GMMMG Greater Manchester Medicines Management Group NHS

HIGH COST DRUGS SUBGROUP

Managed entry of Dibotermin alfa (InductOs®) for the treatment of non-union fracture in adults (CCG commissioned)

Recommendation	This recommendation applies to the use of Dibotermin alfa (InductOs® 1.5mg/ml powder) within its CCG commissioned, licensed indication (for the treatment of acute tibia fractures in adults, as an adjunct to standard care using open fracture reduction and intramedullary unreamed nail fixation, and use outside of this license as detailed below but only when used by a non-union specialist as a GM trauma centre (MFT-ORC and SRFT). Use out with this recommendation will not be supported. **CCG commissioning of Dibotermin alfa is recommended:** • Only for use by non-union specialists at GM trauma centres (i.e. MFT-ORC and SRFT) • For the management of established fracture non-union of Tibia, Femur, Radius, Ulna, Clavicle, Humerus based on FDA definition after 6-9 months with amenable cavity under the direction of a consultant who specialises in non-union • Management of delayed bone union failure to achieve any progress towards union radiographically over 3/12 period in the first 6 months since injury or surgery based on the FDA definition and under the direction of orthopaedic consultant who specialises in non- union. • Docking site for bone transport • Membrane induced osteogenesis for managing bone defects • Management of avascular necrosis of the femoral head **CCG commissioning of Dibotermin alfa is not recommended:** • For use by anyone other than a non-union specialist at a GM trauma centre (MFT-ORC and SRFT) • For repeat doses or sequential use - due to the possible development of antibody production. • Closed tibial fractures • Revision of previous spinal surgery (NHSE commissioned) • Spinal fusion Paediatrics - BMP is not recommended in skeletally immature individuals

Drug/Indication	Dibotermin alfa (recombinant human Bone Morphogenetic Protein-2; rhBMP-2) is an osteoinductive protein which when carried on an absorbable collagen sponge (ACS) matrix can result in the induction of new bone tissue at the site of implantation. InductOs (Medtronic Ltd) is a single-use medicinal product that contains 12 mg of dibotermin alfa, a solvent and an ACS matrix made from bovine Type I collagen. It is prepared for use by reconstituting the lyophilised dibotermin alfa in water to form a 1.5 mg/mL solution, which is then applied to the ACS for implantation. InductOs is licensed for the treatment of acute tibia fractures in adults, as an adjunct to standard care using open fracture reduction and intramedullary unreamed nail fixation. (*CCG commissioned*) It is also licensed for single level lumbar interbody spine fusion as a substitute for autogenous bone graft in adults with degenerative disc disease who have had at least six months of non-operative treatment for this condition. (*NHSE commissioned – not considered in this review*)[1]
Clinical Trial Data – Efficacy	The safety and efficacy of the rhBMP-2 implant (InductOs) was evaluated in a Phase III, multi-centre, randomised, double-blind study in 450 patients with open tibial shaft fractures requiring surgical management. The BMP-2 Evaluation in Surgery for Tibial Trauma (BESTT) trial compared the addition of an rhBMP-2 implant at two different concentrations (0.75-mg/mL, and the approved concentration 1.50-mg/mL) with standard care only (intramedullary (IM) nail fixation and routine soft tissue management). Randomization was stratified by the severity of the open wound. The primary outcome measure was the proportion of patients requiring secondary interventions due to delayed union or non-union within 12 months post-surgery.[2] After 12 months, patients with rhBMP-2 implants were significantly less likely to require secondary intervention (37% at 0.75 mg/mL and 26% at 1.5 mg/mL) than patients receiving standard care only (46%; P=0.0004). In patients receiving the 1.5 mg/ml rhBMP-2 implant the relative risk of secondary intervention compared to standard care alone was 0.56 (95% CI 0.40 to 0.78; p=0.0005). There were no significant differences between treatment groups for the median time to secondary interventions. However, the use of rhBMP-2 implants reduced the invasiveness of procedures, promoted faster healing, and resulted in greater overall treatment success (54% at 0.75 mg/mL and 65% at 1.5 mg/mL vs. 47% for nail fixation alone; P=0.0028). A subsequent study pooled data from patients with Gustilo-Anderson type III fractures in the BESTT trial with data from an identically designed randomised controlled trial in the US (n=60). A combined total of 510 patients were randomised, but only the standard of care (control, n=169) and 1.50mg/ml groups (n=169) were compared. Two subgroup analyses were performed: Gustilo-Anderson type IIIA or IIIB open tibial fractures (n=131), and fractures treated with reamed intramedullary nailing (n=113). In the type III fracture subgroup, the addition of rhBMP-2 significantly reduced the frequency of secondary autologous bone-grafting procedures compared to control (2% vs. 20%, respectively). This represents a relative-risk reduction of 90% (95% CI 41% to 98%; p=0.0005). For invasive secondary interventions, the equivalent figures were 9% and 28% (RR 68%; 95% CI 24% to 86%; p=0.0065). Fracture healing, as measured by average time to full weight bearing improved from 126 days in the control group to 95 days in patients receiving rhBMP-2. There was no difference between the two treatment groups with respect to nail dynamisation. In the reamed intramedullary nailing subgroup, there were no significant differences between the control and the rhBMP-2 groups for bone grafting or invasive

	secondary interventions.[3]
Clinical Trial Data – Safety	In the BESTT trial, the adverse events experienced by patients were consistent with those normally observed in the trauma setting. There was no overall difference in the rate of fracture site infection across treatment groups. However, in the subset of patients with type III fractures, the rate of fracture site infection was significantly lower in the 1.50-mg/mL group compared to the control group (24% vs. 44%; p=0.0219). Overall, pain was significantly lower in the rhBMP-2 groups (67% in the 0.75-mg/mL group and 68% in the 1.50-mg/mL group) than in the control group (79%; p=0.0389). Those treated with 1.50 mg/mL also had significantly fewer hardware failures (11% vs. 22%; p=0.0174), and faster wound healing (83% vs. 65% at six weeks; p=0.0010) compared with the control group. Addition of rhBMP-2 to standard care did not increase the rate of local soft-tissue calcifications or heterotopic ossification at remote sites. In the pooled safety data analysis, the type III fracture subgroup receiving 150mg/ml rhBMP-2 had significantly lower infection rates than in the control group (21% vs 40%, respectively). This represents a relative-risk reduction of 48% (95% CI 8% to 70%; p=0.02). Those receiving rhBMP-2 also had significantly lower screw breakage compared with the control group (11% vs. 25%; p=0.04). Both dibotermin alfa and bovine Type I collagen have been found to elicit immune responses in patients. In all longbone fracture studies in which >500 patients have received InductOs, the presence of antibodies to dibotermin alfa were observed in 6.3% of patients receiving dibotermin alfa vs.1.3% in the control group. All patients who were tested for neutralizing antibodies to dibotermin alfa were negative. Antibodies to bovine Type I collagen developed in 13.0% of patients receiving dibotermin alfa vs.5.3% in the control group. No association with clinical outcome or undesirable effects could be observed in clinical studies. However, the possibility of developing neutralising antibodies or hypersensitivity type reactions cannot be excluded. Therefore, in the absence of any experience, the repeat use of InductOs is not recommended.
Cost Effectiveness/ Affordability	SMC 2007 report restricted the use of dibotermin alfa as recommended above to patients treated with unreamed intramedullary nails, and stated that cost effectiveness has only been shown in Gustilo-Anderson Grade IIIB fractures.[5] Using the BESTT study as a data source, they stated that 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 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. 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. The budget impact estimated by the SMC in 2007 was estimated by the

	manufacturer to be an additional £141k per year for an estimated 79 patients per annum with grade IIIB fractures. Less than 30 patients a year are expected to require treatment across GM (based on responses received from Provider Trusts).
Commissioning implications	The only cost effectiveness analysis was in Gustilo-Anderson Grade IIIB fractures available to the group was as published by the SMC in 2007, which, however the GMMMG HCDSG considered the anticipated cost impact and expected benefits as described by the specialists and noted above. Whilst it is suggested that treatment may result in reduced length of hospital/theatre stay and improved recovery time, these outcomes will need to be captured via Blueteq for ongoing evaluation. This data should be reported back to HCDOG on a biannual basis. Use of this agent is restricted to orthopaedic surgeons with a non-union subspecialty at a GM trauma centre (MFT-ORC and SRFT).
Monitoring	Funding approval will be made by meeting the criteria outlined on completion and submission of the relevant Blueteq form. Blueteq form to capture the following information: • Use of this agent is restricted to orthopaedic surgeons with a non-union subspecialty at a GM trauma centre (MFT-ORC and SRFT) • The patient is skeletally mature (adult) • Please confirm that this request is not for a repeated dose or sequential use of Dibotermin alfa (InductOs®) • Use will be restricted to patients treated with unreamed intramedullary nails. (N.B. Eptotermin alfa (Osigraft®) has been discontinued. • The patient satisfies one of the following five criteria for use in addition to those listed above: 1) The management of established fracture non-union of Tibia, Femur, Radius, Ulna, Clavicle, Humerus based on FDA definition after 6-9 months with amenable cavity under the direction of a consultant who specialises in non-union 2) Management of delayed bone union failure to achieve any progress towards union radiographically over 3/12 period in the first 6 months since injury or surgery based on the FDA definition and under the direction of orthopaedic consultant who specialises in non- union. 3) Docking site for bone transport 4) Membrane induced osteogenesis for managing bone defects 5) Management of avascular necrosis of the femoral head • Outcome data to be recorded: - Was there a need for secondary interventions, if so please

	provide detail - Any relevant infection episodes - Number of outpatient visits attended by patient post treatment - Recovery time (days) - Inpatient duration (days) - Theatre time (hours) - All patients to be followed up and endpoint outcome recorded Data gathered through Blueteq will be reviewed bi-annually by the HCDSG, with assurance provided to GMMMG	
Patient perspective	Most bone fractures heal within 20 weeks, healing time depends on a number of factors e.g. severity of injury, part of the bone fractured, presence of an open wound or fracture fragments. A fracture which does not heal in the time expected is considered a "delayed union". The rate of delayed unions varies by fracture severity from 16-60% for less severe fractures, to 43-100% for more severe fractures. When a fracture is not completed healed within six months, and exhibits motion at the bony ends it is considered to be a "non-union", the rate of non-unions has been reported to range from 4-10%.[2] Non-unions can lead to significant pain, decreased function and can impact on the person's ability and productivity, potentially reducing the patients' health –related quality of life.	
Version D1	**Approved for use by GM Directors of Commissioning**	**Review date**

References:

1. Summary of Product Characteristics: **InductOs (dibotermin alfa) 1.5 mg/ml powder, solvent and matrix for implantation matrix** (accessed on 20/3/2019)

2. 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.

3. 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.

4. Garrison KR, Shemilt I, Donell S, Ryder JJ, Mugford M, Harvey I, Song F, Alt V. Bone morphogenetic protein (BMP) for fracture healing in adults. Cochrane Database of Systematic Reviews 2010, Issue 6. Art. No.: CD006950. DOI: 10.1002/14651858. CD006950.pub2.

5. SMC 2007 recommendation: dibotermin alfa (recombinant human bone morphogenetic protein-2/absorbable collagen sponge; rhBMP-2/ACS), 12mg kit for implant (InductOs ®) (Accessed 20/03/2019)