Scottish Medicines Consortium

Bemiparin, 25,000 IU/ml injection for sub-cutaneous administration
(Zibor®) No. (206/05)
Amdipharm

New indication: treatment of venous thromboembolism

9 September 2005

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

Bemiparin (Zibor®) is not recommended for use within NHS Scotland for the treatment of established deep vein thrombosis, with or without pulmonary embolism, during the acute phase.

Greater numbers of patients had a reduction in thrombus size with bemiparin than unfractionated heparin, but bemiparin has not been compared with other low molecular heparins. Cost effectiveness has not been demonstrated.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Bemiparin 25,000 IU/ml, injection for sub-cutaneous administration (Zibor®)

Licensed indication under review

Treatment of established deep vein thrombosis, with or without pulmonary embolism, during the acute phase.

In the absence of any contra-indication, oral anticoagulation should be commenced 3-5 days after beginning bemiparin, and bemiparin administration can be stopped once the target International Normalised Ratio of 2-3 times the control value has been achieved.

Dosing information under review

Once daily dose of 115 IU/kg to be administered subcutaneously, generally rounded to 5000 IU for patients weighing <50 kg, 7500 IU for those weighing 50-70 kg and 10,000 IU for >70kg.

UK launch date

November 2003

Comparator medications

Unfractionated heparin. Low molecular weight heparins: dalteparin sodium (Fragmin®), enoxaparin sodium (Clexane), tinzaparin sodium (Innohep®).

Cost per treatment period and relevant comparators

Preparation	Dose (Assume 70kg)	Cost for 7 days
Bemiparin 7500 IU in 0.3 ml syringe	**7500 IU sc daily for 7 days in weight range 50-70 kg**	**£60**
Dalteparin 15 000 IU in 0.6ml syringe	15 000 IU sc daily for 7 days in weight range 69-82 kg	£60
Enoxaparin 120 mg in 0.8 ml syringe	105 mg (1.5 mg/kg) sc daily for 7 days	£68
Tinzaparin 14 000 IU in 0.7 ml syringe	12 250 IU (175 IU/kg) sc for 7 days	£88

Summary of evidence on comparative efficacy

Heparin binds to antithrombin (AT) and inhibits a number of clotting factors, including factors IIa (thrombin) and Xa. Low molecular weight heparins (LMWH) are obtained by chemical depolymerisation and fractionation. Amongst other differences, this increases their ability to inhibit Factor Xa but decreases their ability to bind to AT and inhibit IIa. It is thought that a high Xa/IIa ratio may lead to greater antithrombotic activity without increasing the risk of bleeding.

Compared with other LMWH, bemiparin has a particularly high Xa/IIa ratio. It also alters the pharmacokinetic profile, allowing less frequent dosing.

A phase III, randomised, open-label, parallel group clinical trial, with blinded assessment of outcome, was conducted to compare the efficacy and safety of two bemiparin regimens with an unfractionated heparin (UFH) regimen and oral anticoagulants in the acute and long-term treatment of deep vein thrombosis (DVT) of the legs in patients aged 18 years or over.

In this multicentre trial, 378 patients with acute deep vein thrombosis (DVT) were randomised to UFH (Group A), given as an initial 5,000 IU IV bolus followed by an intravenous (IV) infusion of 30,000 to 40,000 IU/day, depending on risk of bleeding according to defined criteria with subsequent dose adjustment based on daily measurement of APTT (1.5 to 2.5 times baseline level) for one week; once daily sub-cutaneous (sc) bemiparin at a dose of 115 IU/kg/day for one week rounded to 5000IU, 7500IU or 10,000IU per day (Group B); or once daily sc bemiparin at a dose of 115 IU/kg/day for 10 days rounded as in Group B (Group C). Groups A and B received an oral anticoagulant from day 3 at a dose of 10 mg/day for the first three days, with subsequent dose adjustment to achieve an International Normalised Ratio between 2-3 for 12 weeks. Patients in Group C were maintained on bemiparin 3,500 IU from day 11 until the end of the 90 days.

For the intention to treat (ITT) population, 54 patients were excluded because of lack of baseline venography or independent assessment of DVT, leaving 324 patients. The analysis of efficacy in the acute phase was based on a per protocol group of 297 who also had an evaluable venogram at day 14. There were 98 evaluable patients in Group A, 105 in Group B and 94 in Group C.

The primary analysis of efficacy compared thrombus regression between groups A and B during the acute phase of treatment. This was based on the venographically determined change in thrombus size between baseline and day 14±2 assessed with use of the Marder score. This gives a maximum score of 40 if all of the veins in the affected limb are occluded by thrombus. Each venous system has a maximum score (e.g. 6 for iliac, 4 for common femoral) and partially occluded veins are given a lower score. Independent practitioners, blind to treatment assignment, assessed venograms for improvement, as well as noting symptomatic recurrence of DVT and pulmonary embolism (PE), documented by lung scanning, for secondary endpoints.

Results were reported as the proportion of patients achieving any improvement in thrombus size, and equivalence between groups A and B was investigated using a modified Mantel Haenszel test. For the power calculation, equivalence was assumed if the proportion of patients showing any improvement was at most 7% less for the group receiving bemiparin than those receiving UFH. No results were given for the magnitude of difference in Marder scores between groups.

The secondary efficacy analysis investigated the feasibility of a three-month treatment with bemaparin (Group C) compared to warfarin (Groups A and B) after the acute phase of treatment. The long-term outcome was patency of the deep venous system as determined by venography or Doppler ultrasound, again with independent blinded assessment. Based on the observations on blood flow by sonography, the results were classified as partial or complete recanalisation of the involved veins.

Assessments were conducted at intervals from day 7±2 to 28±3 days after the last dose of study medication.

Fifty-two percent of patients in Group A (51/98), 72% in Group B (76/105) and 72% in Group C (68/94) showed venographic reduction in thrombus mass on day 14; this 20% greater improvement in Groups B and C indicated not only non-inferiority (p=0.00003) but also superiority of bemiparin over UFH (p=0.004). Although not a primary assessment, Group C was also significantly superior to Group A (p=0.005).

Venographic or Doppler sonographic recanalisation of the thrombus were shown on day 84 in 75.3% (64/85), 79.8% (71/89) and 81.5% (66/81) of patients in groups A, B and C respectively (p = NS). There were no significant differences between the treatment arms in the rates of recurrent VTE throughout the study period (3.6% in Group A, 0.9% in Group B, and 2.9% in Group C). The incidence of bleeding events and mortality was similar in all three groups. Two patients in Group A, two in Group B and three in Group C had heparin-associated thrombocytopenia defined as platelet count below 100,000/mm^3. However, none developed thrombotic or bleeding complications.

Summary of evidence on comparative safety

The incidence of bleeding events and death was similar between groups and generally low.

Summary of clinical effectiveness issues

The magnitude of response in this study is difficult to evaluate as Marder scores were not reported, and patients with any reduction in thrombus size were classified as responders. No evidence of efficacy compared to other low-molecular-weight heparins is presented.

Summary of comparative health economic evidence

A cost consequence analysis is presented based on the Spanish health care system. Minimal details of the analysis underlying this are presented, with only a brief summary of an oral communication at the 18th International Congress on Thrombosis being presented.

The total cost of treatment over three months for UFH followed by oral anticoagulants was €4,128, for bemiparin followed by oral anticoagulants was €3,359, and for bemiparin followed by long term bemiparin was €3,220. The oral communication states that “the reduction in hospital stay length and the effectiveness in preventing death and recurrent VTE were the most important factors on incremental cost effectiveness ratio.” No ICER is presented.

Given the setting of the study and the paucity of information supplied there can be no confidence that the results reported will apply within the Scottish context. The cost effectiveness of bemiparin for the treatment of acute phase of established DVT has not been demonstrated.

Budget impact

The estimated budget impact based upon one medium sized hospital adopting bemiparin for the treatment of 100 patients with VTE is a direct drug cost of £1,890 annually. This is based upon a discounted drug cost of 50-60%, and implies a market penetration of 2%. BNF 48 prices would increase this figure to perhaps around £6,000.

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 ***14 July 2005.***

Drug prices are those available at the time the papers were issued to SMC for consideration.

The undernoted references were supplied with the submission.

Kakkar VV, Gebska M, Kadziola Z, Saba N, Carrasco P. Low-molecular-weight heparin in the acute and long-term treatment of deep-vein-thrombosis. Thromb Haemost. 2003; 89:674-80.