (i.e. creatinine level greater than 265.2mg/dL [3.0mmol/L]), those receiving anticoagulant therapy [20], those who had received LMWH or UFH (greater than 5,000 IU) prior to randomisation, a contraindication to anticoagulant therapy such as a high risk of bleeding or active bleeding and those patients who had pre-randomisation PCI for the index event or pre-randomisation rescue PCI.

Figure1: OASIS-6 Trial Design [4]



[a] or until hospital discharge, whichever is earlier ; [b] in primary PCI, no 24-48 h infusion – only IV bolus
sc – subcutaneously; o.d. – once daily; iv - intravenously

Table 1: Study Drug Regimen and Dosing in Stratum II [4,20]

	Fondaparinux Regimen	Control Regimen
All Patients		
	2.5 mg s.c. once daily (first dose intravenously[a])	UFH at 60 IU/kg (maximum 4,000 IU) followed by intravenous infusion at 12 IU kg/hr[a]
Patients scheduled for PCI		
Pre-randomisation	Fondaparinux Regimen	Control Regimen
Received UFH + Gp IIb/IIIa antagonist	2.5 mg intravenous bolus followed by 2.5 mg s.c. daily for up to 8 days	Measure ACT pre-procedure; UFH as per local practice (maximum, 65 IU/kg)[b]
Received UFH No Gp IIb/IIIa antagonist	5.0 mg intravenous bolus followed by 2.5 mg s.c. daily for up to 8 days	Measure ACT pre-procedure; UFH as per local practice (maximum, 100 IU/kg)[b]
Received Gp IIb/IIIa antagonist No UFH	2.5 mg intravenous bolus followed by 2.5 mg s.c. daily for up to 8 days	UFH - 65 IU/kg as intravenous bolus
No UFH No Gp IIb/IIIa antagonist	5.0 mg intravenous bolus followed by 2.5 mg s.c. daily for up to 8 days	UFH - 100 IU/kg as intravenous bolus

[a] Study drugs were started 2-3 hours after the initial open-label UFH bolus or 2-3 hours after termination of the initial UFH infusion if pre-randomisation UFH was given.
[b] In patients who received UFH prior to randomisation, an ACT check before PCI was recommended. Heparin was administered according to level of ACT as per local practice. In those centres that did not have ACT measurement capability, 5.0 mg fondaparinux (intravenously) or 100 IU/kg UFH was recommended if the pre-randomisation dose of UFH was less that 4000 UI; 2.5 mg fondaparinux (intravenously) or 65 IU/kg UFH was recommended if the pre-randomisation UFH dose was between 4,000 – 5,000 IU. Patients who received more than 5,000 IU of pre-randomisation UFH were excluded from the trial.
sc – subcutaneously; ACT – activated clotting time; Gp - glycoprotein.

Table 2: Efficacy of fondaparinux at days nine, 30 and study end on death or re-infarction [22]

Efficacy of Fondaparinux at Days 9 and 30 and Study End on Death or Reinfarction					
	No. (%) of Patients			Hazard Ratio (95% Confidence Interval)	*P* Value
	Placebo or Unfractionated Heparin % (n = 6056)	Fondaparinux (n = 6036)	Absolute Difference		
Death or reinfarction					
Day 9	537 (8.9)	444 (7.4)	93 (−1.5)	0.83 (0.73-0.94)	.003
Day 30*	677 (11.2)	585 (9.7)	92 (−1.5)	0.86 (0.77-0.96)	.008
Study end (3-6 mo)	857 (14.8)	756 (13.4)	101 (−1.5)	0.88 (0.79-0.97)	.008
Death					
Day 9	425 (7.0)	368 (6.1)	57 (−0.9)	0.87 (0.75-1.00)	.04
Day 30*	540 (8.9)	470 (7.8)	70 (−1.1)	0.87 (0.77-0.98)	.03
Study end (3-6 mo)	674 (11.6)	598 (10.5)	75 (−1.0)	0.88 (0.79-0.99)	.03
Reinfarction					
Day 9	136 (2.3)	92 (1.6)	44 (−0.7)	0.67 (0.52-0.88)	.004
Day 30*	175 (3.0)	142 (2.5)	31 (−0.5)	0.81 (0.65-1.01)	.06
Study end (3-6 mo)	245 (4.6)	200 (3.8)	45 (−0.8)	0.81 (0.67-0.97)	.03

*Primary efficacy outcome.

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

Appendix 3. Clinical Expert Summary

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

Appendix 5. Company Response - included as a separate document