Scottish Medicines Consortium

dibotermin alfa (recombinant human bone morphogenetic protein-2/absorbable collagen sponge; rhBMP-2/ACS), 12mg kit for implant (InductOs ®) No. (365/07)

Medtronic

6 April 2007

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

dibotermin alfa (InductOs ®) is accepted for restricted use within NHS Scotland for the treatment of acute tibia fractures in adults, as an adjunct to standard care using open fracture reduction and intramedullary nail fixation in patients in whom there is a substantial risk of non-union.

It is restricted to patients treated with unreamed intramedullary nails. Cost effectiveness has only been shown in Gustilo-Anderson Grade IIIB fractures.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

Dibotermin alfa is indicated for the treatment of acute tibia fractures in adults, as an adjunct to standard care using open fracture reduction and intramedullary nail fixation.

Dosing information

Once reconstituted, the dibotermin alfa solution (8ml) is evenly distributed on an absorbable bovine Type I collagen matrix. The number of matrix kits used and the volume of dibotermin alfa to be implanted are determined by the fracture anatomy and the ability to close the wound without overly packing or compressing the product. Generally each fracture site is treated with the contents of one kit and the maximum dosage is limited to 2 kits. Dibotermin alfa should not be used in concentrations higher than 1.5 mg/ml (12mg per vial).

Product availability date

July 2003

Summary of evidence on comparative efficacy

Dibotermin alfa (recombinant human Bone Morphogenetic Protein-2; rhBMP-2) is an osteoinductive protein which when carried on an absorbable collagen sponge (ACS) can induce new bone tissue at the site of implantation. It binds to receptors on the surface of mesenchymal cells and causes cells to differentiate into cartilage-and bone-forming cells. The differentiated cells form trabecular bone as the matrix is degraded, with vascular invasion evident at the same time. The bone formation process develops from the outside of the implant towards the centre until the entire implant is replaced by trabecular bone.

A single blinded phase III study recruited 450 patients with an age range of 17 to 87 years who had sustained an open tibial fracture, of which the major fracture component was diaphyseal. Patients were equally randomised to control standard of care only (intramedullary nail fixation and routine soft tissue management); control and a 0.75mg/ml rhBMP-2 implant or control and a 1.50mg/ml rhBMP-2 implant. Patients were stratified on the basis of Gustilo-Anderson classification of open fractures: this ranges from I to IIIC and is based on increasing soft tissue injury, bone damage and contamination. Definitive fracture fixation with intramedullary nailing (reamed or unreamed) was performed no later than 14 days (median 1 day) after the injury. The primary efficacy end point was the proportion of patients who received secondary interventions to promote fracture union within the follow-up period of twelve months after definitive wound closure. Efficacy and safety analyses were carried out in the intent-to-treat population.

There was follow-up for a full 12 months in 421 patients. Comparing groups receiving the implant with the control group, there was a significant, concentration-dependent decrease in the proportion of patients requiring secondary interventions: 46%, 37% and 26% for control, 0.75mg/ml and 1.50mg/ml implants respectively. The relative risk of secondary intervention for the rhBMP-2 1.5 mg/ml group compared to control was 0.56 (95% confidence intervals 0.40 to 0.78). There were no significant differences between treatment groups for the median time to secondary interventions. Both the number and invasiveness of the interventions were significantly lower in the 1.50mg/ml implant than in the control group.

The rate of secondary interventions was also reported to be significantly lower in the 1.50mg/ml group after adjustment for reaming and for fracture severity on the Gustilo-Anderson classification. However, the European Public Assessment Report (EPAR) for this

product states that, in the sub-group of patients with reamed nailing, the unadjusted rate of secondary intervention was the same (24%) in both groups.

A second study combined the patient data from the trial described above with a previously unpublished United States study, both using the same study design and protocol, to perform subgroup analyses.

A total of 510 patients were randomised: 450 from the above trial and 60 from the US study, however only the control and the 1.50mg/ml groups were compared in the per protocol population; each group having 169 patients in a per-protocol analysis. The two sub-groups analysed were Gustilo-Anderson type IIIA or IIIB open tibial fractures (131patients) and fractures treated with reamed intramedullary nailing (113 patients).

In the type III fracture subgroup the proportion of patients receiving secondary autologous bone-grafting procedures to treat delayed union or non-union of fractures was 20% in the control group and 2% in the rhBMP group, representing a relative risk reduction of 90% (95% confidence intervals 41% to 98%). For invasive secondary interventions, the equivalent figures were 28% and 9% representing a relative risk reduction of 68% (95% confidence intervals 24% to 86%). Fracture healing, as measured by time to full weight bearing was 95.1 days in patients treated with rhBMP-2 compared to 126.6 days for the control group. No difference was observed between the two treatment groups with respect to nail dynamisation.

In the reamed intramedullary nailing subgroup, using the same outcome criteria, no significant difference between the control and the rhBMP-2 groups was observed for bone grafting or invasive secondary interventions.

Summary of evidence on comparative safety

Local adverse events included leg pain, oedema, infection, knee and ankle pain and hardware failure. Overall, pain was significantly lower in the rhBMP-2 implant groups; 67%, 68% and 79% in the 0.75mg/ml, 1.50mg/ml and control group respectively. Antibodies to BMP-2 and type-I bovine collagen have been reported to occur in 6-10% and 5-20% respectively of patients treated with this product. Patients with hardware failure (mostly screw breakage or bending) were significantly lower in patients treated with the 1.50mg rhBMP-2 implant compared to the control group; 11% and 22% respectively. In the subset of patients with type III fractures, the rate of fracture site infection was significantly lower in the 1.50mg/ml group compared to control group; 24% vs. 44% respectively. One patient died in each of the three groups but none of the deaths were considered to be due to the implant.

In the pooled data analysis, the type III fracture patients receiving 1.50mg/ml had significantly lower screw breakage; 11% vs. 25%, and significantly lower infection rates; 21% vs. 40% than in the control group respectively. In the reamed intramedullary nailing subgroup although the infection rate was lower than the control group the difference was not significant.

Summary of clinical effectiveness issues

The marketing authorisation has been granted for adjunctive treatment of acute tibia fractures and makes no further restriction. However the trials included only patients with open tibial fractures and required that rhBMP-2 be implanted within 14 days of the occurrence of the fracture with the intention of promoting union of the fracture. Thus there are no data for closed fractures or for the management of later fracture complications such as non-union.

In one study patients treated with 1.50mg/ml rhBMP-2 had significantly fewer secondary interventions than the control group after adjustment for reamed or unreamed intramedullary nailing; however in the sub-group of patients with reamed nailing, the event rates were identical in each group. In the pooled analysis there was no significant difference between 1.50mg/ml rhBMP-2 and control in the sub-group of patients with reamed nailing. The marketing authorisation for this product was granted on condition that rhBMP-2 plus standard care be compared to standard care in a randomised controlled trial in patients with reamed intramedullary nailing.

In both studies, rhBMP-2 was associated with a significant reduction in the secondary intervention rate compared with the control groups when data were analysed in sub groups stratified by the Gustilo-Anderson classification of wound severity. However wound severity was predictive of outcome. In the main study, patients in the control group with type IIIB fractures were twice as likely to have a secondary intervention as those with a less severe fracture. In the pooled analyses patients in the subgroup with type III fractures were three times more likely to have a secondary intervention in the control group than the patients receiving rhBMP-2.

Smokers who had received the 1.50mg/ml rhBMP-2 implant had a significantly lower rate of secondary intervention than control patients; 30% vs.52% respectively. Limited data were presented regarding diabetic patients or long term steroid users or other high risk patient group.

Neither study was originally sized for subgroup analysis, and the pooled analysis was not much larger than the main study.

Local adverse events reported in studies were stated to be typical of those observed in the orthopaedic environment. A reduction in pain associated with rhBMP-2 was attributed to a faster rate of wound healing compared to the control group. In trials, there was no evident relationship between the antibodies and clinical outcome or adverse events indicating an allergic response, however the EPAR comments that the current database is too small to be conclusive.

Summary of comparative health economic evidence

A cost-utility evaluation was submitted by the manufacturer of rhBMP-2 as an adjunct to standard care involving intramedullary nail fixation and routine soft tissue management compared to standard care alone in the treatment of open tibial fractures. The comparator chosen was appropriate for practice in Scotland. The main data source for efficacy was the primary phase III clinical trial for rhBMP-2 (the BESTT study). Although adding rhBMP-2 increases the costs of treatment of open tibial fractures, partial cost offsets were obtained from a reduction in need for secondary interventions, lower rate of infections and reduced number of outpatient visits due to faster healing time for the rhBMP-2 patients. Utility gains

were obtained from faster healing time for patients receiving rhBMP-2, resulting in a net incremental cost per QALY gained of £14,007. However, this overall result was derived from an analysis of fracture sub-groups based on the Gustilo-Anderson severity grade, with higher grade equating to greater severity. For fracture grades covered in the economic evaluation, the estimate of incremental cost per QALY gained for the rhBMP-2 patients with grade IIIA fractures was over £30,000 and for grade II fractures was over £54,000, whereas for grade IIIB fractures incremental cost-effectiveness was estimated at £1,600 per QALY gained. The overall result of £14,007 was based on an analysis of the estimated proportion of patients with fractures of each grade annually in Scotland.

A strength of the economic evaluation submitted was the availability of clinical trial data directly comparing rhBMP-2 with an appropriate comparator and the use of NHS relevant cost data. In addition, disutility associated with secondary interventions and infections were not measured, which could be expected to have favoured the rhBMP-2 group if they had been included. In terms of weaknesses the one-way sensitivity analyses performed did not enable a full assessment of uncertainty for the sub-groups, especially the more cost-effective grade IIIB sub-group. A probabilistic sensitivity analysis performed lacked transparency in the input variables and was not performed for the fracture grade sub-groups. In the economic evaluation no distinction was made between patients who received reamed and unreamed intramedullary nail fixation, despite clinical evidence of no significant differences between rhBMP-2 and standard care for reamed sub-groups.

The economic case for rhBMP-2 for all patients with open tibial fractures has not been demonstrated, although there is a case for cost-effectiveness for a sub-group with grade IIIB fractures.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: comparators

Routine soft-tissue debridement and reconstruction and skeletal stabilisation with intramedullary nail fixation is standard practice for the treatment of open tibial fractures and has been used as the comparator in this submission.

Additional information: costs

Implant	Cost per kit (£)
Dibotermin alfa 12mg rhBMP-2/ACS (InductOs)	**1790 (excluding VAT)**

Additional information: budget impact

The budget impact of rhBMP-2 is estimated by the manufacturer to be an additional £141k per year for an estimated 79 patients per annum with grade IIIB fractures.

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 30 March 2007.

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 references were supplied with the submission.

Govender S, Csimma C, Genant HK, Valentin-Opran A, Amit Y, Arbel R, et al. Recombinant human bone morphogenetic protein-2 for treatment of open tibial fractures: a prospective, controlled, randomized study of four hundred and fifty patients. J Bone Joint Surg 2002;84-A(12):2123-34.

Swiontkowski MF, Aro HT, Donell S, Esterhai JL, Goulet J, Jones A, et al. Recombinant human bone morphogenetic protein-2 in open tibial fractures. A subgroup analysis of data combined from two prospective randomized studies. J Bone Joint Surg 2006;88-A (6):1258-65.