All Wales Medicines Strategy Group

Grŵp Strategaeth Meddyginiaethau Cymru Gyfan

Final Appraisal Report

Enoxaparin (Clexane®)

Sanofi-Aventis

Advice No: 0610 – April 2010

Recommendation of AWMSG

Enoxaparin (Clexane®) is recommended as an option for use within NHS Wales for the treatment of acute ST-segment elevation myocardial infarction (STEMI).

AWMSG is of the opinion that enoxaparin (Clexane®) is not suitable for shared care within NHS Wales.

This report should be cited as:

ABBREVIATIONS

aPTT	Activated partial thromboplastin time
ACS	Acute coronary syndromes
ASA	Acetylsalicylic acid
AWMSG	All Wales Medicines Strategy Group
BNF	British National Formulary
CI	Confidence interval
ECG	Electrocardiogram
ESC	European Society of Cardiology
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio
ICH	Intra-cranial haemorrhage
ITT	Intention-to-treat
IV	Intravenous
LMWH	Low molecular weight heparin
MI	Myocardial Infarction
NHS	National Health Service
NSTEMI	Non-ST segment elevation myocardial infarction
PI	Percutaneous coronary intervention
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RR	Relative risk
RRR	Relative risk reduction
SC	Subcutaneous
STEMI	ST-segment elevation myocardial infarction
SPC	Summary of Product Characteristics
TIMI	Thrombolysis in myocardial infarction
UFH	Unfractionated heparin
WMP	Welsh Medicines Partnership

1.0 RECOMMENDATION OF AWMSG:

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

Date: Wednesday 28th April 2010

The recommendation of AWMSG is:

Enoxaparin (Clexane®) is recommended as an option for use within NHS Wales for the treatment of acute ST-segment elevation myocardial infarction (STEMI).

AWMSG is of the opinion that enoxaparin (Clexane®) is not suitable for shared care within NHS Wales.

2.0 PRODUCT DETAILS

2.1 Licensed indication

Enoxaparin (Clexane®) is indicated for the treatment of acute ST-segment elevation myocardial infarction (STEMI) including patients to be managed medically or with subsequent percutaneous coronary intervention (PCI) in conjunction with thrombolytic drugs (fibrin or non-fibrin specific)[1].

The other licensed indications for enoxaparin can be found in the summary of product characteristics (SPC)[1]. The company submission and this assessment report focuses on the use of enoxaparin in patients with STEMI, which is a licence extension[2]

2.2 Dosing

The recommended dose of enoxaparin is a single intravenous (IV) bolus of 30mg plus a 1mg/kg subcutaneous (SC) dose followed by 1mg/kg administered SC every 12 hours (max 100mg for the first two doses only, followed by 1mg/kg dosing for the remaining doses). For treatment of acute STEMI in elderly patients (≥75 years of age), an initial IV bolus should not be used. Dosing should be initiated with 0.75mg/kg SC every 12 hours (maximum 75mg for the first two doses only, followed by 0.75mg/kg dosing for the remaining doses). The recommended duration of enoxaparin treatment is eight days or until hospital discharge[1].

When administered in conjunction with a thrombolytic (fibrin specific or non-fibrin specific) enoxaparin should be given between 15 minutes before and 30 minutes after the start of fibrinolytic therapy. The SPC states that all patients should receive acetylsalicylic acid (ASA) as soon as they are identified as having STEMI and this should be maintained (75 to 325mg once daily) unless contraindicated[1].

For patients managed with PCI, if the last enoxaparin SC administration was given less than eight hours before balloon inflation, no additional dosing is needed. If the last SC administration was given more than eight hours before balloon inflation, an IV bolus of 0.3mg/kg should be administered. In patients with severe renal impairment (creatinine clearance < 30 ml/min) dosage adjustments are recommended. For more information on the method of administration and dosing adjustments please refer to the SPC[1].

2.3 Market authorisation date

28th May 2009[1]

2.4 UK Launch date

May 2009[2]

3.0 DECISION CONTEXT

3.1 Background

STEMI is characterised by coronary arterial occlusion leading to acute ischaemic chest pain. For patients with a clinical presentation of myocardial infarction (MI) and persistent ST-segment elevation, early mechanical reperfusion by PCI or pharmacological reperfusion with a thrombolytic agent should be performed unless clear contraindications are present[2-4].

The European Society of Cardiology (ESC) guidelines state that primary PCI is the preferred reperfusion therapy for STEMI when it can be carried out within 90 to 120 minutes from first medical contact[4]. For patients not meeting these requirements reperfusion with a thrombolytic agent, which could be fibrin-specific (such as a tissue plasminogen activator i.e. alteplase) or fibrin non-specific (such as streptokinase) is recommended as a suitable alternative to PCI, when performed within 12 hours of presentation[3-5]. Treatment should be in conjunction with antiplatelet therapy (i.e. aspirin and clopidogrel) and anticoagulant therapy (i.e. low molecular weight heparin [LMWH], unfractionated heparin [UFH], or fondaparinux)[2-5]. Anticoagulant treatment should be continued for up to eight days, or until PCI or hospital discharge[3-5].

The incidence of STEMI in Wales is estimated at 3,158 cases per year[2]. It is estimated that 2,119 of these patients (67%) will receive thrombolytic therapy and that a proportion of these patients are likely to receive enoxaparin as an adjunct to thrombolysis (see section 8.1)[2]. Enoxaparin is a LMWH characterised by a higher ratio of antithrombotic activity to anticoagulant activity than UFH. At recommended doses, it does not significantly influence platelet aggregation, binding of fibrinogen to platelets or global blood clotting tests[1]. Enoxaparin is the only LMWH licensed for the treatment of STEMI[3].

3.2 Comparators

- Unfractionated heparin (UFH)
- Fondaparinux (Arixtra®)

3.3 Guidance and related advice

- ESC guidelines for the management of acute myocardial infarction in patients presenting with persistent ST-segment elevation updated in 2007[4].
- Scottish Intercollegiate Guidelines Network (SIGN). Acute Coronary Syndromes. National Clinical Guidelines No.93; February 2007[5].

4.0 EXECUTIVE SUMMARY

4.1 Review of the evidence on clinical effectiveness

The company submission includes three randomised controlled trials and five open label studies. In the pivotal ExTRACT-TIMI-25 study, STEMI patients receiving pharmacologic reperfusion with fibrinolytic therapy, aspirin and/or clopidogrel hydrogen sulphate were treated with enoxaparin or UFH. The primary composite endpoint of death from any cause or non-fatal MI in the first 30 days after randomisation improved significantly with enoxaparin treatment compared to UFH. The Secondary composite endpoint of death from any cause, non-fatal MI or recurrent myocardial ischaemia leading to urgent revascularisation in the first 30 days after randomisation and the pre-specified net clinical benefit composite endpoints of (1) death, non-fatal MI or non-fatal disabling stroke; (2) death, non-fatal MI or non-fatal major bleeding and (3) death, non-fatal MI or non-fatal intracranial haemorrhage (ICH) were also significantly improved with enoxaparin treatment compared to UFH treatment. Subgroup analysis of the pivotal trial supported these findings; however there were no significant differences between treatment groups for patients who were ≥75 years of age. Results from the open label studies generally supported the beneficial role of enoxaparin treatment compared to UFH. The pivotal trial reported significantly more bleeding episodes with enoxaparin compared to UFH treatment; however all other adverse events were similar between treatment groups.

4.2 Review of the evidence on cost-effectiveness

The company submission describes cost utility analyses of enoxaparin compared against UFH and fondaparinux. Direct comparative data from the ExTRACT-TIMI 25 trial are used for the comparison of enoxaparin and UFH, and indirect comparisons of trial data are used to model enoxaparin against fondaparinux. Two scenarios are considered: 1) treatment with enoxaparin or fondaparinux is for 7 days, UFH is for 2 days and length of hospital stay is 10 days; 2) treatment with enoxaparin and UFH is 2 days and length of hospital stay is 5 days.

In Scenario 1, the incremental cost per quality-adjusted life year (QALY) gained for enoxaparin versus UFH is £15,164. For the comparison of enoxaparin versus fondaparinux, the incremental cost per QALY gained is £15,959. In Scenario 2, the incremental cost per QALY gained for enoxaparin versus UFH is £13,504. The extent to which treatment and outcomes in the ExTRACT-TIMI 25 trial reflects that in current practice is unclear, as there are potentially important differences in rates of PCI and clopidogrel hydrogen sulphate use which could change the modelled efficacy and safety outcomes. The duration of enoxaparin use is significantly longer than UFH use in Scenario 1, which would suggest that Scenario 2 provides a more comparable analysis. However, the modelled duration of anticoagulation with both enoxaparin and UFH may be suboptimal in Scenario 2. There are a number of limitations with the analyses and the extent to which they will reflect cost effectiveness in practice is uncertain. The modelled outputs appear relatively insensitive to the parameter values that have been explored in sensitivity analyses.

4.3 Limitations of the evidence

- There are no direct comparative trials of enoxaparin and fondaparinux in STEMI patients. The economic model relies on indirect comparisons of trial data using data from the ExTRACT-TIMI 25 study and the OASIS-6 trial. In these two studies there are some important differences in the trial populations in relation to rates of PCI and clopidogrel hydrogen sulphate use.
- The economic model uses efficacy and safety data from the ExTRACT-TIMI 25 trial to compare enoxaparin against UFH. The extent to which the efficacy and safety outcomes that are modelled will be achieved in practice is unclear, due to the low use of PCI and clopidogrel hydrogen sulphate in this trial.

5.0 SUMMARY OF THE EVIDENCE ON EFFICACY AND SAFETY

The main clinical evidence comes from the randomised controlled trial, the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction treatment (ExTRACT) – Thrombolysis In Myocardial Infarction (TIMI) 25 study[6]. In addition several published sub-group analyses of this pivotal trial have also been provided by the company[2]; along with a further seven studies as supporting evidence[7-14]. Only the main clinical evidence however is highlighted below.

5.1 Clinical Evidence

5.1.1 Pivotal Study - ExTRACT-TIMI 25

This was a randomised, double-blind comparator controlled trial designed to compare enoxaparin and UFH therapy (in combination with fibrinolytic therapy i.e. streptokinase, tenecteplase, alteplase or reteplase) in patients with STEMI (n=20,506). The majority (97.1%) of patients received study therapy within 30 minutes of fibrinolytic therapy. All patients received aspirin, and clopidogrel hydrogen sulphate could be used in cases of aspirin allergy or in addition to aspirin at the discretion of the physician.

STEMI was treated with medical therapy alone in 74.3% of patients, PCI in 23% of patients (as rescue in 2.8% and as an urgent elective procedure in 20.2%) and coronary-artery bypass surgery in 2.8% of patients. Patients were well matched for baseline characteristics with the exception of clopidogrel hydrogen sulphate treatment during index hospitalisation (27.2% versus 28.7% for enoxaparin and UFH respectively, $p<0.01$)[2,6].

The intent-to-treat (ITT) population included 20,479 patients (enoxaparin; n=10,256; UFH; n=10,223) and the primary composite endpoint was death from any cause or non-fatal MI in the first 30 days after randomisation. Death or non-fatal MI within 30 days occurred in 1,017 (9.9%) patients in the enoxaparin treatment group compared with 1,223 (12.0%) in the UFH group (relative risk reduction (RRR) of 17%; relative risk (RR)=0.83, 95% confidence interval [CI]; 0.77,0.90; $p<0.001$). The main secondary endpoint was the composite of death from any cause, non-fatal MI or recurrent myocardial ischaemia leading to urgent revasculisation in the first 30 days after randomisation. This was significantly reduced from 14.5% in the UFH group to 11.7% in the enoxaparin group ($p<0.001$). The rates of all three pre-specified net clinical benefit composite endpoints in this study were significantly lower at 30 days in the enoxaparin group than in the UFH group[6]. For these results and other secondary endpoints refer to Appendix 1, Table 1A[2,6].

5.1.2 Summary of subgroup analysis from ExTRACT-TIMI 25

Pre-specified subgroup analysis for fibrinolytic agent, infarct location, time to treatment, sex, age, prior MI and presence of diabetes showed a greater treatment benefit with enoxaparin compared with UFH for the primary endpoint of death or non-fatal myocardial infarction (for the primary endpoint results of the most relevant subgroup analysis see Table 1B, Appendix 1). There was also a significant treatment benefit of enoxaparin compared with UFH in patients who underwent PCI (23% reduction in relative risk) or who were treated medically (16% reduction in relative risk) within 30 days of randomisation. Treatment with enoxaparin was associated with a greater reduction in the frequency of PCI than those treated with UFH (22.8% versus 24.2%, $p=0.027$) as well as a greater 12-hour median delay in the timing of performance of PCI (121.7 hours versus 109.2 hours; $p=0.006$)[2,6].

5.2 Safety

The most common treatment-related adverse events observed in the enoxaparin trials were major and minor bleeding and ICH[2].

In the ExTRACT-TIMI-25 trial there were significantly more major and minor bleeding events with enoxaparin compared to UFH. At 30 days, major bleeding rates (including ICH) for enoxaparin were 2.1% versus 1.4% for UFH ($p<0.001$); minor bleeding rates for enoxaparin were 2.6% versus 1.8% for UFH ($p<0.001$)[2,6]. There were however no significant differences between the two treatment groups in terms of the incidence of thrombocytopenia, ICH episodes at day 30 and stroke rates at day 30. The overall incidence of adverse events resulting in death was not significantly different for the enoxaparin and UFH treatment groups[2]. The most frequently reported adverse event leading to death in both groups was cardiogenic shock. Among the patients who had a major bleeding episode the mortality rate at 30 days was significantly greater in the enoxaparin treatment group compared to the UFH group (0.8% versus 0.4%, respectively; $p=0.001$)[2].

In a subgroup analysis of the ExTRACT-TIMI-25 trial by Sinnaeve and colleagues[16] the authors state that the clinical benefit of enoxaparin in patients >65 years were offset due to an increase in major bleeding complications in this group of patients[2]. The SPC states that elderly patients may be at increased risk of bleeding complications within the therapeutic dosage ranges and advises careful clinical monitoring[1].

6.0 SUMMARY OF CLINICAL EFFECTIVENESS ISSUES

- There is a lack of a direct comparison between fondaparinux and LMWHs, and the significantly different inclusion criteria between relevant trials makes indirect comparisons challenging[5].
- In the pivotal trial, the results were obtained up to 30 days post-treatment and no longer term efficacy or safety data were made available at the time of the submission.
- In the ExTRACT-TIMI 25 study although enoxaparin was associated with a significant reduction in the primary endpoint of death or non fatal MI at 30 days compared to UFH; this reduction was driven by a reduced incidence of non-fatal MI (3% versus 4.5%, $p<0.001$) as there were no significant differences in mortality between groups[6].
- In the ExTRACT-TIMI 25 study the median duration of treatment with enoxaparin was seven days compared with two days with UFH which may have reduced the anti-thrombotic effect of UFH and therefore contributed to the differences observed in primary and secondary composite endpoints and the increase in bleeding observed with enoxaparin[2,6].
- Subgroup analysis of the pivotal trial for age showed that in aged ≥75 years there were no significant differences between enoxaparin and UFH treatment groups. These patients also experienced an increase in bleeding events compared to those <75 years of age.
- Enoxaparin in the only licensed LMWH for STEMI and the dosage regimen for enoxaparin has advantages compared with UFH as despite an initial IV bolus dose (in patients <75 years of age) it can be administered SC[1,3].
- Enoxaparin is not recommended in children as dosage has not been established[1].

7.0 REVIEW OF HEALTH ECONOMIC EVIDENCE

7.1 Context

The company submission[2] describes cost utility analyses of enoxaparin compared against UFH and fondaparinux as adjuncts to thrombolytic therapy in patients who have experienced acute STEMI (see Table 2A, Appendix 2). The company considers that the comparison of enoxaparin with UFH is most relevant as expert opinion suggests that fondaparinux is not usually used in these patients in Wales.

The ExTRACT-TIMI 25 study[6] is used to provide direct comparative data for enoxaparin and UFH. There are reportedly no direct comparative data for enoxaparin and fondaparinux in this indication, and the analysis is based on data derived from an indirect comparison of the ExTRACT-TIMI 25 study and the OASIS-6 trial of fondaparinux and UFH[17] (see Table 2B, Appendix 2).

In the ExTRACT-TIMI 25 and OASIS-6 trials, enoxaparin and fondaparinux were administered for a median of 7 days and UFH for 2 days[6,17]. This is what has been modelled for the base case analysis (Scenario 1), with a length of hospital stay of 10 days[2]. A further scenario is provided for the comparison of enoxaparin and UFH, based on company-sought expert opinion, in which treatment with either agents is assumed to be administered for two days, and length of hospital stay is assumed to be five days (Scenario 2).

The perspective of the analyses is NHS Wales and a life time horizon of analysis is used in the base case[1].

7.2 Methods

Modelling approach: A two-stage model has been developed. The first stage consists of a decision analytic model to represent the course of acute treatment over the first 30 days following STEMI. The second stage consists of a Markov model comprising three health states to extrapolate to the remainder of life: survivors of STEMI without major bleed, survivors who experienced major bleed in the first 30 days, and survivors who experienced major bleed that resulted in neurological impairment in the first 30 days.

Inputs – First 30 days: For the comparison of enoxaparin and UFH, data from ExTRACT-TIMI 25 have been used to model deaths, reinfarctions, revascularisations and adverse events (minor or major bleeding, including intracranial haemorrhage, and neurological disability). Data from the UFH arm of the trial provide the baseline risks and the treatment effect of enoxaparin is estimated relative to these. For Scenario 1, 30-day outcomes data are used. For Scenario 2, efficacy outcomes at 48-hours and adverse event rates at 30 days as observed in the ExTRACT-TIMI 25 study are used.

For the comparison of enoxaparin and fondaparinux, data from the indirect comparison are used[2] (see Table 2B, Appendix 2). Adverse event data from the indirect comparison relate only to severe haemorrhage at 9 days, and where comparative data were unavailable, the risk of events with fondaparinux was assumed to be the same as for enoxaparin[2].

Baseline utility values for patients who experience a STEMI are derived from published US-based sources[18]. A disutility is applied for those who experience reinfarction/ revascularisation, major bleed or stroke within 30 days, based on values obtained at 6 months in a subset of GISSI-2 trial population[19]. Resource use is reported to be derived from treatment guidelines, registry data, literature and interviews with three Welsh cardiologists. Scottish resource use and costs are largely assumed. Costs of thrombolytics, and other acute medicines, for the index event are excluded as these are assumed to be the same across all arms of the model. Nursing and pharmacy costs associated with drug administration are not included.

Inputs – after 30 days: Long-term survival data are based on Scottish survival rates at 1, 3, 5 and 10 years following acute MI, which have been extrapolated using a Weibull function. From age 77 years, survival rates from general population are used in the model, as the company reports that the modelled Weibull survival curve following acute MI converges with the general population survival curve at this age. Patients who experienced a major bleed in the first 30 days are assumed to be at increased risk of death in the first 6 months based on a meta-analysis of three trials in non-ST elevated acute coronary syndromes (ACS)[20]. A hazard ratio for death of 1.54 is assumed in the base case analyses.

Utility values for patients who experienced stroke were derived from a meta-analysis of quality of life estimates for stroke[21]. It is assumed in the base case that stroke results in severe disability, with a utility value for moderate disability tested in sensitivity analysis. For non-stroke patients, an age-standardised population utility score is used (i.e. it is assumed there is no further impact on quality of life beyond 30 days for patients who have experienced acute STEMI and no stroke). Resource use in the long term relates to readmission costs, which are derived from a previous health technology assessment (HTA) in non-ST segment elevation myocardial infarction (NSTEMI) patients[22], and long-term costs of disabling stroke, which are based on a published cost of illness study that takes account of the likely long term care setting[23]. Drug treatment at discharge is assumed to remain constant throughout the remaining life, except for clopidogrel hydrogen sulphate, which is assumed to be used in 89% of patients initially and only 5% patients after one year.

7.3 Results

Base case analyses under Scenario 1: The incremental cost per QALY gained for enoxaparin versus UFH is £15,164, based on additional costs of around £600 and a gain of 0.038 QALYs. For the comparison of enoxaparin versus fondaparinux, the incremental cost per QALY gained is £15,959, based on additional costs of around £400 and a gain of 0.025 QALYs[2].

Base case analysis under Scenario 2: The incremental cost per QALY gained for enoxaparin versus UFH is £13,504, based on additional costs of around £200 and a gain of 0.014 QALYs. No comparison of enoxaparin and fondaparinux was made under this scenario.

Table 1. Base case analyses[2]

Scenario 1: Enoxaparin / Fondapariunux 7 days, UFH 2 days, LOS 10 days				
	Enoxaparin vs. UFH		**Enoxaparin vs. Fondaparinux**	
Life years	7.764	7.716	7.758	7.724
QALYs	6.036	5.998	6.031	6.006
Total costs	£89,880	£89,296	£89,810	£89,405
ICER (enoxaparin vs. comparator)	£15,164 per QALY gained		£15,959 per QALY gained	
Scenario 2: Enoxaparin 2 days, UFH 2 days, LOS 5 days				
	Enoxaparin vs. UFH		**Enoxaparin vs. Fondaparinux**	
Life years	7.773	7.716	-	-
QALYs	6.012	5.998	-	-
Total costs	£89,501	£89,308	-	-
ICER (enoxaparin vs. comparator)	£13,504 per QALY gained		-	

ICER = incremental cost effectiveness ratio; LOS = length of hospital stay; QALY = quality-adjusted life year; UFH = unfractionated heparin

Sensitivity analyses

A wide range of one and two way sensitivity and scenario analyses have been conducted, the majority of which lead to only marginal changes in the modelled incremental cost effectiveness ratios (ICERs). When the relative risk of death at six months following a major bleed is increased from 1.54 in the base case analyses to 3.5, the ICER for enoxaparin versus UFH increases marginally to £15,285 per QALY gained under Scenario 1, and reduces to £10,032 per QALY gained under Scenario 2. The ICER versus fondaparinux increases to £18,131 per QALY gained.

When the proportion of the population aged 75 years and over is increased from 12.4% in the base case to 25%, the ICER under Scenario 1 decreases marginally to £14,688 per QALY gained and under Scenario 2 increases marginally to £13,839. The modelled outputs appear robust to assumptions of stroke severity following a major bleed, and whether or not vial wastage is assumed. Threshold analyses indicate that the ICER remains below £20,000 per QALY gained when compared against enoxaparin, irrespective of the assumed rates of ICH and as long as the rates of major bleeds remains below 7% for enoxaparin[1].

Probabilistic sensitivity analysis (PSA) has been conducted using 10,000 simulations. The probabilities of enoxaparin being cost effective compared with UFH at willingness to pay thresholds of £20,000 and £30,000 per QALY are 85% and 99%, respectively. The PSA for the comparison of enoxaparin versus fondaparinux suggests probabilities of cost-effectiveness at the £20,000 and £30,000 per QALY thresholds of 57% and 63%, respectively, but in 31% of the simulations, enoxaparin was both less effective and less expensive than fondaparinux. This finding is driven largely by the relative risk of death estimated from the indirect comparison[2].

7.4 WMP critique of the company's economic evidence

Scenario 1 compares enoxaparin against significantly shorter UFH use, and the relative efficacy of fondaparinux derived from the indirect comparison is also based on longer duration of treatment with fondaparinux than UFH. The authors of both the ExTRACT TIMI-25[6] and the OASIS-6[17] trial reports note that the observed differences in effect in these trials may be due to the longer duration of treatment with enoxaparin and fondapariunx compared with UFH. Therefore, Scenario 2, which compares enoxaparin against UFH over the same duration, would seem to provide a fairer reflection of the relative effectiveness of enoxaparin. However, Scenario 2 models two days of treatment with enoxaparin and UFH, which according to the 2007 SIGN guidance,[5] is insufficient – anticoagulation is recommended for eight days or until hospital discharge or coronary revascularisation.

There are a number of strengths and limitations to the evidence that has been presented.

Strengths of the economic evidence provided in the company submission include:

- The availability and use of direct comparative data for the analysis of enoxaparin compared with UFH.
- In the absence of direct comparative evidence for enoxaparin and fondaparinux an indirect comparison has been conducted using data from the largest available trials.
- Multiple sensitivity and scenario analyses have been conducted to explore the impact of modelling assumptions.

Limitations of the economic evidence provided in the company submission include:

- The extent to which ExTRACT-TIMI 25 reflects the STEMI population and their treatment in Wales is unclear. In the trial, UFH was used for a median of 2 days, enoxaparin was used for 7 days, PCI was performed in 23% of patients and clopidogrel hydrogen sulphate was initiated in around 27% of patients. The SIGN guideline on ACS recommends anticoagulant use should be longer than 2 days, and PCI is recommended routinely. Clopidogrel is also recommended routinely in addition to aspirin[5]. Therefore, efficacy and safety outcomes in practice may be different to those observed in the ExTRACT-TIMI trial and modelled here.

- Efficacy data for the analysis of enoxaparin versus fondaparinux are derived from indirect comparisons of trial data, which have inherent limitations. The OASIS-6 trial of fondaparinux had a complex design and the relevant data to inform the indirect comparison against enoxaparin is from a sub-group of the whole population. The company submission notes similarities between the ExTRACT-TIMI 25 and OASIS-6 populations, but there are some important differences related to the extent of use of PCI and clopidogrel hydrogen sulphate which would be expected to impact on relative efficacy and safety outcomes used in the current model.

7.5 Review of published evidence on cost-effectiveness

Standard literature searches conducted by WMP have identified one published cost effectiveness analysis of enoxaparin in the treatment of acute STEMI[24]. This compared enoxaparin against UFH in a US health care setting, using patient-level clinical outcomes and resource use from the ExTRACT-TIMI 25 trial, and estimates of life expectancy gains as a result of the prevention of the clinical events on the basis of the Framingham Heart Study. As in the current analysis, 30-day costs were higher for enoxaparin ($102; 95% CI $108 to $314). Patients receiving enoxaparin gained an average of 0.12 life-years relative to patients given UFH, which is greater than in the current analysis. Estimated total lifetime costs were $1,207 higher in the enoxaparin group (95% CI $491 to $1,923). The ICER for enoxaparin compared with UFH was $5,700 per life-year gained. Using PSA and a willingness-to-pay threshold of $50,000, there was a 90% probability that enoxaparin is cost effective over the lifetime horizon of analysis. Due to differences in the health care setting and the approach to modelling survival it is not possible to directly compare the current analysis with this published analysis, although the overall conclusions appear similar.

8.0 REVIEW OF EVIDENCE ON BUDGET IMPACT

8.1 Methods

The annual number of incident STEMI cases in Wales is assumed to be 3,158, based on estimates used in the AWMSG appraisal of fondaparinux in 2008[25]. Reportedly based on Scottish incidence data for MI between 2002 and 2007[26], the company estimates a 5% decline each year in incident cases for STEMI, such that there are 3000 cases in Wales in 2010, decreasing to 2,444 cases in 2014[2].

Based on company market research data on file, it is estimated that 67.1% of STEMI patients receive thrombolytic treatment. Two scenarios are presented: Scenario A assumes that there is currently no use of enoxaparin in this patient population; and Scenario B assumes 35% current use of enoxaparin. In both scenarios, enoxaparin is assumed to make up 50% of the market share by 2011, rising to 65% by 2014. The budget impact analysis considers enoxaparin as an alternative to UFH only, as it is assumed that fondparinux is not currently used in Wales for the treatment of STEMI.

The analysis considers drug acquisition costs for enoxaparin and UFH as assumed in the economic model (based on 76kg adult, UFH administered for 2 days and enoxaparin administered for 7 days). Direct savings with enoxaparin treatment included in the analysis relate to aPTT tests and infusion pumps that are required with UFH but not with enoxaparin. The analysis does not consider nursing and pharmacy costs associated with preparation and administration[2].

8.2 Results

The annual budget impact estimates included in the company submission are summarised in Table 2.

8.3 Critique

The budget impact estimates rely on the same assumptions as the economic model, as discussed in section 7. The budget impact analysis would therefore seem subject to some uncertainty and should be interpreted with caution.

Table 2. Annual budget impact estimate for each of the next 5 years as reported in the company submission[2]

	2010	2011	2012	2013	2014
Scenario A – no current use of enoxaparin in STEMI					
Number of enoxaparin treated patients	403	956	999	1,036	1,066
Additional drug costs with enoxaparin	£31,123	£73,981	£77,244	£80,053	£82,388
Cost savings with enoxaparin*	£7,741	£18,384	£19,211	£19,910	£20,491
Net budget impact	£23,383	£55,534	£58,033	£60,143	£61,898
Scenario B – assumed 35% current use of enoxaparin in STEMI					
Number of enoxaparin treated patients	906	956	999	1,036	1,066
Additional drug costs with enoxaparin	£15,562	£22,175	£28,089	£33,356	£38,025
Cost savings with enoxaparin*	£3,870	£5,515	£6,986	£8,296	£9,457
Net budget impact	£11,691	£16,660	£21,103	£25,060	£28,568
* Relate to aPTT and infusion pump only					

8.4 Comparative unit costs

Table 3 provides example costs for enoxaparin and the comparators fondaparinux and UFH, based on a 76kg adult aged less than 75 years and assuming vial wastage. The SIGN guideline on ACS indicates treatment should be for up to 8 days.

Table 3. Example comparator costs[3]

Drug	Example dose*	First day acquisition cost	8 day treatment cost
Enoxaparin (Clexane®)	30mg IV bolus initially, then 1mg/kg SC twice daily	£21.33† + £10.38	£105.24
Fondaparinux (Arixtra®)	2.5mg IV on day 1, followed by 2.5 mg SC once daily	£6.41	£51.28
UFH (Non-prop)	4000U IV bolus then 1000U/hr IV infusion	£0.72 + £1.90	£15.92
This table does not imply therapeutic equivalence of the regimens and doses * Based on 76 kg adult aged less than 75 years; † Based on cost of 300mg multidose vial and assuming drug wastage as per the economic model; IV=intravenous; SC=subcutaneous			

9.0 ADDITIONAL INFORMATION

9.1 Shared care arrangements
Enoxaparin (Clexane®) would not be suitable for shared care within NHS Wales.

9.2 Previous AWMSG advice
The All Wales Medicines Strategy Group (AWMSG) issued guidance on the use of fondaparinux (Arixtra®) in May 2008. This guidance states that fondaparinux should be recommended as an option for use in the treatment of STEMI in patients who are managed with thrombolytics or who are initially to receive no other form of reperfusion therapy[25].

9.3 Ongoing studies
The company submission includes details on one ongoing trial investigating STEMI treated with Primary Angioplasty and Intravenous Lovenox or Unfractionated heparin (ATOLL) from which evidence is likely to be available within the next 12 months[2].

9.4 Patient organisation information
One patient organisation submission was made by AntiCoagulation Europe.

9.5 Medical expert summary
Medical expert views were provided.

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Appendix 1. Additional Clinical Information

Table 1A. Pivotal ExTRACT-TIMI 25 trial: Enoxaparin versus unfractionated heparin (UFH)

Ref	Study type	No. patients	Inclusion/ exclusion criteria	Baseline characteristics	Treatment regimens	Outcomes (Enoxaparin versus UFH)
ExTRACT-TIMI 25[2,6]	Randomised, double-blind, comparator controlled 674 sites in 48 countries (including 4 centres in Wales)	Randomised n= 20, 506 ITT = 20, 479 Enoxaparin n= 10, 256 UFH n= 10, 223 73% treated with medical therapy alone 23% received PCI (2% rescue therapy; 20.2% as an urgent elective procedure) 2,8% received coronary artery bypass surgery	Inclusion criteria: • ≥18 years of age • ≥ 20mins ischaemic symptoms at rest ≤6 hours before randomisation • ST-segment elevation of at least 0.1mV in 2 limb leads or 0.2mV in at least 2 contiguous precordial leads or left bundle branch blockade • Scheduled to undergo fibrinolysis (with streptokinase, tenecteplase, alteplase or reteplase) Exclusion criteria: • Cardiogenic shock • Pericarditis • Symptoms of aortic dissection • Contraindications to fibrinolysis • LMWH within prior 8 hrs • Renal insufficiency • Life expectancy <12 months	Median age: 60yrs Male: 76.7% Aged ≥ 75 years:12.4% Median Weight: 76kg Hypertension: 44% Hyperlipidaemia: 18.3% Current smoker: 47.4% Diabetes Mellitus: 15.1% Prior myocardial infarction: 13% Prior angina pectoris: 28% Prior PCI: 3.2% Fibrinolytic treatment: Streptokinase: 20.2% Tenecteplase: 19.5% Alteplase: 54.6% Reteplase: 5.5% None: 0.3%	1:1 enoxaparin versus UFH Patients received aspirin (&/or antiplatelet agents) + fibrinolytic therapy Study medication was administered between 15mins before and 30mins after fibrinolytic therapy and within 30mins of randomisation **Enoxaparin:** Patients <75 years: 30mg IV bolus followed 15mins later by 1.0mg/kg SC repeated every 12 hrs Patients ≥75 years: 0.75mg/kg SC every 12hrs First 2 doses were limited to 100mg for patients <75years and 75mg for those ≥ 75 years. Treatment continued for a maximum of 8 days. **UFH:** 60U/kg IV bolus (max 4000U), followed within 15mins by an infusion of 12U/kg/hr (initial max of 1000U/hr) for 48hrs Adjustments were made according to aPTT. Infusion for 48hrs or longer at the physicians discretion	**Primary Composite Endpoint (ITT):** **Death or non-fatal MI in the first 30 days after randomisation:** Enoxaparin: 1, 017/10, 256 (9.9%) UFH: 1, 223/10,223 (12%) RR = 0.83 (p<0.001; 95% CI 0.77,0.90) This advantage of enoxaparin was consistent across subgroups. **Secondary Composite Endpoint:** **Death, non-fatal MI or recurrent myocardial ischaemia leading to urgent revascularisation in the first 30 days:** Enoxaparin: 1, 199/10, 256 (11.7%) UFH: 1, 479/10,223 (14.5%) (p<0.001) **Additional secondary endpoints (measures of net clinical benefit at 30 days):** **(1) Death or non-fatal MI or non-fatal disabling stroke** 10.1% vs 12.3%; RR = 0.82; 95% CI (0.76, 0.89) p<0.001 **(2) Death or non-fatal MI or non-fatal major bleeding** 11% vs 12.8%; RR = 0.86; 9% CI (0.80, 0.93) p<0.001 **(3) Death or non-fatal MI or non-fatal intracranial haemorrhage** 10.1% vs 12.2%; RR= 0.83; 95% CI (0.77, 0.90) p<0.001 **Other Outcomes (Enoxaparin versus UFH)** **(1) Death at 48hrs, 8dys and 30dys** 48hrs: 3.7% vs 3.8% (NS); 8dys: 5.5% vs 5.9% (NS); 30 dys: 6.9% vs 7.5% (NS) **(2) Non-fatal MI at 48hrs, 8dys and 30 dys** 48hrs: 0.9% vs 1.4% (p=0.002); 8dys: 1.8% vs 3.4% (p<0.001); 30 dys: 3.0% vs 4.5% (p<0.001) **(3) Urgent revascularisation at 48hrs, 8 dys and 30 dys** 48hrs: 0.7% vs 0.9% (p=0.02); 8dys: 1.4% vs 2.4% (p<0.001); 30 dys: 2.1% vs 2.8% (p<0.001)

aPTT: activated partial thromboplastin time; CI: confidence interval; Dys: days; hrs: hours; IV: intravenous; LMWH: low molecular weight heparin; MI: myocardial infarction; NS: not significant; RR: relative risk; SC: subcutaneous; UFH: unfractionated heparin; vs: versus; yrs: years

Appendix 1. Continued

Table 1B. Summary of most relevant subgroup Analysis from ExTRACT-TIMI 25 trial: Enoxaparin versus unfractionated heparin (UFH)[2,6]

Ref	No. patients	Baseline characteristics	Primary Composite Endpoint (Death or non-fatal MI in the first at 30 days (Enoxaparin versus UFH)
(1) Percutaneous coronary Intervention			
Gibson et al (2007)[27]	23% of total study population underwent PCI (n = 4,676)	**For PCI group:** Median age: 57yrs Male: 82.5% Aged ≥ 75 yrs: 7.3% Median Weight: 76kg	PCI: 10.7% versus 13.8% (RR = 0.77, 95% CI 0.66,0.90; p=0.001) When adjusted for baseline characteristics including age, time to PCI, and type of fibrinolytic agent, the reduction in death or non-fatal MI associated with enoxaparin remained statistically significant versus UFH.
(2) Age			
White et al (2007)[28]	Patients ≥75 yrs: 2,532 (12.4%) Patients < 75 yrs: 17,947 (88%)	Male: Age >75: 52.5% Age <75: 80.1% Median Weight: 74kg	Patients >75 yrs: 24.8% versus 26.3% NS Patients <75 yrs: 7.9% versus 9.9% (RR = 0.80, 95% CI 0.72,0.87; p<0.0001)
(3) Fibrinolytic Therapy			
Giraldez et al (2007) [29]	Fibrin Specific: Tenecteplase: 3,986 (19.5%) Alteplase: 11,175 (54.6%) Reteplase: 1,122 (5.5%) Streptokinase: 4,139 (20.2%)	Median age: 60yrs Male: 75.9% Age ≥ 75 yrs: 13.3% Median Weight: 76kg	Fibrin Specific Therapy: 9.8% versus 12.0% (odds ratio$_{adj}$ 0.78; 95% CI 0.70, 0.87; p=0.001) Streptokinase Therapy: 10.2% versus 11.8% NS
(4) Sex			
Mega et al (2007) [30]	Female: 4,783 (23%) Male: 15,696 (77%)	**Median age:** Female: 68yrs; Male: 57yrs **Median Weight:** Female: 70kg; Male: 79kg	Female: 15.4% versus 18.3% (p=0.007) Male: 8.2% versus 10.1% (p<0.001)
(5) Diabetes			
Morrow et al (2007) [31]	Diabetes: 3,060 (15%) No diabetes: 17,189 (85%)	**Median age:** Diabetes: 63yrs No diabetes: 58yrs **Male:** Diabetes: 66%; No diabetes: 79% **Age ≥ 75 yrs:** Diabetes: 15%; No diabetes: 12% **Median Weight:** 76kg	Diabetes: 13.6% versus 17.1% (RR 0.80; 95% CI 0.67,0.94, p=0.007) No diabetes: 9.2% versus 11.1%
CI: Confidence interval; MI: Myocardial infarction; NS: not significant; RR: relative risk; UFH: unfractionated heparin; yrs: years;			

Appendix 2. Additional Health Economic Model Information

Table 2A. Health economic model detail[2]

Base Case Model		Appropriate?
Comparator(s)	Enoxaparin compared against UFH or fondaparinux as adjuvant to thrombolytic therapy	Yes – as requested by WMP. The company considers the comparison of enoxaparin with UFH to be the most important, and states that the opinion of 3 Welsh cardiologists the company has sought is that fondaparinux is not used in Wales in this indication.
Population	Acute STEMI patients scheduled for fibrinolysis. Assumed body weight 76kg and 12.4% of population aged 75 years or older, as per ExTRACT-TIMI 25 study.	Yes – population meets licensed indication. Proportion of patients aged 75 years or older may be greater in Wales and as age influences enoxaparin dose regimen, this is explored in sensitivity analysis.
Model type and description	Two stage model: i) a decision analytic model to represent the course of acute treatment over first 30 days following acute event; ii) Markov model using extrapolated survival data to model remainder of lifetime from 30 days post acute event to death.	Model type appears adequate.
Perspective	Considers direct medical costs only, from perspective of NHS Wales	Yes
Time Horizon	Lifetime (maximum of 100 years of age)	Yes
Discount rate	Costs and outcomes discounted at 3.5% per annum, rates of 0% and 6% explored in sensitivity analysis	Yes
Efficacy	Up to 30 days: Enoxaparin vs. UFH: based on direct comparative data from ExTRACT-TIMI 25 trial[6] Enoxaparin vs. fondaparinux: based on indirect comparison of ExTRACT-TIMI 25 trial[6] and OASIS-6 trial[17] of fondaparinux vs. UFH. Post 30 days: Survival data for patients experiencing major bleed derived from meta-analysis of three trials in non-ST elevated ACS[20]. Long term survival data based on Scottish survival rates at 1, 3, 5 and 10 years following acute MI, which has been extrapolated usng Weibull function. From age 77 years, survival rates from general population are used in the model, as the company reports that the modelled Weibull survival curve following acute MI converges with the general population survival curve at this age. All patients are assumed to have died by age 100 years.	Yes – use of direct data from the pivotal trial for the comparison of enoxaparin and UFH is appropriate to model early phase. However, length of treatment with enoxaparin was longer than with UFH (median 7 days versus 2 days), which may impact upon outcomes beyond 48 hours post the acute STEMI. In absence of direct comparative evidence an indirect comparison may be appropriate, but there are inherent limitations in indirect comparisons and there were some relevant differences between the trial populations in relation to use of clopidogrel hydrogen sulphate (58.5% in OASIS-6 vs. 27.5% in ExTRACT-TIMI 25). As in the ExTRACT-TIMI 25 study, length of treatment with fondaparimux was longer than with UFH (6.6 days versus 37.6 hours). Survival data modelled based on Scottish survival rates post MI. In the absence of Welsh data this would be appropriate. Company submission states opinion of 3 Welsh cardiologists was sought to verify approach.
Adverse effects	Adverse events relate to minor and major bleeding episodes, including ICH and neurological impairment following ICH. Enoxaparin vs. UFH: based on 30-day direct comparative data from ExTRACT-TIMI 25 trial[6]	Yes – use of direct data from the pivotal trial for the comparison of enoxaparin and UFH is appropriate to model adverse events. The indirect comparison of enoxaparin and fondaparinux would seem appropriate in the absence of other data. However, there were some relevant differences between the trial populations in relation to use of clopidogrel hydrogen

	Enoxaparin vs. fondaparinux: based on indirect comparison of ExTRACT-TIMI 25 trial[6] and OASIS-6 trial[17] of fondaparinux vs. UFH. Note: only severe haemorrhage at 9 days could be compared in the indirect comparison. Patients who experience a severe bleed are assumed to have a higher risk of death in the first 6 months following STEMI, based on the meta-analysis of three trials in non-ST elevated ACS[20]. The hazard ratio for death has been tested in scenario analyses	sulphate (58.5% in OASIS-6 vs. 27.5% in ExTRACT-TIMI 25). Despite higher rates of use of clopidogrel hydrogen sulphate in the OASIS-6 trial, the indirect comparison suggests that patients receiving enoxaparin were more likely to experience severe haemorrhage at 9 days than patients receiving fondaparinux, although the 95% CI suggests the difference was not statistically significant.
Utility values	Utility values in first 30 days for acute MI patients who survive are based on a US catalogue of EQ-5D derived scores for chronic conditions[18]. A disutility is applied for those who experience reinfarction/ revascularisation, major bleed or stroke within 30 days, based on values obtained at 6 months in subset of GISSI-2 trial population[19]. For period post 30 days, utility values for stroke were derived from a meta-analysis of quality of life estimates for stroke[21]. For all other (non-stroke) patients, an age-standardised population utility score is used (i.e. assumes no further impact on quality of life beyond 30 days for patients who have experienced acute STEMI and no stroke).	No relevant trial-derived utility values available so used those from literature. Approach was reported to have been validated by 3 Welsh cardiologists but would appear subject to some uncertainty. In base case analysis those who experience stroke are assumed to have severely disabling stroke, which would appear to favour enoxaparin due to lower rates of disabling stroke compared with UFH[21]. Sensitivity analysis was conducted using assumption of moderately disabling stroke. Rates of disabling stroke are assumed to be the same for fondaparinux and enoxaparin as the indirect comparison is reported to have been able to compare only rates of severe haemorrhage (and not rates of ICH/neurological disability). It should be noted that rates of severe haemorrhage were numerically greater for enoxaparin compared with fondaparinux, despite lower rates of use of clopidogrel hydrogen sulphate (see above).
Resource use and costs	Resource use is reported to be derived from treatment guidelines, registry data, literature and interviews with 3 Welsh cardiologists. Scottish resource use and costs are assumed. Drug costs are based on BNF. It is assumed in the base case analysis that average length of stay in hospital would be 10 days, with 30% on coronary care unit and 70% on cardiac ward. Half of those who died due to STEMI were assumed to be dead on arrival at hospital and other half die within 48 hours. Drug treatment at discharge assumed to remain constant throughout long term, except for clopidogrel hydrogen sulphate, which is assumed to be used in only 5% patients after 1 year. Costs of thrombolytics, and other acute medicines, for index event are excluded as these are assumed to be the same across all arms of the model. Nursing and pharmacy costs associated with administration are not included. Annual readmission costs are based on a previous HTA in NSTEMI[22]. Long-term costs of disabling stroke are based on a published cost of illness study[23].	Yes - is appropriate to use these sources of resource use in the absence of other sources. There appear to be some minor errors in doses and costs reported to have been assumed for enoxaparin. Also, the cost assumed for aPTT tests appears to be greater than in the cited source. The company suggests that the analysis will be biased in favour of UFH as nursing and pharmacy costs are not included, but this is likely to favour enoxaparin, which requires twice daily administration, rather than UFH that is infused via pump and fondaparinux which requires once daily administration.
Model Provided?	Yes	Yes

Table 2B. Summary results of indirect comparison of ExTRACT TIMI 25[6] and OASIS-6[17] trials

Outcome	Enoxaparin vs. UFH Direct comparison	Enoxaparin vs. Fondaparinux Indirect comparison	Notes
Death – 8 or 9 days*	OR 0.916 (95% CI 0.814 to 1.032) RR 0.921 (95% CI 0.824 to 1.030)	OR 0.956 (95% CI 0.745 to 1.226) RR 0.959 (95% CI 0.758 to 1.213)	Numerically favours enoxaparin but not statistically significantly different
Death – 30 days	OR 0.917 (95% CI 0.824 to 1.019) RR 0.923 (95% CI 0.836 to 1.018)	OR 0.943 (95% CI 0.755 to 1.178) RR 0.947 (95% CI 0.770 to 1.165)	
Reinfarctions – 8 or 9 days*	OR 0.508 (95% CI 0.424 to 0.610) RR 0.517 (95% CI 0.433 to 0.617)	OR 0.743 (95% CI 0.485 to 1.139) RR 0.751 (95% CI 0.493 to 1.143)	Numerically favours enoxaparin - statistically significant difference between enoxaparin and UFH only
Reinfarctions – 30 days	OR 0.662 (95% CI 0.572 to 0.767) RR 0.673 (95% CI 0.584 to 0.775)	OR 0.799 (95% CI 0.560 to 1.140) RR 0.808 (95% CI 0.572 to 1.142)	
Severe / major haemorrhage† – 8 or 9 days*	OR 1.497 (95% CI 1.191 to 1.883) RR 1.488 (95% CI 1.187 to 1.865)	OR 1.587 (95% CI 0.934 to 2.697) RR 1.577 (95% CI 0.933 to 2.663)	Numerically favours UFH and fondaparinux - statistically significant difference between enoxaparin and UFH only

* Outcomes assessed at 8 days in ExTRACT TIMI 25 and 9 days in OASIS-6 – assumed to be comparable
† Defined as fatal haemorrhage, intracranial haemorrhage, cardiac tamponade or clinically significant haemorrhage with decrease in haemoglobin >5g/dL, with each blood transfusion unit counting for 1.0g/dL
OR = Odds ratio; RR = Relative risk