New Medicine Assessment

Dibotermin alfa (InductOs®)

For the treatment of acute tibia fractures in adults, as an adjunct to standard care using open fracture reduction and intramedullary unreamed nail fixation (licensed indication) AND use outside of the licensed indication for the treatment of non-union long bone fractures

Recommendation:

RED - Dibotermin alfa is recommended in Lancashire and South Cumbria for the treatment of acute tibia grade IIIB fractures in adults (as assessed on the Gustilo-Anderson scale), as an adjunct to standard care using open fracture reduction and intramedullary unreamed nail fixation in hospital settings.

BLACK – Dibotermin alfa is not recommended in Lancashire and South Cumbria for use outside of the licensed indication for the treatment of non-union long bone fractures.

Summary of supporting evidence:

- The EPAR concluded that efficacy and safety of dibotermin alfa are acceptable for the patient population studied, that is: for patients with an open tibial shaft fracture requiring surgical management with intramedullary nailing.
- Economic modelling submitted to the Scottish Medicines Consortium (SMC) suggests that the cost of treatment with dibotermin alfa may be partially offset by reductions in the need for secondary interventions, lower rates of infection and reduced number of outpatient visits due to faster healing times.
- Data presented has not revealed any significant safety concerns about the use of dibotermin alfa. In particular, there was no difference in the occurrence of infections across treatment groups, dibotermin alfa does not appear to increase the incidence of bone disorders, such as local soft tissue or heterotopic ossification.
- The EPAR concluded that efficacy and safety have not been demonstrated in patients with other long-bone fractures that require open surgical management. The benefit for the patient in reduction of secondary intervention and time to fracture healing in patients with other long-bone fractures is not clear.
- Authors of a Cochrane review conclude that further well-designed RCTs and economic evaluations are needed to assess the clinical effectiveness and cost-effectiveness of BMP for acute fractures of the tibia and, in particular, tibial non-unions.

Date: June 2020

Details of Review

Name of medicine (generic & brand name)**:**

Dibotermin alfa (InductOs®). [1]

Strength(s) and form(s):

1.5 mg/ml powder, solvent and matrix. [1]

Dose and administration:

The appropriate dose is determined by the volume of wetted matrix required for the intended indication.

If the surgical setting requires that only a portion of the product is needed, the wetted matrix should be cut to the desired size, and the unused portion must be discarded. [1]

Dosing table for InductOs 4 mg pack

InductOs wetted matrices (4 mg pack)	Dimensions of wetted matrix	Volume of wetted matrix	Concentration of wetted matrix	Dibotermin alfa dose
1 matrix	2.5 cm x 5 cm	1.3 cm^3	1.5 mg/cm^3	2 mg
2 matrices	2 x (2.5 cm x 5 cm)	2.7 cm^3	1.5 mg/cm^3	4 mg

Dosing table for InductOs 12 mg pack

Portion of InductOs wetted matrix (12 mg pack)	Dimensions of wetted matrix	Volume of wetted matrix	Concentration of wetted matrix	Dibotermin alfa dose
1/6 of the matrix	2.5 cm x 5 cm	1.3 cm^3	1.5 mg/cm^3	2 mg
1/3 of the matrix	2.5 cm x 10 cm	2.7 cm^3	1.5 mg/cm^3	4 mg
2/3 of the matrix	5 cm x 10 cm	5.3 cm^3	1.5 mg/cm^3	8 mg
Entire matrix	7.5 cm x 10 cm	8 cm^3	1.5 mg/cm^3	12 mg

BNF therapeutic class / mode of action:

Osteoinductive protein (Bone Morphogenetic Protein). [1]

Licensed indication(s):

Single-level lumbar interbody 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. (NHS England commissioned and not considered as part of this review). [1]

Treatment of acute tibia fractures in adults, as an adjunct to standard care using open fracture reduction and intramedullary unreamed nail fixation. (CCG commissioned). [1]

Proposed use (if different from, or in addition to, licensed indication above):

Treatment of non-union long bone fractures. (In addition to licensed indication of treatment of acute tibia fractures in adults).

Course and cost:

A 12mg implant pack costs £2023.40.

Packs are single use and the product SPC does not recommend repeat use of InductOs®.

Current standard of care/comparator therapies:

- Intramedullary nail fixation and routine soft tissue care.

Relevant NICE guidance:

Fractures (complex): assessment and management (NICE guideline 37)

Background and context

Complex fractures make up the minority of the 1.8 million fractures that occur in England each year but are associated with considerable morbidity and are a large burden on healthcare resources. The treatment of complex fractures is often complicated and usually involves multiple healthcare professionals and specialists. [2]

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.

Routine soft-tissue debridement and reconstruction and skeletal stabilisation with intramedullary nail fixation is standard practice for the treatment of open fractures. [3]

East Lancashire CCG received a request from Salford Royal NHS Foundation Trust to fund dibotermin alfa for the treatment of non-union distal femur fracture. Consequently, the Lancashire and South Cumbria Medicines Management Group agreed to prioritise dibotermin alfa for a New Medicines Review.

Summary of evidence

Summary of efficacy data in proposed use:

Cochrane Review 2010 [4]

A Cochrane review has been conducted to assess the incremental effectiveness and costs of bone morphogenetic protein (BMP) on fracture healing in acute fractures and nonunions compared with standards of care.

Eleven RCTs, all at high risk of bias, and four economic evaluations were included. Apart from one study, the times to fracture healing were comparable between the BMP and control groups. There was some evidence for increased healing rates, without requiring a secondary procedure, of BMP compared with usual care control in acute, mainly open, tibial fractures (risk ratio (RR) 1.19, 95% CI 0.99 to 1.43). The pooled RR for achieving union for nonunited fractures was 1.02 (95% CI 0.90 to 1.15). One study found no difference in union for patients who had corrective osteotomy for radial malunions. Data from three RCTs indicated that fewer secondary procedures

were required for acute fracture patients treated with BMP versus controls (RR 0.65, 95% CI 0.50 to 0.83).

The authors of the review concluded that there is a paucity of data on the use of BMP in fracture healing as well as considerable industry involvement in currently available evidence. There is limited evidence to suggest that BMP may be more effective than controls for acute tibial fracture healing, however, the use of BMP for treating nonunion remains unclear. The limited available economic evidence indicates that BMP treatment for acute open tibial fractures may be more favourable economically when used in patients with the most severe fractures. Well-designed RCTs and economic evaluations of BMP for treating fracture locations other than the tibia are also needed.

Systematic review 2017 [5]

A systematic review was performed of data published between 2000 and 2016 identifying 10 randomized controlled trials (RCTs), 7 comparative studies, 18 case series, and 9 case reports. Mixed results were found among RCTs and comparative papers: 11 reported positive results for BMPs augmentation, 3 obtained no significant effects, and 2 showed negative results.

The authors concluded that due to the mixed findings of the review, further well-designed comparative studies are needed to confirm findings and optimise BMP use both in terms of best delivery method and most successful indications for the treatment of bone pathologies.

RCT by the METRC 2019 [6]

A randomised trial was conducted of thirty patients (18–65 years of age) with Gustilo[1] classified Type II, IIIA, or IIIB open tibia fracture and bone defect treated with an intramedullary nail in sixteen US trauma centres. Trial participants were treated with either allograft chips on a soaked absorbable collagen sponge soaked with recombinant bone morphogenetic protein-2 (rhBMP-2) or with bone grafts harvested from anterior/posterior iliac crests and implanted within the fracture defect. The primary outcome was radiographic union within 52 weeks without secondary intervention.

Twenty-three patients had union data at 52 weeks: 7/12 (58.3%) in rhBMP-2 group were radiographically united compared with 9/11 (81.8%) in the ICBG group, resulting in a treatment difference of -0.23 (90% CI: -0.55 to 0.10). Patients treated with rhBMP-2 had lower rates of clinical healing at 52 weeks (27% vs. 54%), higher mean Short Musculoskeletal Function Assessment scores (dysfunction: 33.3 vs. 23.7; bother score [measure of bothersome symptoms]: 32.8 vs. 21.4) and experienced more complications (5 vs. 3).

Summary of other efficacy data:

N/A

Summary of safety data:

The EPAR for InductOs®

According to the EPAR for InductOs®, the safety of dibotermin alfa has been evaluated in 13 studies. Two separate data sets were generated. The first includes the orthopaedic trauma studies (long-bone fracture data set). The second includes all studies (all-studies data set). [7]

Long-bone fracture data set

[1] Classification of open fractures according to wound size, level of contamination and osseous injury.

The long-bone fracture data set comprises 588 patients. A total of 202 patients were treated with standard of care (SOC), 12 with 0.43 mg/ml dibotermin alfa /Absorbable Collagen Sponge (ACS), 172 with 0.75 mg/ml and 202 with 1.50 mg/ml. The all-studies data set comprises 1000 patients, and includes 348 patients who received 1.50 mg/ml dibotermin alfa /ACS, 239 patients treated with 0.75 mg/ml, and 48 patients treated with 0.43 mg/ml.

The most frequently reported adverse events (AEs) (reported by at least 10%) are representative of the morbidity observed in the trauma setting (pain, oedema, anaemia). The frequency of these AEs was similar across treatment groups with the exception of pain (more frequent in the SOC group compared to dibotermin alfa /ACS groups). There was no difference in the frequency of infection across treatment groups.

The frequency of serious AEs was similar in the SOC (42%) and dibotermin alfa /ACS groups (38%). Five deaths were reported in this data set, one patient randomised to SOC and 4 patients randomised to dibotermin alfa /ACS. All cases were considered unrelated to administration of dibotermin alfa /ACS. Six patients underwent amputation of the limb under study. Three of these patients received dibotermin alfa /ACS before amputation. Five of the cases were considered unrelated to treatment. In one case, the relationship to dibotermin alfa /ACS was reported as unknown. [7]

All-studies data set

The most frequently reported AEs (at least 10% of patients) were pain, oedema, anaemia, and hyperglycaemia. With the exception of pain, oedema, and rash (erythema) which were observed more frequently in SOC patients, the frequency of AEs was similar across treatment groups. All deaths and serious AEs were reported in the long-bone fracture data set. Serious AEs were evenly distributed across treatment groups. [7]

Summary of Product characteristics InductOs®

The SPC for InductOs® summarises the AEs in the following table:

System organ class	Frequencies		
	Very common	Common	Unknown
General disorders and administration site conditions		Device dislocation[1*] Fluid collection[2*]	
Musculoskeletal and connective tissue disorders		Heterotopic ossification[1, 3*]	Osteolysis* Resorption bone increased*
Nervous system disorders		Radiculopathic events[1, 4]	
Infections and infestations	Localised infection[5*]		

[1]

The SPC states that InductOs® is contraindicated for patients with:

- Hypersensitivity to the active substance or to any of the product excipients
- Skeletal immaturity
- Any active malignancy or patient undergoing treatment for a malignancy
- An active infection at the operative site
- Persistent compartment syndrome or neurovascular residua of compartment syndrome

- Pathological fractures such as those observed in (but not limited to) Paget's disease or in metastatic bone. [1]

The SPC contains special warnings that InductOs® may cause heterotopic ossification at the site of implantation and resorption of surrounding trabecular bone. Fluid collections and immune responses have also been reported with the use of dibotermin alfa. [1]

Strengths and limitations of the evidence:

Strengths

- The EPAR concluded that efficacy and safety of dibotermin alfa are acceptable for the patient population studied, that is: for patients with an open tibial shaft fracture requiring surgical management with intramedullary nailing.
- Economic modelling submitted to the Scottish Medicines Consortium (SMC) suggests that the cost of treatment with dibotermin alfa may be partially offset by reductions in the need for secondary interventions, lower rates of infection and reduced number of outpatient visits due to faster healing times.
- Data presented has not revealed any significant safety concerns about the use of dibotermin alfa. In particular, there was no difference in the occurrence of infections across treatment groups, dibotermin alfa does not appear to increase the incidence of bone disorders, such as local soft tissue or heterotopic ossification.

Limitations

- The EPAR concluded that efficacy and safety have not been demonstrated in patients with other long-bone fractures that require open surgical management. The benefit for the patient in reduction of secondary intervention and time to fracture healing in patients with other long-bone fractures is not clear.
- Authors of a Cochrane review conclude that further well-designed RCTs and economic evaluations are needed to assess the clinical effectiveness and cost-effectiveness of BMP for acute fractures of the tibia and, in particular, tibial non-unions.
- A 2017 systematic review identified mixed findings relating to the efficacy of dibotermin alfa and the authors recommended that further research/studies are necessary to assess the effectiveness of dibotermin alfa in bone pathologies.
- The SMC concluded that 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 evidence on cost effectiveness:

The Manufacturer of InductOs® submitted a cost-utility evaluation to the SMC for 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. [3]

Prescribing and risk management issues:

InductOs® should be used by an appropriately qualified surgeon. InductOs® should only be used in patients who are skeletally mature (adult). In the absence of any experience, the repeat use of InductOs® is not recommended.

Commissioning considerations:

Comparative unit costs:

Dibotermin alfa is an adjunct treatment to standard care involving intramedullary nail fixation. Therefore, adding dibotermin alfa to standard treatment confers an additional cost of £2023.40.

Innovation, need and equity implications of the intervention:

Most fractures heal within 20 weeks. A fracture that does not heal in the time expected, as established by the clinician, is considered a delayed union. The rate of delayed unions varies by fracture severity from 16% to 60% for less severe fractures to 43% to 100% for more severe fractures. A fracture that demonstrates motion at the bony ends and is not completely healed within six months is considered a nonunion. Nonunions can lead to significant pain, inhibition of function and decreased personal and professional productivity (i.e. paid and unpaid), with the potential for associated reductions in patients' health-related quality of life. [4]

Financial implications of the intervention:

The only cost effectiveness analysis data available from the SMC was conducted in patients with Gustilo-Anderson Grade IIIB fractures.

Applying assumptions used in the SMC recommendations to the population of Lancashire and South Cumbria, there are an estimated 24 patients per annum with grade IIIB fractures requiring

rhBMP-2 which would lead to a cost of **£48,500**.

A 2017 study investigating the rate of nonunion fracture in the adult population of Scotland identified 4,715 nonunion fractures over a five-year period (average of 943 fractures per annum). [9]

Applying the same incidence rates to the population of Lancashire and South Cumbria, the estimated number of nonunion fractures would be 306 per annum. The associated costs to treat with dibotermin alfa are estimated below:

- Cost to treat 10% of all nonunion fractures (31 patients) = £62,750
- Cost to treat 20% of all nonunion fractures (61 patients) = £123,500
- Cost to treat 10% of all nonunion fractures (92 patients) = 186,250

Service Impact Issues Identified:

As the anticipated number of patients requiring the intervention is estimated to be small and patients would require contact with specialist services irrespective of the use of dibotermin alfa, the anticipated service impact is not expected to be significant.

Equality and Inclusion Issues Identified:

See the screening form (included with the paper)

Cross Border Issues Identified:

Pan Mersey APC do not currently hold a commissioning position for the use of dibotermin alfa.

GMMMG recommend the use of dibotermin alfa in both the licensed indication (as an adjunct to standard care using open fracture reduction and intramedullary unreamed nail fixation) **AND** outside of this licensed use as outlined below:

- 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.

As some Lancashire and South Cumbria patients may be treated by nonunion specialists in Greater Manchester trauma centres, there may be a risk of inequity if the LSCMMG recommendations differ from the GMMMG commissioning positions.

Legal Issues Identified:

N/A

Media/ Public Interest:

N/A

References

[1] Electronic Medicines Compendium, "Summary of Product Characteristics InductOs (dibotermin alfa)," Medtronic Limited, 9 September 2002. [Online]. Available: https://www.medicines.org.uk/emc/product/4265. [Accessed 4 March 2020].

[2] National Institute for Health and Care Excellence, "Fractures (complex): assessment and management," November 2017. [Online]. Available: https://www.nice.org.uk/guidance/ng37. [Accessed March 2020].

[3] Scottish Medicines Consortium, "Medicines advice: Dibotermin alfa (InductOs)," [Online]. Available: https://www.scottishmedicines.org.uk/media/1566/dibotermin_alfa__inductos__final_april_2007_amended_for_website.pdf. [Accessed March 2020].

[4] KR Garrison et al, "Bone morphogenetic protein (BMP) for fracture healing in adults," Cochrane Database of Systematic Reviews, vol. DOI: 10.1002/14651858.CD006950.pub2., no. 6, p. Art. No.: CD006950, 2010.

[5] GS Krishnakumar et al, "Clinical application of bone morphogenetic proteins for bone healing: a systematic review," International Orthopaedics, vol. 41, pp. 1073-1083, 2017.

[6] The Major Extremity Trauma Research Consortium, "A Randomized Controlled Trial Comparing rhBMP-2/Absorbable Collagen Sponge Versus Autograft for the Treatment of Tibia Fractures with Critical Size Defects," Journal Orthopaedic Trauma, vol. 33, pp. 384-391, 2019.

[7] European Medicines Agency, "Public Assessment Report Scientific Discussion InductOs (dibotermin alfa/ACS)," 21 October 2005. [Online]. Available: https://www.ema.europa.eu/en/documents/scientific-discussion/inductos-epar-scientific-discussion_en.pdf. [Accessed 5 March 2020].

[8] KR Garrison et al, "Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review," Health Technology Assessment, vol. 11, no. 30, 2007.

[9] LA Mills et al, "The risk of non-union per fracture: current myths and revised figures from a population of over 4 million adults," Acta Orthopaedica, vol. 88, no. 4, pp. 434-439, 2017.

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

Appendix 1 – Information used to inform the GMMMG position (shared by the Regional Drug & Therapeutics Centre)

GMMG commissioning position document

Item 2.4b Dibotermin Alfa - GMMMG evalua

Documents used to inform GMMMG commissioning position

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SMC-dibotermin_alfa

Consultation responses document

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