Bemiparin cannot be recommended for prescribing; alternative therapies are available for which the evidence for efficacy is much stronger.

**Category D:** cannot be recommended for prescribing because of inadequate evidence for efficacy and/or safety

**Strength of evidence for efficacy and safety**

The committee felt that, compared with the other low molecular weight heparins, the evidence for the efficacy and safety of bemiparin was weak and its place in therapy low. Three studies evaluated bemiparin for the prevention of venous thromboembolism and one study evaluated bemiparin for the treatment of venous thromboembolism.

Patients numbers in the trials were low. There were no outcome events in one of the trials assessing bemiparin for prevention of venous thromboembolism, suggesting lack of power. There is little experience locally with the use of bemiparin.

MTRAC reviewed this drug because of changes in practice in the prescribing of low molecular weight heparins.

**Licensed indication**

This guidance relates to the following indications:

- The prevention of thromboembolic disease in patients undergoing general and orthopaedic surgery.
- Treatment of established deep vein thrombosis with or without pulmonary embolus, during the acute phase.

Please refer to the Summaries of Product Characteristics (SPCs) for the full list of licensed indications.

**Background information**

The term venous thromboembolism (VTE) includes both deep vein thrombosis (DVT) in the leg and pulmonary embolism (PE).

It was reported in 2004 that each year 25,000 hospitalised patients die from VTE, including those admitted for surgery and for medical care of serious illnesses.

Prevention of thromboembolic events associated with surgery includes mechanical prophylaxis (such as compression stockings) and low molecular weight heparins (LMWHs), recommended for most patients whilst they are inpatients in hospital. A LMWH is generally preferred over natural unfractionated heparin (UFH). Fondaparinux, within its licensed indications, may be used as an alternative to LMWH.

No specific guidance for individual LMWHs was given. No guidance from NICE has been issued on the treatment of VTE.

**Clinical efficacy**

**Prevention of VTE**

One double-blind randomised controlled trial (RCT) compared bemiparin (3,500 IU/day subcutaneously [sc] + placebo injection) with UFH (5,000 IU sc twice daily) for the prevention of VTE in 298 patients undergoing hip-replacement surgery. Treatment was started two hours before surgery and continued for at least eight days postoperatively. The primary outcome measure was the incidence of DVT detected by screening all patients on day 12 ± 4 after surgery using bilateral venography. Of the 217 patients who had evaluable venograms, significantly fewer bemiparin-treated patients had a DVT than those receiving UFH treatment (9% vs. 21%; p = 0.03). The incidence of VTE, the secondary endpoint, was also significantly lower in bemiparin-treated patients vs. UFH in the 16 days following surgery (7% vs. 19%; p = 0.01).

A second double-blind RCT compared bemiparin (2,500 IU sc + placebo) with UFH (5,000 IU sc twice daily) in 166 patients undergoing abdominal surgery. Treatment was started two hours before surgery and continued for 7 days. The main outcome measure was the incidence of DVT detected by screening all patients after surgery using Doppler ultrasound and plethysmography. Positive results were to be
confirmed with venography. In this study, there were no incidences of DVT in either treatment group during the eight days of treatment after surgery, suggesting that the study was underpowered. A third double-blind RCT compared bemiparin (3,500 IU/day sc + placebo) with enoxaparin (40 mg/day sc + placebo) for prevention of VTE in 333 patients undergoing knee-replacement surgery. Bemiparin treatment was started 6 hours postoperatively and continued for up to 12 days. The primary outcome measure was the combined incidence of venographic DVT, symptomatic documented PE and death from all causes. All patients were screened using venography during days 8 to 12 following surgery. There was no significant difference between treatment groups for the primary composite endpoint (incidence 32% vs. 37% for enoxaparin, RR for bemiparin = 0.87; 95% CI 0.65 to 1.17). There were also no significant differences between the groups for the individual endpoints of total DVT or symptomatic PE. No patients died during the study.

**Treatment of VTE**

One open-label RCT compared bemiparin (115 IU/kg/day) with UFH (5,000 IU bolus dose, then continuous intravenous infusion adjusted to target APTT) in 378 patients with a venogram-confirmed DVT. Patients received 7 ± 2 days of acute treatment; concomitant oral anticoagulation was started on day 3 and continued for 12 weeks. A third treatment arm that evaluated bemiparin as monotherapy for 12 weeks was not considered further because such a regimen is contrary to the SPC. The primary outcome measure was the venographically-determined change in thrombus size during the first 14 days of treatment, assessed in 297 patients, using the Marder score (points accumulated for each leg vein occluded and degree of occlusion; maximum score 40). The assessment was blinded. Mortality and the recurrence of VTE were secondary endpoints, assessed in 324 patients.

Significantly more bemiparin-treated patients showed an improved Marder score (reduction in thrombus size or distribution of thrombi in leg veins) compared with UFH-treated patients (72% vs. 52%, p = 0.004). For the secondary outcome, the incidence of VTE was not significantly different for bemiparin and UFH-treated patients (0.8% vs. 3.6%) during three months follow up and treatment with oral anticoagulation.

**Adverse effects**

Reporting of adverse events focussed on haemorrhagic complications, haematoma at wounds and injection sites, and thrombocytopenia. One of three studies reporting major haemorrhagic events found significantly fewer events with bemiparin treatment vs. UFH (3.7% vs. 0 for bemiparin, p = 0.035). There was a significant difference between treatment groups in one of two studies reporting wound haematoma (6% with bemiparin vs. 18% for UFH, p = 0.015).

**Additional information**

- The recommended daily dose for prevention of VTE is 2,500 IU for general surgery and 3,500 IU for orthopaedic surgery, given sc for 7 to 10 days.
- For treatment of VTE the recommended dose is 115 IU/kg body weight as a daily sc injection for at least 7 days until adequate oral anticoagulation is established.
- At current prices, 10 days’ supply of bemiparin (3,500 IU once daily) for prevention of VTE costs £27.50, and 7 days’ supply of bemiparin (115 IU/kg/day) for acute treatment of VTE costs £59 (for a 70 kg adult).

**References**