NHS Calderdale Clinical Commissioning Group

NHS Yorkshire and Humber Commissioning Support

Commissioning Statement

Treatment	**Bone morphogenic protein** Dibotermin alfa (rhBMP-2) *(InductOs®)* Eptotermin alfa (OP-1) *(Osigraft®; Opgenra®)*
For the treatment of	Bone fractures: promotion of ectopic bone formation
Commissioning position	**Calderdale CCG commissions the use of bone morphogenic protein (BMP) for the promotion of ectopic bone formation for the following:** **1. Acute tibial fractures with Grade IIIB fractures (i.e. more severe cases):** • BMP (**Dibotermin alfa**) is recommended 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. The economic case for dibotermin 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.[1)] **2. Non-union of long bones exceeding nine months which have been assessed for bone autograft AND found to be unsuitable for such a procedure:** • BMP (**Eptotermin alfa**) should only be considered third-line **AND** • Treatment is restricted to named consultants for use in tibial, ulnar, radial, humoral, femoral and clavicular non-union. In non-unions there is no evidence that BMP is more or less effective than bone graft; however, it is currently used when bone graft and other treatments have failed.[2)] **Calderdale CCG *does not* routinely commission the use of bone morphogenic protein for the following conditions:** • Closed tibial fractures ◦ There is no evidence that BMP is more or less effective than conventional treatment for closed tibial fractures.[2)] • Revision of previous spinal surgery ◦ This service/condition is commissioned by NHS England • Spinal fusion ◦ There is no supporting evidence and is not considered to be cost-effective • Paediatrics ◦ BMP is not recommended in skeletally immature individuals

	• Repeat doses ○ BMP is not recommended for repeat dosing or sequential use due to the possible development of antibody production **North Kirklees CCG / Greater Huddersfield CCG / Wakefield CCG / Calderdale CCG**
Date effective from	18 December 2014
Policy to be reviewed by	November 2017 Policy will be reviewed earlier if NICE guidance is published or further significant clinical or financial information becomes available

Background information	BMPs are growth factors that promote ectopic bone formation and can be extracted from demineralised bone matrix.
	
	There are three clinical BMPs licensed in the UK with different licensed indications:
	• Dibotermin alfa (rhBMP-2)(InductOs®), licensed for:
	  ○ Single-level (L4 - S1) anterior lumbar spine fusion as a substitute for autogenous bone graft in adults with degenerative disc disease who have had at least 6 months of non-operative treatment for this condition.
	  ○ The treatment of acute tibia fractures in adults, as an adjunct to standard care using open fracture reduction and intramedullary unreamed nail fixation.
	
	• Eptotermin alfa (OP-1) (Osigraft®) licensed for :
	  ○ Treatment of nonunion of tibia of at least 9 month duration, secondary to trauma, in skeletally mature patients, in cases where previous treatment with autograft has failed or use of autograft is unfeasible.
	
	• Eptotermin alfa (Opgenra®) licensed for:
	  ○ Posterior lateral fusion
	
	The use of BMP is associated with a reduced operating time, improvement in clinical outcomes and a shorter hospital stay as compared with autograft.[2]
	
	National Guidance:
	Dibotermin alfa 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.[1]

Summary of evidence/ rationale	**Clinical effectiveness:** A Cochrane review looking at the evidence for BMP for fracture healing in adults included 11 trials. All were flawed which means that their results ma y be biased. Four trials involved people with acute fractures of the tibia (shin bone). Evidence from these trials showed that BMP may enhance healing of these fractures, and that people with these fractures when treated with BMP

required fewer subsequent procedures. Six trials testing BMP for fractures that had not healed during first course of treatment (non-unions) showed BMP was neither better or worse at healing than bone grafts. One small trial found no difference between BMP and done grafts in people whose bone had been cut so in order to treat a healed but misaligned fracture. Trial participants who received BMP experienced similar adverse effects to those not receiving BMP (infection, hardware failure, heterotopic bone formation and immunogenic reactions). However, patients given BMP instead of bone autografts will have avoided problems associated with extraction of the bone from another site in their body. 3)

A Health Technology Assessment reviewed three trials (n=494, 2 trials used rhBMP-2 and one rhBMP-7), which showed that use of BMP increased fracture union among patients with acute tibial fractures [pooled odds ratio (OR) 1.65 (95% CI 1.12 to 2.45]. Analysis was dominated by data from a large trial for use in open tibial fracture (OTF). The use of BMP reduced the number of secondary interventions in patients with acute tibial fractures compared with controls. Additional BMP treatment plus conventional interventions was found to be more effective than conventional intervention alone for successful union of acute open tibial fractures. 2)

The marketing authorisation for dibotermin 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.1)

Data indicates that BMP increases fracture union among patients with acute tibial fractures and high dose BMP is more effective than a lower dose for open tibial fractures.2)

The healing rate with BMP is not statistically significantly different from the autogenous bone grafting group for patients with tibial non-union fractures, but BMP reduces the number of secondary interventions in patients with acute tibial fractures compared with controls.2)

There is very limited evidence that BMP in scaphoid non-union is safe and may help to accelerate non-union healing when used in conjunction with either autograft or allograft.2)

There is evidence that dibotermin is more effective than autogenous bone graft for radiographic fusion in patients with single-level degenerative disc disease.2)

No significant difference was found when eptotermin was compared with autograft for degenerative spondylolisthesis with spinal stenosis and spondylolysis.2)

In non-unions there is no evidence that BMP is more or less effective than bone graft; however, it is currently used when bone graft and other treatments have failed.2)

A systemic review of thirteen RCTs and 31 cohort studies showed that for lumbar spine fusion, dibotermin and iliac crest bone graft were similar in overall success, fusion, and other effectiveness measures and in risk for any

adverse event, although rates were high across interventions (77% to 93% at 24 months from surgery). For anterior lumbar interbody fusion, dibotermin was associated with non-significantly increased risk for retrograde ejaculation and uro-genital problems. For anterior cervical spine fusion, dibotermin was associated with increased risk for wound complications and dysphagia. At 24 months, the cancer risk was increased with dibotermin (risk ratio, 3.45 [95% CI, 1.98 to 6.00]), but event rates were low and cancer was heterogeneous.[4]

The largest number of spinal fusion cases using BMP devices has been for anterior lumbar interbody fusion. Although radiologic fusion occurs at a consistently faster rate among recipients of the BMP device than among recipients of autologous bone grafts, clinical outcomes (pain and disability) appear no different. Regardless of technique, improvements in pain and disability are reported by similar proportions of participants in all the arms of all the trials. One small scale trial has reported radiologic fusion in all participants in both BMP and autologous bone graft arms and improvement in neck pain scores for all participants. BMP devices for lumbar fusion are safe and appear equivalent to autologous bone graft procedures for spinal fusion in terms of patient outcomes with the notable exception that patients undergoing autologous bone graft report pain at the donor site. Laparoscopic approaches yield reductions in postoperative length of stay compared to conventional open approaches.[5]

Safety

The FDA issued a warning in July 2008 that use of recombinant human bone morphogenetic protein products (e.g.dibotermin and eptotermin) in cervical spine fusion had been associated with at least 38 reports of swelling of neck and throat tissue, with resultant compression of the airway or vulnerable neurological structures. Complications were often life-threatening, and had required respiratory support and/or tracheotomy in some cases. The use of alternative treatments or enrolment in approved clinical studies was recommended when treating cervical spine problems [6]:

- Evidence of comparative safety data for dibotermin showed that the local adverse events include leg pain, oedema, infection, knee, ankle pain and hardware failure. Overall, pain was significantly lower in the dibotermin 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 dibotermin 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 safety data analysis for dibotermin 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. [1)] **Cost effectiveness/resource impact:** The budget impact of dibotermin is estimated by the manufacturer to be an additional £141,000 per year for an estimated 79 patients per annum with grade IIIB fractures.[1)] The use of BMP is associated with a reduced operating time, improvement in clinical outcomes and a shorter hospital stay as compared with autograft.[2)] The proportion of secondary interventions tends to be lower with BMP than control groups, but this is not of statistical significance.[2)] Trial data on time to return to work postoperatively are sometimes difficult to interpret because of unclear or inappropriate data analysis methods.[2)] BMP may eliminate the need for autogenous bone grafting so that costs and complications related to harvesting autograft can be avoided.[2)] A cost-utility evaluation was submitted by the manufacturer of dibotermin for the Scottish Medicines Consortium review[1)]. The evaluation looked at dibotermin 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: • Although adding dibotermin 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 dibotermin patients. • Utility gains were obtained from faster healing time for patients receiving dibotermin, 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 dibotermin 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 dibotermin 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.[1)] The incremental cost of BMP for open tibial fractures is estimated to be about £3.5 million per year in the UK. The estimated incremental cost per quality-adjusted life-year (QALY) gained is £32,603. The probability that cost per QALY gained is less than £30,000 for open tibial fracture is 35.5%. The cost-effectiveness ratio is sensitive to the price of BMP and the severity of open tibial fractures. The cost-effectiveness of additional BMP may be improved if the price of BMP is reduced or if BMP is mainly used in severe cases.

	References: 1. Scottish Medicines Consortium. Dbotermin alfa (recombinant human bone morphogenetic protein-2/absorbable collagen sponge; rhBMP-2/ACS), 12mg kit for implant InductOs. No. (365/07), 6 April 2007 http://www.scottishmedicines.org.uk/Home 2. Garrison K R et al. Clinical effectiveness and cost effectiveness of BMPs in the non-healing of fractures and spinal fusion: a systematic review. Health Technology Assessment August 2007; 11 (30) accessed via http://www.journalslibrary.nihr.ac.uk/__data/assets/pdf_file/0007/64681/FullReport-hta11300.pdf 3. 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. 4. Rongwei Fu et.al. Effectiveness and Harms of Recombinant Human Bone Morphogenetic Protein-2 in Spine Fusion. A systemic review and meta-analysis. Annals of Internal Medicine 2013; 158: 890-902. 5. Bone Morphogenetic Proteins & Spinal Surgery for Degenerative Disc Disease. Ontario Health Technology Assessment Series 2004; Vol. 4, No. 4. http://www.health.gov.on.ca/english/providers/program/mas/tech/reviews/pdf/rev_bmp_030104.pdf 6. FDA Public Health Notification: Life-threatening complications associated with recombinant human bone morphogenetic protein in cervical spine fusion. July 2008 http://www.fda.gov/medicaldevices/safety/alertsandnotices/publichealthnotifications/
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