NHS
Pan Mersey
Area Prescribing Committee

Dibotermin Alfa (InductOs®)

The Pan Mersey Area Prescribing Committee recommends the prescribing of Dibotermin Alfa formulation (InductOs®) by specialists only for the licensed indication (acute tibia fractures in adults, as an adjunct to standard care) and use outside of this license as detailed below by a non-union specialist only.

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Only for use by non-union specialists at Liverpool University Hospitals Foundation Trust (LUHFT)

Approved unlicensed use will consist of;

- Management of established fracture non-union of tibia, femur, radius, ulna, clavicle, humerus based on FDA definition after 6-9 months with amenable cavity
- 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
- Docking site for bone transport
- Membrane induced osteogenesis for managing bone defects
- Management of avascular necrosis of the femoral head

It will not be approved for;

- For use by anyone other than a non-union specialist at LUHFT
- 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 in paediatrics - BMP is not recommended in skeletally immature individuals

This drug will be prescribed by orthopaedic surgeons specialising in management of non-union fractures. It will remain a hospital only drug as it is an intraosseous implant administered in theatre.

Relevant NICE Guidance:
Fractures (complex): assessment and management (NG 37)

Note: Patients who are not eligible for treatment under this statement may be considered on an individual basis where their GP or consultant believes exceptional circumstances exist that warrant deviation from the rule of this policy. In this situation, follow locally defined processes.

Dibotermin Alfa (InductOs®) for acute tibia fractures in adults

Effectiveness

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.

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 with standard care only. 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. 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.

A subsequent study pooled data from the BESTT trial with data from an identically designed randomised controlled trial in the US (n=60). 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%. For invasive secondary interventions, the equivalent figures were 9% and 28%. 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.

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). Overall, pain was significantly lower in the rhBMP-2 groups (67% in the 0.75-mg/mL group and 68% in the 1.5-mg/mL group) than in the control group. Those treated with 1.5 mg/mL also had significantly fewer hardware failures (11% vs. 22%) and faster wound healing (83% vs. 65% at six weeks) 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.

There is evidence derived from observational studies and case series which demonstrates the efficacy of bone morphogenetic proteins in management of femoral, calvarias, humeral, ulnar, patellar and clavicular fractures. Bone morphogenetic proteins were determined to be as effective as autologous bone-grafting without the risk of donor site morbidity and with a reduced risk of recipient site infection.[6]

Safety

The surgeons at LUHFT have used bone morphogenetic protein with success from 2007 for specific indications, and have presented data in national specialist society meetings on the efficacy of this in specific situations where autologous bone graft is not available, challenging to procure, contraindicated, or to minimise patient stay, or for patient choice.

Dibotermin Alfa (InductOs®) is contraindicated for patients with; skeletal immaturity, an 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. For further cautions please refer to the product SPC. Common adverse effects include; localised infection, device dislocation, fluid collection, heterotopic ossification, radiculopathic events, osteolysis and increased bone resorption.

The possibility of developing neutralising antibodies or hypersensitivity type reactions cannot be excluded. Therefore, in the absence of any experience, the repeat use of Dibotermin Alfa (InductOs®) is not recommended.

Cost
Cost per patient per year (including VAT): £2505.60
Number of patients per year to be treated for the whole organisation: 25 patients per year (estimated)
Overall financial impact: £62,640 per annum (£3,480 per 100,000 population)
PBRe (CCG commissioned) for licensed and unlicensed indications

Patient factors
The safety and efficacy of Dibotermin Alfa (InductOs®) in patients with metabolic bone diseases or autoimmune diseases including rheumatoid arthritis has not been established.
No studies have been performed in patients with hepatic, renal or cardiac impairment.
For these special populations, the physician is advised to give a careful consideration to the benefits and risks for the specific patient before using Dibotermin Alfa (InductOs®). A close monitoring of the patient for any adverse reactions and the success of the treatment is recommended.

Prescribing information

The volume of InductOs to be implanted is 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 12 mg pack. The maximum dosage is limited to 24 mg (2 entire 12 mg pack matrices).

Doses for other bones are typically based on volumetric assessment of the non-union site – typically lower for upper limb fractures.

Implementation notes

All patients are monitored as per clinical guidelines for management of non-union fracture – patients are counselled preoperatively about risk of heterotopic ossification, and on discharge about redness in wound that can be misinterpreted as infection. All patients are followed up clinically and radiologically.

There is no change from established practice.
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.

References

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