enoxaparin 20mg, 40mg, 60mg, 80mg, 100mg 120mg and 150mg pre-filled syringes *and 300mg multidose vial* (Clexane®) (Clexane®) No. (380/07)

Sanofi-aventis

4 May 2007 *(issued 5 June 2009)*

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

ADVICE: following a full submission

enoxaparin (Clexane®) is accepted for use within NHS Scotland 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).

In clinical studies using a median of seven days of enoxaparin treatment, enoxaparin demonstrated a reduction in death or non-fatal MI compared to unfractionated heparin.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

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).

Dosing information

A single intravenous (IV) bolus of 30mg plus a 1mg/kg subcutaneous (SC) dose followed by 1mg/kg SC every 12 hours. A maximum dose of 100mg is recommended for the first two SC doses. Dose reductions are recommended for patients ≥ 75 years or for those with renal impairment (creatinine clearance <30ml/minute). The recommended duration is 8 days or until hospital discharge if earlier.

Product availability date

01 May 2007

Summary of evidence on comparative efficacy

Enoxaparin is a low molecular weight heparin characterised by a higher ratio of antithrombotic acivity to anticoagulant activity than unfractionated heparin (UFH). At licensed doses it does not significantly affect platelet aggregation, binding of fibrinogen to platelets or global blood clotting tests.

The key efficacy data come from the results of one large published study, which enrolled 20,506 patients with STEMI who were scheduled to undergo fibrinolysis. Patients received streptokinase, tenecteplase, alteplase or reteplase at the discretion of the investigator. All patients received aspirin, and clopidogrel could be used in cases of aspirin allergy or in addition to aspirin at the discretion of the investigator. Patients were randomised to receive enoxaparin or UFH in a double-blind, double-dummy manner. Enoxaparin was administered as a 30mg IV bolus followed by 1mg/kg SC repeated at 12-hourly intervals and continued until hospital discharge or for a maximum of 8 days. In patients aged ≥75 years, the IV bolus was omitted and the SC dose was reduced to 0.75mg/kg every 12 hours. A maximum dose of 100mg (or 75mg for patients ≥75 years) was used for the first two SC injections. The dose was reduced to 1mg/kg SC every 24 hours in patients with a creatinine clearance <30ml/minute. UFH was given as an IV bolus (60U/kg, maximum 4000U) followed by an IV infusion (12U/kg/h, initial maximum 1000U/h) for at least 48 hours with dose adjustments to maintain the activated partial thromboplastin time (aPTT) at 1.5-2.0 times the control. The primary endpoint was a composite of death or non-fatal MI after 30 days.

The median duration of treatment with enoxaparin was 7.0 days compared with 2.0 days with UFH. At 30 days, the primary endpoint of death or non-fatal MI had occurred in 1,017/10,256 (9.9%) of enoxaparin patients and 1,223/10,223 (12%) of UFH patients; corresponding to an absolute risk reduction of 2.1%, a relative risk reduction (RRR) of 17%: relative risk 0.83 (95% confidence intervals (CI): 0.77, 0.90), $p<0.001$. The treatment effect was demonstrated over a range of pre-specified subgroups (sex, age, infarct location, diabetes, prior MI, fibrinolytic agent and time to treatment). The difference in mortality at 30 days was not significant (6.9% versus 7.5% respectively, $p=0.11$). However, the rate of non-fatal MI was significant lower (3.0% versus 4.5% respectively, $p<0.001$).

The main secondary endpoint was the composite of death, non-fatal MI or recurrent ischaemia leading to urgent revascularisation at 30 days. This was significantly reduced from

14% in the UFH group to 12% in the enoxaparin group (p<0.001). A measure of net clinical benefit was assessed as the composite of death, non fatal MI or non-fatal disabling stroke. At 30 days this occurred in 10% of enoxaparin and 12% of UFH patients (p<0.001).

A further 7 smaller studies have evaluated the efficacy of enoxaparin compared with UFH in the treatment of patients with STEMI. The results have generally supported those of the key study. In addition, a meta-analysis has been performed on 6 studies, which provided results on mortality (n=6), recurrent MI (n=4) and refractory ischaemia or angina (n=3). The results found significant differences in favour of enoxaparin for recurrent MI (3.2% versus 5.5%, RRR 41%, p<0.001), refractory ischaemia/angina (4.7% versus 6.7%, RRR 30%, p=0.003), death/MI (8.2% versus 11%, RRR 26%, p<0.001) and death/MI/refractory ischaemia/angina (12% versus 17%, RRR 28%, p<0.001). The difference between treatments was not significant for death (5.3% versus 6.2%, RRR 14%, p=0.19).

Summary of evidence on comparative safety

The key safety issue around the use of anticoagulant therapy is the risk of bleeding. In the key study, bleeding was assessed according to the TIMI criteria. Major bleeding (including intracranial haemorrhage) was reported in 2.1% of enoxaparin and 1.4% of UFH treated patients, corresponding to an absolute increase in risk of 0.7% and a 53% increase in relative risk (p<0.001). A total of 38% (80 patients) in the enoxaparin and 32% (44 patients) in the UFH group who had a major bleed died (p=0.25). There was no significant difference between the treatments in the incidence of intracranial haemorrhage (0.8% versus 0.7% respectively, p=0.14). Minor bleeding episodes were significantly more common in the enoxaparin than the UFH group (2.6% versus 1.8%, p<0.001).

Summary of clinical effectiveness issues

In the key study, when administered in conjunction with fibrinolytics, enoxaparin was associated with a significant reduction in the primary endpoint (death or non-fatal MI) at 30 days compared to UFH. This reduction was driven by a reduced incidence of non-fatal MI and there was no significant difference in mortality between the groups. This benefit has to be balanced against an excess of major and minor bleeding in the enoxaparin group. The study excluded patients who had a haemorrhagic risk. Therefore, treatment of these patients in routine clinical practice may result in higher incidences of bleeding than those experienced in the study population.

The duration of therapy with UFH was considerably shorter than that for enoxaparin and the study cannot be considered as a direct comparison of the individual drugs but rather a comparison of the drug regimens. The longer period of administration of enoxaparin may in part account for both the reduction in cardiac events and the increase in bleeding. Recent guidance favours more prolonged treatment (>48 hours) and recommends that anticoagulant therapy should be continued for 8 days or until hospital discharge or coronary revascularisation.

In addition to long-term aspirin, recent guidance also recommends immediate treatment with clopidogrel which should be continued for up to 4 weeks for patients with ST-segment elevation acute coronary syndrome. Less than 30% of patients in the key study received clopidogrel and it is unclear how combined use would affect both efficacy and safety outcomes in this study.

In the key study, reduced doses of enoxaparin were used in patients aged ≥75 years. For other licensed indications, dose reductions for enoxaparin are only recommended in patients who have renal impairment. This may lead to potential confusion in routine clinical practice.

The Scottish Intercollegiate Guidelines Network (SIGN) guidance recommends fondaparinux, a selective synthetic inhibitor of Factor Xa, as an alternative to low molecular weight heparin for patients with ST-segment elevation acute coronary syndrome. Enoxaparin is the only low molecular weight heparin licensed for this indication. There have been no direct comparisons of enoxaparin and fondaparinux in this patient group. For patients with ST-segment elevation acute coronary syndrome who do not receive reperfusion therapy, SIGN recommends immediate treatment with fondaparinux.

Summary of comparative health economic evidence

The manufacturer submitted a lifetime cost-utility analysis comparing enoxaparin with UFH, used as in the key study. Quality of life values were taken from published literature sources and resource use was informed by Scottish clinicians. The results of the analysis indicated an incremental cost per QALY for enoxaparin of £13,406 which was relatively insensitive to changes in key parameters. The manufacturer also modelled a scenario after consulting with Scottish experts. This scenario assumed enoxaparin would be used for 3 days, inpatient stay for both treatment groups would be 5 days and that the efficacy data at the 48 hour point would apply. The resulting cost per QALY was £11,881.

The analysis was generally well conducted. A key issue, however, relates to the duration of UFH treatment. Recent SIGN guidelines suggest that the 48 hours of UFH treatment used in the model may not be appropriate although SMC experts indicate that this duration of treatment is still in use. The impact of changing the cost assumptions around the use of UFH was investigated in a sensitivity analysis. While the precise impact on cost-effectiveness is uncertain, it was possible to say that enoxaparin would still be cost-effective unless the efficacy of UFH was very close to that shown by enoxaparin.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

SIGN recently published a guideline on Acute Coronary Syndromes. In patients with ST-segment elevation acute coronary syndrome, this recommends the use of fondaparinux or a low molecular weight heparin at various stages and as maintenance in-hospital medication. Fondaparinux is recommended for patients with ST-segment elevation acute coronary syndrome who do not receive reperfusion therapy.

Additional information: comparators

The most likely comparators are UFH or fondaparinux.

Additional information: costs

Drug	Dose	Cost per day	Cost for up to 8 days
Enoxaparin	**30mg IV bolus plus 1mg/kg SC twice daily**	**£22.20 £9.50 to £10.80***	**£93.45 - £103.20**
Fondaparinux	2.5mg IV on day one then SC daily	£6.67	£53.36
UFH	4000U IV bolus plus 1000U/h IV infusion	£0.54 £1.52	£12.70

Costs accessed from eVadis on 7 March 2007. Cost for the enoxaparin 300mg multi-dose vial used for the IV bolus is provided from the manufacturer.
*enoxaparin cost based on 60-80 kg bodyweight

Additional information: budget impact

The manufacturer presented two budget impact scenarios; one which assumes that there is currently no use of enoxaparin in this indication (scenario A) and one that acknowledges the current levels of off-label use of enoxaparin of 35% (scenario B). Expert advice suggests that there may be use of enoxaparin for this indication and therefore scenario B is more probable.

In scenario A the net budget impact was £28k in year one rising to £116k in year five. Under scenario B the figures were £21k and £77k in years one to five respectively. These figures take account of the drug acquisition cost differences and the savings in costs of tests and infusions for UFH. These calculations assumed a median duration of enoxaparin treatment of 7 days. However, expert opinion suggested that 3 days might be more realistic and therefore that the budget impact figures presented above would be overestimates.

In Scenario A patient numbers were 512 in year one rising to 2144 in year five. The figures assume market shares of 20% in year one and 90% by year five. For scenario B the patient numbers were 1280 and 2263 respectively. Market shares in this scenario were 50% in year one and 95% in year five.

Advice context:

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

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

This assessment is based on data submitted by the applicant company up to and including 29 May 2009.

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

The undernoted reference was supplied with the submission. Those shaded grey are additional to the reference supplied with the submission.

Antman EM, Morrow DA, McCabe CH, Murphy SA, Ruda M, Sadowski Z, et al. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. N Engl J Med 2006;354(14):1477-88.

Theroux P, Welsh RC. Meta-analysis of randomised trials comparing enoxaparin versus unfractionated heparin as adjunctive therapy to fibrinolysis in ST-elevation acute myocardial infarction. Am J Cardiol 2003; 91: 860-864.

Gibbons RJ, Fuster V. Therapy for patients with acute coronary syndromes – new opportunities. [Editorial] New Engl J Med 2006; 354 : 1524-1527.