Summary of product characteristics: InductOs™ 1.5 mg/ml powder, solvent and matrix for implantation matrix. Refer to Summary of Product Characteristics (SmPC) before prescribing or using the product. Failure to follow the product preparation instructions and the method of administration may compromise the safety and efficacy of InductOs™.
Therapeutic indications: InductOs™ is indicated 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 6 months of non-operative treatment for this condition. InductOs™ is indicated for the treatment of acute tibia fractures in adults, as an adjunct to standard care using open fracture reduction and intramedullary unreamed nail fixation.
Qualitative and quantitative composition: One vial contains 12 mg (12 mg pack) dibotermin alfa. After reconstitution, InductOs™ contains 1.5 mg/ml dibotermin alfa. Dibotermin alfa (recombinant human Bone Morphogenetic Protein-2; rhBMP-2) is a human protein derived from a recombinant Chinese Hamster Ovary (CHO) cell line.
Pharmaceutical form: Powder, solvent and matrix for implantation matrix.
The powder is white. The solvent is a clear colourless liquid. The matrix is white.
Posology and method of administration: The appropriate dose is determined by the volume of wetted matrix required for the intended indication. 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

Lumbar interbody fusion surgery: The required volume of InductOs™ is determined by the intervertebral disc space and the size, shape, and internal volume of the lumbar interbody fusion device(s) being used. Typically, 4 mg (2.7 cm^3 of wetted matrix) of InductOs™ is used in the intervertebral disc space.
The maximum dosage is limited to 8 mg (5.3 cm^3 of wetted matrix). InductOs™ must be placed within the lumbar interbody fusion device(s) or in the anterior portion of the intervertebral disc space.
Acute tibia fracture surgery: 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 pack. The maximum dosage is limited to 24 mg (2 entire 12 mg pack matrices).
Paediatric population: The safety and efficacy of InductOs™ in children below 18 years of age have not been established. No data is available.
Method of administration: The medicinal product is administered by implantation.
InductOs™ should be used by an appropriately qualified surgeon.
InductOs™ must be prepared exactly in accordance with the directions for preparation. Forceps should be used to handle InductOs™. During handling and implantation, minimize fluid loss from the matrix. Do not squeeze.
Lumbar interbody fusion surgery: InductOs™ must not be used alone for this indication, but should be used with an approved (CE marked) lumbar interbody fusion device(s). Compatibility has been demonstrated with titanium, polyetheretherketone (PEEK), and allograft bone. Care and caution must be used to prevent overfilling the lumbar interbody fusion device and/or the anterior portion of the intervertebral disc space. InductOs™ is implanted after the removal per standard practice of the disc material and the cartilaginous portions of the vertebral endplates, and after haemostasis is achieved. InductOs™ must not be implanted posterior to the lumbar interbody fusion device, where direct access to the spinal canal and/or nerve root(s) is possible. A physical barrier between the matrix and any neurological tissue must be re-created by using, for example, local bone or allograft. Once implanted, the inside of the intervertebral disc space must not be irrigated. Outside the intervertebral disc space, the surgical field should be irrigated as needed, and any fluid loss from the wetted matrix should be washed away.
Acute tibia fracture surgery: InductOs™ should be folded or cut as needed prior to implantation. InductOs™ is implanted after the completion of standard fracture and wound management (i.e. at the time of soft tissue closure). InductOs™ should be placed bridging the fracture region and making good contact with the major proximal and distal fragments. To achieve maximum potential efficacy, it is important to attain complete soft tissue coverage of InductOs™ following its implantation.
Contraindications:
InductOs™ is contraindicated for patients with:
- Hypersensitivity to the active substance or to any of the excipients listed
- 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

Special warnings and precautions for use
Cervical spine surgery: The safety and efficacy of InductOs™ in cervical spine surgery have not been established, and InductOs™ should not be used in this condition. Localised oedema associated with the use of InductOs™ has been reported in patients undergoing cervical spine surgery. The oedema was delayed in onset and usually occurred in the first week post-operation. In some cases, the oedema was severe enough to result in airway compromise.
Malignancy: InductOs™ should not be used in patients with history or clinical suspicion of malignancy at the site of application.
Heterotopic ossification: Use of InductOs™ may cause heterotopic ossification at the site of implantation and/or the surrounding tissues, which may result in complications.
Bone resorption increased: InductOs™ can cause initial resorption of surrounding trabecular bone as evidenced by radiolucency. Therefore, in the absence of clinical data, the product should not be used for direct applications to trabecular bone where transient bone resorption may create a risk of bone fragility.
Fluid collections: Formation of a fluid collection (pseudocyst, localised oedema, implant site effusion), sometimes encapsulated and in some cases resulting in nerve compression and pain, has been reported associated with the use of InductOs™. Clinical intervention (aspiration and/or surgical removal) may be required if symptoms persist.
Immune response: Both dibotermin alfa and bovine Type I collagen have been found to elicit immune responses in patients. Anti-dibotermin alfa antibodies: In spine fusion studies, 1.3% of patients receiving InductOs™ developed antibodies to dibotermin alfa versus 0.8% of patients receiving autogenous bone graft. In long-bone fracture studies, 6.3 % of patients receiving dibotermin alfa with bovine Type I collagen matrix developed antibodies to dibotermin alfa versus 1.3 % in the control group. All patients who were tested for neutralizing antibodies to bone morphogenetic protein-2 were negative. Anti-bovine Type I collagen antibodies: In spine fusion studies, 13.5 % of patients receiving InductOs™ developed antibodies to bovine Type I collagen versus 14.3 % of patients receiving autogenous bone graft. In long-bone fracture studies, 13.0 % of patients receiving dibotermin alfa with bovine Type I collagen matrix developed antibodies to bovine Type I collagen versus 5.3 % of control patients. None of the patients with positive titers to bovine Type I collagen had cross-reacting antibodies to human type I collagen.
Although no association with clinical outcome or undesirable effects could be observed in clinical studies, the possibility of developing neutralising antibodies or hypersensitivity type reactions cannot be excluded. The possibility of an immune response to the product should be considered in cases where an undesirable effect with immunological background is suspected. Special consideration of risks and benefits should be given for patients who have previously received injectable collagen. In the absence of any experience, the repeat use of InductOs™ is not recommended.
Special populations: The safety and efficacy of the use of InductOs™ in patients with known autoimmune disease have not been established. These autoimmune diseases include rheumatoid arthritis, systemic lupus erythematosus, scleroderma, Sjögren's syndrome and dermatomyositis/polymyositis. The safety and efficacy of InductOs™ have not been demonstrated in patients with metabolic bone diseases. 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 InductOs™.
A close monitoring of the patient for any adverse reactions and the success of the treatment is recommended.
Excipients: This medicinal product contains less than 1 mmol (23 mg) sodium per maximum dose (two 12 mg packs), i.e. it is essentially 'sodium-free'.
Special warnings and precautions for use specific to lumbar interbody fusion:
The safety and efficacy of InductOs™ have not been established in the following conditions:
- Used with interbody fusion devices made from material other than titanium, PEEK or bone
- Implanted at locations other than lumbar spine
- Used in surgical techniques other than lumbar interbody fusion

To avoid exaggerated pharmacological effects of InductOs™, care and caution should be used to prevent overfilling the lumbar interbody fusion device and/or the anterior portion of the intervertebral disc space.
Heterotopic ossification: Bone formation outside the intervertebral disc space is not desirable as it may have a deleterious impact on local neurovascular structures. In clinical trials when degenerative disc disease was treated by a posterior lumbar interbody fusion procedure with dibotermin alfa, posterior bone formation was observed in CT scans. In some cases it may lead to nerve compression potentially requiring surgical intervention (see section 4.8). As a precaution, a physical barrier between the matrix and any neurological tissue must be re-created.
Device dislocation: Device dislocation can occur after the use of InductOs™ in spinal fusion surgery that may necessitate surgical revision.
Special warnings and precautions for use specific to acute tibia fractures:
InductOs™ is intended for use in patients with the following:
- Adequate fracture reduction and stabilization to ensure mechanical stability
- Adequate neurovascular status (e.g. absence of compartment syndrome, low risk of amputation)
- Adequate haemostasis (i.e., providing a relatively dry implantation site)
- Absence of large segmental defect repair of long bones, in which significant soft tissue compression can occur

The implant may only be administered to the fracture site under adequate vision and with utmost care. Efficacy information in tibia fracture is available only from controlled clinical trials in which open tibial fractures were treated using intramedullary nail. In a clinical study in which the intramedullary canal was reamed to cortical chatter, an increased rate of infection was observed in the InductOs™ treated group versus the standard of care control. The use of InductOs™ with reamed nails in open tibial fracture repair is not recommended. InductOs™ does not provide mechanical stability and should not be used to fill a void in the presence of compressive forces. Long bone fracture and soft tissue management procedures should be based on standard practice, including control of infection.
Interaction with other medicinal products and other forms of interaction:
No interaction studies have been performed. As dibotermin alfa is a protein and has not been identified in the general circulation, it is an unlikely candidate for pharmacokinetic drug interactions. In acute tibia fracture clinical trials, more InductOs™ patients receiving concomitant NSAIDs for 14 consecutive days experienced mild or moderate adverse events related to wound healing (e.g., wound drainage) than InductOs™ patients not taking NSAIDs. Although patient outcome was not affected, an interaction between NSAIDs and InductOs™ cannot be excluded. Information from clinical studies in acute tibia fractures indicated that the use of InductOs™ in patients receiving glucocorticoids was not associated with any apparent adverse reactions. In non-clinical studies, concurrent administration of glucocorticoids depressed bone repair (measured as a % change from control), but the effects of InductOs™ were not altered. In an in vitro study, dibotermin alfa was shown to bind to fibrin-based haemostatic agents or sealants. The use of these products in close proximity to InductOs™ is not recommended as this may lead to bone formation at the site of implant of the fibrin-based haemostatic agent or sealant.
Fertility, pregnancy and lactation: InductOs™ is not recommended during pregnancy and in women of childbearing potential not using contraception.
A decision must be made whether to discontinue breast-feeding or to abstain from InductOs™ therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. No impact on fertility was detected in non-clinical studies. No clinical data are available; potential risk for human is unknown.

Undesirable effects

Summary of the safety profile: The most common adverse reactions for InductOs™ in lumbar interbody fusion surgery were radiculopathic events, and in acute tibia fracture surgery it was localised infection. The most severe adverse reaction is localised oedema in cervical spine surgery. The incidence of adverse reactions with InductOs™ was not affected by gender, age or race.

Tabulated list of adverse reactions: Over 1700 patients have received InductOs™ in clinical studies. In the long-bone fracture studies, over 500 patients received InductOs™. In lumbar interbody fusion studies, over 600 patients received InductOs™. The remaining patients participated in studies using InductOs™ for indications not currently approved in the EU. These data are supplemented with information from use of InductOs™ in the general population. The frequency of adverse reactions in patients exposed to treatment with InductOs™ is presented in the table below. Frequencies are defined as very common (≥1/10) or common (≥1/100 to <1/10). No reactions are observed with the frequency uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000) or very rare (<1/10,000). The frequencies of adverse reactions identified during post-marketing use of InductOs™ are not known as these reactions were reported from a population of uncertain size.

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. Observed during use in lumbar interbody fusion
2. Fluid collection includes localised oedema, pseudocyst and implant site effusion.
3. Heterotopic ossification includes exostosis, extraskeletal ossification, postoperative heterotopic calcification, bone formation increased and implant site calcification.
4. Radiculopathic events includes radiculitis, lumbar radiculopathy, radicular pain, radiculitis lumbosacral, radiculopathy and sciatica.
5. Observed during use in acute tibia fractures

[*] Additional information provided below

Description of selected adverse reactions: New bone formation and bone remodelling. As part of the pharmacological mechanism of action of dibotermin alfa, bone remodelling occurs. In this process, both bone resorption and formation occur. In some circumstances an exaggeration of these processes can lead to complications such as nerve compression (due to heterotopic ossification) or device dislocation (associated with bone resorption or osteolysis). During two years follow-up in clinical trials for lumbar interbody fusion using a posterior approach, heterotopic ossification seen on radiographs occurred more often in patients treated with InductOs™ compared with autograft. This radiographic finding may be asymptomatic or symptomatic.

Fluid collection: Due to the angiogenic activity of InductOs™, fluid collection (pseudocyst, localised oedema, implant site effusion) can occur, sometimes encapsulated, sometimes resulting in nerve compression and/or pain.

Localised oedema was common when InductOs™ was used for cervical spine fusion. The oedema was delayed in onset and, in some cases, severe enough to result in airway compromise.

Localised infection: Localised infection specific to the fractured limb was very common (≥1/10) in patients in a clinical study in which the intramedullary canal was reamed to cortical chatter. An increased rate of infection was observed in the InductOs™ treated group versus the standard of care control group (19 % versus 9 %, respectively). For use with unreamed nails, estimated rates of infection were similar between treatment and control groups in a study (21 % versus 23 %, respectively).

Overdose: In case of overdose (i.e. a patient receives a concentration or amount of dibotermin alfa greater than recommended), treatment should be supportive. Use of InductOs™ in patients undergoing cervical spine surgery in amounts lower than or similar to those for lumbar interbody fusion has been associated with reports of localised oedema severe enough to result in airway compromise.

Pharmacodynamic properties: Mode of action:

Pharmacotherapeutic group: Drugs for treatment of bone diseases, Bone Morphogenetic Proteins, ATC code: M05BC01

Dibotermin alfa is an osteoinductive protein that results in the induction of new bone tissue at the site of implantation. Dibotermin alfa 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 InductOs™ implant is replaced by trabecular bone. Placement of InductOs™ into trabecular bone resulted in transient resorption of the bone surrounding the implant, followed by replacement with new, more dense bone. Remodelling of the surrounding bone occurs in a manner that is consistent with the biomechanical forces placed on it. The ability of InductOs™ to support bone remodelling may be responsible for the biological and biomechanical integration of the new bone induced by InductOs™ with that of the surrounding bone. Radiographic, biomechanical and histologic evaluation of the induced bone indicates that it functions biologically and biomechanically as native bone. Furthermore, non-clinical studies have indicated that the bone induced by InductOs™, if fractured, can repair itself in a manner indistinguishable from native bone. Non-clinical studies have suggested that bone formation initiated by InductOs™ is a self-limiting process, forming a well-defined volume of bone. This self-limitation is likely due to the loss of dibotermin alfa from the implant site, as well as the presence of BMP inhibitors in the surrounding tissues. In addition, several non-clinical studies indicate that there is a negative feedback mechanism at the molecular level that limits bone induction by BMPs. Histological evidence from animal studies of lumbar interbody fusion using anterior or posterior surgical approaches showed dibotermin alfa administered with titanium, PEEK or allograft interbody devices was biocompatible and produced consistently high rates of fusion independent of surgical approach or device material with less fibrous tissue evident compared with autograft. Clinical pharmacology studies demonstrate that the matrix alone is not osteoinductive and is no longer present in biopsies taken as early as 16 weeks post implantation.

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Adverse events should be reported.
Reporting forms and information can be found at www.hpra.ie.
Adverse events should also be reported to Medtronic BioPharma
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