Scottish Medicines Consortium

Bemiparin, 3500 IU in 0.2 ml injection for sub-cutaneous administration (Zibor®) No. (204/05)

Amdipharm

New chemical entity: prevention of thromboembolic disease: orthopaedic surgery

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 prevention of thromboembolic events in patients undergoing orthopaedic surgery.

Bemiparin was associated with a lower incidence of thromboembolic complications than unfractionated heparin and was non-inferior to another low molecular weight heparin. The cost effectiveness has not been convincingly addressed for the Scottish context.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Bemiparin, 3500 IU injection for sub-cutaneous administration (Zibor®)

Licensed indication under review

Prevention of thromboembolic disease in patients undergoing orthopaedic surgery (with high risk of thromboembolism).

Dosing information under review

On the day of surgery, 3500 IU to be administered sub-cutaneously (sc) 2 hours before or 6 hours after surgery. On subsequent days, 3 500 IU every 24 hours.

UK launch date

November 2003

Comparator medications

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

Cost per treatment period and relevant comparators

The prices given below are for a peri-operative dose(s) and seven days' post-operative treatment with the recommended dose of low molecular weight heparins licensed for this indication. In practice, doses may be adjusted in the light of monitoring and response, and duration will vary according to patient factors and response.

Preparation	Dose	Cost
Bemiparin 3500 IU in 0.2 ml syringe	**3500 IU sc on the day of surgery then daily for 7 days**	**£36**
Dalteparin 5000 IU in 0.2ml syringe	5000 IU sc on the day of surgery then daily for 7 days	£23
Enoxaparin 40 mg in 0.4 ml syringe	40 mg sc on the day of surgery then daily for 7 days	£34
Reviparin 1432 IU in 0.25 ml syringe	1432 IU sc on the day of surgery then daily for 7 days	£29
Tinzaparin 4500 IU in 0.45 ml syringe	4500 IU sc on the day of surgery then daily for 7 days*	£28.50

* or according to body weight e.g. 3500 IU for patient weighing 70 kg at a cost of £22.17

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.

At a dose of 3500 IU daily sub-cutaneous (sc), there have been two controlled trials and one pilot study in orthopaedic surgery (classified as high risk of venous thromboembolism (VTE)), comparing pre- or post-operative bemiparin to sc UFH or enoxaparin given post-operatively.

The first compared bemiparin 3500 IU daily to unfractionated heparin 5000 IU twice daily, both started two hours before elective total hip replacement in patients aged ≥40 years, and continued over at least 8 days. Entry criteria required that patients were expected to be hospitalised for 12±4 days. The primary end point was the combined incidence of deep vein thrombosis (DVT), as determined by mandatory bilateral elective venography performed on the post-operative day 12±4, and/or symptomatic pulmonary embolism (PE) confirmed by ventilation-perfusion lung scanning.

The study was conducted on an intention-to-treat basis (ITT) basis, and data for the primary analysis included all patients who received study medication less 39 patients who violated protocol because of discharge less than 8 days post-operatively, leaving n=259. The analysis for DVT included patients with an evaluable venogram (n=217).

There was a significantly lower incidence with bemaparin than with UFH for VTE) (9/125 [7. 2%] vs 25/134 [18.7%]: OR 3.0 95% CI 1.3, 6.6 p=0.01) and for DVT (OR 2.7 95% CI 1.2, 6.0 p=0.03).

At the same dose, a pilot study indicated that a ten-day course of bemiparin was efficacious in preventing DVT when started 6 hours after hip replacement surgery. In a subsequent double blind trial, this regimen was compared to 10 days' enoxaparin 4000 IU daily starting 12 hours before elective knee replacement surgery. Consecutive eligible patients at 20 Spanish hospitals aged ≥18 years and scheduled to undergo primary total knee replacement (TKR) with an estimated hospital stay of 10±2 days were enrolled.

The primary efficacy endpoint VTE was a composite of the rate of total venographic DVT, symptomatic documented PE and deaths from all causes. The primary efficacy analysis was performed on an ITT basis, including data on all patients who had received at least one dose of study medication, had undergone the appropriate surgery and had no major protocol violations. The rates for this primary endpoint were analysed in a sequential scheme where, if non-inferiority could be demonstrated, a superiority test was performed. The minimum clinically relevant difference as defined in the protocol was 20% reduction in incidence of VTE for bemiparin compared with enoxaparin.

Secondary end-points included an additional composite efficacy endpoint (proximal DVT and/or symptomatic and well-documented non-fatal PE and/or VTE-related deaths), and individual components of these composite endpoints.

Eighty-seven percent of all randomised patients (333 of 381 patients) were evaluable for efficacy. For the primary endpoint VTE was 32.1% (53/165) and the absolute difference in risk was 4.8% in favour of bemiparin (-4.8%, 95% Confidence Intervals -15%, 5.6%, non-inferiority p = 0.02; superiority p = 0.36).

The incidence of the additional composite endpoint was 3/165 (1.9%) for bemiparin and 9/168 (5.4%), representing an absolute difference of -3.6% (95% CI -7.7%, 0.5%). Non inferiority of bemaparin over enoxaparin was shown for the additional composite endpoint and for total DVT. There were no significant differences between treatments in superiority analysis of any parameter for which non-inferiority was shown or for any other endpoint.

There were no VTE-related deaths in any of these studies. Results are summarised below.

Efficacy of sc bemiparin in the prevention of venous thromboembolism in high risk surgical patients.

		n evaluable	Patients with VTE (%)	Patients with DVT (%)	Patients with PE (%)	VTE-related deaths
Total hip replacement						
BEM 3500 IU daily for 12 days	2h before surgery.	125	9 (7.2)*	9/101 (8.9)**	1 (0.8)	0
UFH 5000 IU twice daily for 12 days	2h before surgery	134	25 (19)*	24/116 (21)**	2 (1.5)	0
BEM 3500 IU daily for 10 days	6h after surgery (pilot study)	57	4 (7.0)	4 (7.0)	0	0
Total knee replacement						
BEM 3500 IU daily for 10 days	6h after surgery	165	53 (32)~	53 (32)	0	0
ENO 4000 IU daily for 10 days	12h before surgery	168	62 (37)~	61 (36)	2 (1.2)	0

VTE= venous thromboembolism DVT= deep vein thrombosis PE= pulmonary embolism
BEM= bemiparin UFH= unfractionated heparin ENO= enoxaparin. All doses given sub-cutaneously
* p BEM vs UFH = 0.01 ** p BEM vs UFH = 0.03 ~ Non-inferiority p BEM vs ENO = 0.02

In an open observational study a total of 7959 patients undergoing orthopaedic surgery received bemiparin over a median of 28 days. Bemiparin 3500 IU/day was used in 85% of patients (high risk of VTE) and 2500 IU was used in the remainder at moderate risk. The incidence of objectively confirmed VTE was 80/7959 (1.0%), consisting of 13 proximal DVTs, 65 distal DVTs and four non-fatal PEs. In another open observational study, 3500 IU/day of bemiparin administered 6 hours after hip or knee replacement surgery was associated with confirmed VTE in 3/1009 patients (0.3%) consisting of two cases of proximal DVT, one distal DVT and no cases of PE.

Summary of evidence on comparative safety

In prophylaxis of VTE in orthopaedic surgery, there were no significant differences between bemiparin and UFH or enoxaparin for the incidence of major bleeding or wound haematoma. The incidence of major bleeding was 5/149 (3.4%) for bemiparin and 6/149 (4.0%) for UFH in total hip replacement surgery, while it was 3/189 (1.6%) and 3/191 (1.6%) for bemiparin and enoxaparin respectively in total knee replacement.

In total hip replacement, the incidence of wound haematoma was 8/149 (5.4%) for bemiparin and 7/149 (4.7%) for UFH, while in total knee replacement it was 35/189 (19%) for bemiparin and 42/191 (22%) for enoxaparin.

There was one death during the treatment period in these two studies, occurring with bemiparin in total hip replacement. The incidence of injection site complications was significantly higher in the enoxaparin group undergoing total knee replacement than with bemaparin (61/191 [23%) vs 42/189 [32%] $p<0.05$) and was not reported in the other study.

Pooled data are available from published post-marketing surveillance studies involving 10,012 patients receiving bemiparin for surgical prophylaxis of VTE of whom 83% (at high risk of VTE) were exposed to 3500 IU per day and the remainder (at low/moderate risk of VTE) were exposed to 2500 IU/day. The incidences of adverse events were as follows: major bleeding 37/1012 (0.37%); mild to moderate thrombocytopenia, not requiring treatment discontinuation 47/1012 (0.47%) and mild to moderate injection site reaction 31/1012 (0.31%). There were 49 deaths (0.49%) of which three were considered thromboembolic. No case of spinal haematoma, type II severe thrombocytopenia, general allergic reaction, cutaneous necrosis or any other rare or unexpected adverse drug reaction was reported.

Summary of clinical effectiveness issues

Bemiparin was associated with a significantly reduced rate of embolic complications compared to UFH in patients undergoing orthopaedic surgery. It was as effective as enoxaparin in a comparative study with in patients undergoing elective knee replacement surgery.; there was no difference in the incidence of major bleeding or wound haematoma. Limited clinical data indicate that bemiparin is effective in DVT prevention when started six hours after hip replacement surgery. No other comparative data with other LMWHs are presented.

Summary of comparative health economic evidence

A cost effectiveness model for total knee replacement is presented based on the Spanish health care system, analysing the cost of complications arising using either enoxaparin (begun pre-operatively) or bemiparin (begun post-operatively). The clinical data source is the main clinical trial, with Spanish unit costs being applied.

Average cost savings of €144.48 are identified over a six week period as a result of using bemiparin rather than enoxaparin. The central estimate of effectiveness within trial is a reduction in all VTE events from the use of bemiparin of 4.2% and as a consequence, the submission states that bemiparin dominates.

A cost effectiveness model for total hip replacement is presented, also based on the Spanish health care system.. This analyses data from a cross-over trial with 61 patients receiving bemiparin, and 62 patients receiving other LMWHs (19% enoxaparin, 81% dalteparin).

The main result is that bemiparin offers cost savings on average of €33.47 per patient, while being statistically significantly better in terms of in fewer complications and costs related to the surgical wound and loss through drainage. No other clinical outcomes were statistically significant between the two groups.

For total knee replacement the two main weaknesses are the use of Spanish unit costs and the failure to explore the possibility that the difference in efficacy between bemiparin and enoxaparin is not statistically significant and therefore the possibility remains that enoxaparin may be equivalent or superior. Similar criticisms apply to the total hip replacement study.

The application of UK unit costs appears likely to reduce, though not eliminate, the savings identified within the submission. The exploration of the possibility of enoxaparin being better in terms of the primary endpoint would result in bemiparin still yielding cost savings but no longer being dominant. To the extent that the primary endpoint is linked with the composite endpoint of symptomatic VTEs, the exploration of the possibility of enoxaparin being better in terms of the primary endpoint might see enoxaparin yield cost savings and come to dominate bemiparin in these circumstances.

The cost effectiveness of bemiparin in orthopaedic surgery has not been addressed in the Scottish context.

Budget impact

The manufacturer estimated a budget impact based upon a 3% market penetration in total knee replacement and total hip replacement operations; i.e. 270 patients, coupled with a stated discount of 50-60% on the NHS list price based upon unidentified contract offers to give a daily cost per patient of £0.80. This yields an annual direct drug cost of £1,512. The application of the NHS list price costs would increase this to around £9,720 for the direct drug costs.

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, Howes J, Sharma V, Kadziola Z. A comparative, double blind, randomized trial of a new second generation LMWH (Bemiparin) and UFH in the prevention of post-operative venous thromboembolism. The Bemiparin Assessment Group. Thromb Haemost. 2000; 83:523-9.

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Otero-Fernández R, Gómez-Outes A, Martínez-González J, Maeso R, Fontcuberta J. Evaluation of the effectiveness and safety of bemiparin, a second-generation low-molecular-weight heparin, in several orthopaedic settings. 18th International Congress on Thrombosis. June 20 - 24, 2004, Ljubljana (Slovenia). Pathophysiol Haemost Thromb. 2004; 33 (suppl.2): 61.

Abad JI, Gómez-Outes A, Martínez-González J, Maeso R, Rocha. E. Observational study of bemiparin, first dose administered 6 hours after surgery, in hip or knee replacement surgery. 18th International Congress on Thrombosis. June 20 - 24, 2004, Ljubljana (Slovenia). Pathophysiol Haemost Thromb. 2004; ; 33 (suppl.2): 73.