ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

InductOs 1.5 mg/ml powder, solvent and matrix for implantation matrix

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 4 mg (4 mg pack) or 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.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder, solvent and matrix for implantation matrix.

The powder is white. The solvent is a clear colourless liquid. The matrix is white.

4 CLINICAL PARTICULARS

4.1 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.

See section 5.1.

4.2 Posology and method of administration

InductOs should be used by an appropriately qualified surgeon.

Posology

InductOs must be prepared exactly in accordance with the directions for preparation (see section 6.6).

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.

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

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. Care must be taken not to compress the product or overfill the volume intended for new bone formation (see section 4.4).

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) of InductOs in the intervertebral disc space. 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 12 mg 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 are available.

Method of administration

The medicinal product is administered by implantation.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.
Failure to follow the method of administration of InductOs may compromise its safety and efficacy.

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 (see section 4.4).

Pre-Implantation
4 mg pack:
The matrix is pre-cut in 2 pieces each of 2.5 x 5 cm.

12 mg pack:
The matrix is in 1 piece of 7.5 cm x 10 cm. The wetted matrix should be cut into 6 equal pieces (approximately 2.5 x 5 cm) as an aid for dose selection. The selected pieces can be further cut as required.

The hollow geometry of the lumbar interbody fusion device must be carefully and loosely filled with the volume of InductOs corresponding to the internal volume of the device.

Implantation
As per standard practice, disc material and the cartilaginous portions of the vertebral endplates should be removed, preserving the cortical portions of the endplates, and haemostasis should be achieved (see section 4.5).

For instructions to implant the lumbar interbody fusion device, please refer to the manufacturer's instructions for use.

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. If leakage into the spinal canal and the nerve root is possible, a physical barrier between the matrix and any neurological tissue must be re-created by using, for example, local bone or allograft (see section 4.5).

Post-Implantation
Once InductOs and the lumbar interbody fusion device(s) are 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.

If a surgical drain is required, the drain should be placed remotely from the implantation site or, preferably, one layer superficial to the implantation site.

Acute tibia fracture surgery

Pre-Implantation
Definitive fracture reduction, fixation, and haemostasis should be achieved prior to InductOs implantation.

InductOs should be folded or cut as needed prior to implantation.

Implantation
InductOs is implanted after the completion of standard fracture and wound management (i.e. at the time of soft-tissue closure).

To the extent possible, the accessible surface area of the fracture (fracture lines and defects) should be covered with InductOs. InductOs should be placed bridging the fracture region and making good contact with the major proximal and distal fragments.

InductOs may be placed into a void (loosely packed), folded, rolled or wrapped, as the geometry of the fracture requires. InductOs does not provide mechanical stability and should not be used to fill a void in the presence of compressive forces.

Post-Implantation
Once InductOs is implanted, do not irrigate the wound.

If a surgical drain is required, the drain should be placed remotely from the implantation site or, preferably, one layer superficially to the implantation site.

To achieve maximum potential efficacy, it is important to attain complete soft-tissue coverage of InductOs following its implantation.

4.3 Contraindications

InductOs is contraindicated for patients with:
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1
- 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

4.4 Special warnings and precautions for use

Failure to follow the product preparation instructions in section 6.6 and the method of administration in section 4.2 may compromise the safety and efficacy of InductOs.

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 (see section 4.3).

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 (see section 4.8).

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 (see section 4.8).

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 (see section 4.3). 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 (see section 4.2).

Device dislocation
Device dislocation can occur after the use of InductOs in spinal fusion surgery that may necessitate surgical revision (see section 4.8).

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 (see section 4.2).

Efficacy information in tibia fracture is available only from controlled clinical trials in which open tibial fractures were treated using intramedullary nail fixation (see section 5.1). 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 (see section 4.8). 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.

4.5 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-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 (see section 4.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of dibotermin alfa in pregnant women.

Animal studies have shown reproductive toxicity (see section 5.3).

Due to the unknown risks to the foetus associated with the potential development of neutralising antibodies to dibotermin alfa, InductOs is not recommended during pregnancy and in women of childbearing potential not using contraception (see section 4.4).

Breast-feeding

There is no information on the excretion of dibotermin alfa/metabolites in human milk. Considering the type of product, systemic exposure of the suckling infant is not expected, however a risk to the newborn/infant cannot be excluded.

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.

Fertility

No impact on fertility was detected in non-clinical studies. No clinical data are available; potential risk for human is unknown.

4.7 Effects on ability to drive and use machines

InductOs has no or negligible influence on the ability to drive and use machines.

4.8 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 (see section 5.1). 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 (see section 4.4). 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 (see section 4.4).

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; see section 4.4). For use with unreamed nails, estimated rates of infection were similar between treatment and control groups in a study (21% *versus* 23%, respectively).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare

professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 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 (see section 4.4).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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. Remodeling 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 remodeling 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.

Pharmacodynamic information specific to lumbar interbody fusion studies

The efficacy and safety of InductOs were demonstrated in a randomised, controlled, multicenter, non-inferiority study of 279 patients aged 19–78 years undergoing an open anterior lumbar interbody fusion procedure. Patients had received at least six months of non-operative treatment prior to treatment with InductOs for anterior lumbar spine fusion. Patients were randomised to receive a

titanium interbody fusion device filled with either InductOs or autogenous bone graft taken from the iliac crest.

At 24 months post-operation, InductOs was demonstrated to be statistically non-inferior to autogenous bone graft with a success rate for radiologically determined fusion of 94.4% for InductOs *versus* 88.9% for autogenous bone graft (95% two-sided CI of the difference: -1.53, 12.46). For pain and disability (Oswestry score), the success rate was 72.9% in the group using InductOs *versus* 72.5% in the group using autogenous bone graft (95% two-sided CI of the difference: -11.2, 12.0).

A post-hoc meta-analysis of 6 controlled clinical trials with data from patients treated with InductOs or autogenous bone graft administered using CE-marked interbody fusion devices or allograft bone spacers and various surgical approaches showed that, at 24 months post-surgery, InductOs was associated with a higher fusion success rate (95%, 241 out of 255 patients) compared with autogenous bone graft (85 %, 177 out of 209 patients), with an odds ratio of 3.26 (95% CI: 1.172, 9.075; P = 0.024). The estimated absolute difference in fusion success rate between InductOs and autogenous bone graft was 11.7% (95% CI: 0.8%, 22.5%; P = 0.035).

In a pooled safety data analysis of 8 clinical trials at 24 months post-surgery, the frequency of patients with pseudarthrosis was approximately 2-fold lower following treatment with InductOs (4.8%, 22 out of 456 patients) compared with autogenous bone graft (12.7%, 31 out of 244 patients).

Pharmacodynamic information specific to acute tibia fracture studies

The efficacy of InductOs was demonstrated in a multinational, randomized, controlled, single-blind study of 450 patients (age range 18 to 87 years; 81% male) with open tibial shaft fractures requiring surgical management. Patients received (in a 1:1:1 ratio) standard care (control group) consisting of intramedullary (IM) nail fixation and routine soft-tissue management, standard care plus InductOs 0.75 mg/ml, or standard care plus InductOs 1.5 mg/ml. Patients were followed for 12 months after soft-tissue closure.

In the acute tibia fracture pivotal trial, InductOs increased the probability of fracture healing; patients treated with InductOs 1.5 mg/ml had a 44% reduced risk for treatment failure (secondary intervention to promote fracture healing) compared with patients in the standard-care group (RR = 0.56; 95% CI = 0.40 to 0.78). These results were independently corroborated by a radiology panel blinded to treatment. The number of secondary and subsequent interventions was significantly reduced for the InductOs patients, particularly with regard to more invasive interventions, such as bone graft and exchange nailing (P = 0.0326).

The proportion of patients healed after treatment with InductOs 1.5 mg/ml was significantly higher at all visits from 10 weeks to 12 months post-operative, suggesting accelerated fracture healing.

InductOs 1.5 mg/ml was significantly effective (compared to standard care) in patients both with or without a history of smoking.

Severity of fractures: Treatment with InductOs 1.5 mg/ml was significantly effective in all fracture classes, including severe Gustilo IIIB fractures (52% reduced risk of secondary interventions as compared to standard-care patients).

The proportion of patients with healed soft-tissue wounds was significantly higher at the 6-week post-treatment visit in the InductOs 1.5 mg/ml group compared with the standard-care group (83% *versus* 65%; P= 0.0010). The proportion of patients with hardware failure (locking screws bent or broken) was significantly lower in the InductOs 1.5 mg/ml group as compared to standard-care group (11% *versus* 22%; P= 0.0174).

5.2 Pharmacokinetic properties

InductOs is active at the site of implantation. In two exploratory studies, pre- and post-surgery serum samples were collected from a few long-bone fracture patients. Dibotermin alfa was not detectable in serum.

In animal studies (rats) using InductOs containing radiolabelled dibotermin alfa, the mean residence time at the site of implantation was 4-8 days. Peak levels of circulating dibotermin alfa (0.1% of the implanted dose) were observed within 6 hours following implantation. When injected intravenously, the terminal half-life of dibotermin alfa was 16 minutes in rats and 6.7 minutes in cynomolgus monkeys. It is concluded, therefore, that at the site of implantation, dibotermin alfa is slowly released from the matrix and rapidly cleared when taken up into the systemic circulation.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, acute and repeated exposure toxicity and genotoxicity.

In reproductive toxicity studies in rats, where dibotermin alfa was administered intravenously to maximize systemic exposure, increased foetal weight and increased foetal ossification was observed and a treatment-related effect could not be ruled out. The clinical relevance of these effects is unknown.

Anti-dibotermin antibodies have been investigated in pregnant rabbits following hyper-immunisation with dibotermin alfa to experimentally induce anti-dibotermin alfa antibodies. In some foetuses with decreased body weights, there were decreases in ossification of frontal and parietal bones (4 out of 151 foetuses), which is generally considered to be reversible, and antibody related effects could not be ruled out. There were no other alterations in foetal external, visceral, or skeletal morphology.

Dibotermin alfa has demonstrated variable effects on human tumour cell lines *in vitro*. The available *in vivo* data on human tumour cell lines do not suggest a potential for promotion of tumour growth or metastasis. As a single use product, InductOs has not been tested for *in vivo* carcinogenicity (see also section 4.3).

InductOs has been studied in a canine spinal implantation model. InductOs was implanted directly onto the exposed dura following a laminectomy. Although narrowing of the neuroforamen and stenosis was observed, no mineralization of the dura, no spinal cord stenosis, and no neurological deficits subsequent to the application of InductOs were observed.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Sucrose
Glycine
Glutamic acid
Sodium chloride
Polysorbate 80
Sodium hydroxide

Solvent:
Water for injections

Matrix:
Bovine Type I collagen

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products, except those mentioned in section 6.6.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 30°C. Do not freeze**.**
Store in the original package in order to protect from light.

6.5 Nature and contents of container

InductOs 4 mg pack contains:

- Powder in a vial (10 ml; Type I glass) with a stopper (bromobutyl rubber).
- Solvent in a vial (10 ml; Type I glass) with a stopper (bromobutyl rubber).
- Two matrices (2.5 cm x 5 cm) in a blister package (polyvinyl chloride - PVC).
- Two syringes (5 ml; polypropylene).
- Two needles (stainless steel).

InductOs 12 mg pack contains:

- Powder in a vial (20 ml; Type I glass) with a stopper (bromobutyl rubber).
- Solvent in a vial (10 ml; Type I glass) with a stopper (bromobutyl rubber).
- One matrix (7.5 cm x 10 cm) in a blister package (polyvinyl chloride - PVC).
- Two syringes (10 ml; polypropylene).
- Two needles (stainless steel).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

InductOs is prepared immediately prior to use. Dibotermin alfa must only be used following reconstitution with the solvent and matrix provided in the InductOs pack.

Once prepared, InductOs contains dibotermin alfa at a concentration of 1.5 mg/ml.
InductOs must not be used in concentrations higher than 1.5 mg/ml (see section 4.9).

Product preparation

To prevent overloading the matrix, it is important to reconstitute the dibotermin alfa and to wet the entire matrix as described below.

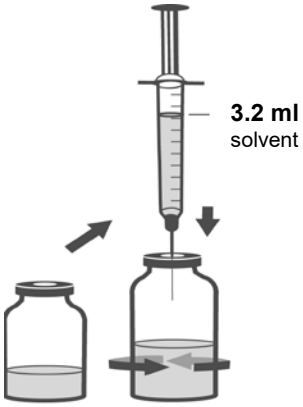
4 mg pack:

In the non-sterile field

1. Using sterile technique, place one syringe, one needle and the matrix inner package in the sterile field.

2. Disinfect the stoppers of the dibotermin alfa and solvent vials.

3. Using the remaining syringe and needle from the pack, reconstitute the dibotermin alfa vial with 3.2 ml of solvent. Slowly inject the solvent into the vial containing the lyophilised dibotermin alfa. Swirl the vial gently to aid reconstitution. Do not shake. Discard syringe and needle after use.



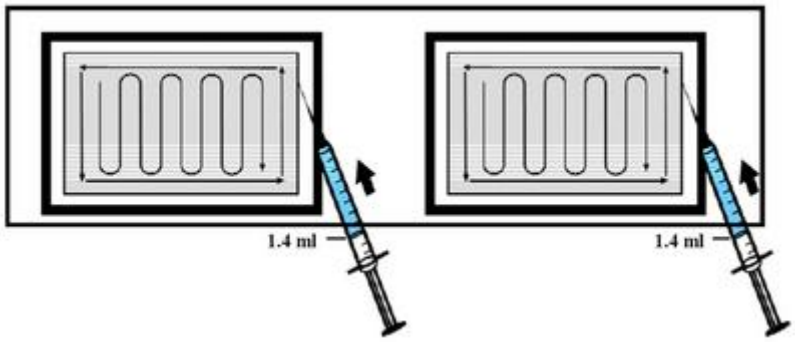
4. Disinfect the stopper of the reconstituted dibotermin alfa vial.

In the sterile field

5. Peel open the interior package of the matrices and leave the matrices in their trays.

6. Using aseptic transfer technique and the syringe and needle from step 1, withdraw 2.8 ml of the reconstituted dibotermin alfa solution from the vial in the non-sterile field, holding up the inverted vial to facilitate withdrawal.

7. Leaving the matrix in its tray, UNIFORMLY distribute 1.4 ml of dibotermin alfa solution on each of the two 2.5 x 5 cm matrices, following the pattern in the figure below.



9. Wait a MINIMUM of 15 minutes before using the prepared InductOs product. The product must be used within 2 hours after preparation.

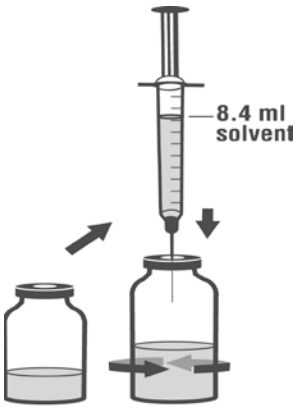
12 mg pack:

In the non-sterile field

1. Using sterile technique, place one syringe, one needle and the matrix inner package in the sterile field.

2. Disinfect the stoppers of the dibotermin alfa and solvent vials.

3. Using the remaining syringe and needle from the pack, reconstitute the dibotermin alfa vial with 8.4 ml of solvent. Slowly inject the solvent into the vial containing the lyophilised dibotermin alfa. Swirl the vial gently to aid reconstitution. Do not shake. Discard syringe and needle after use.



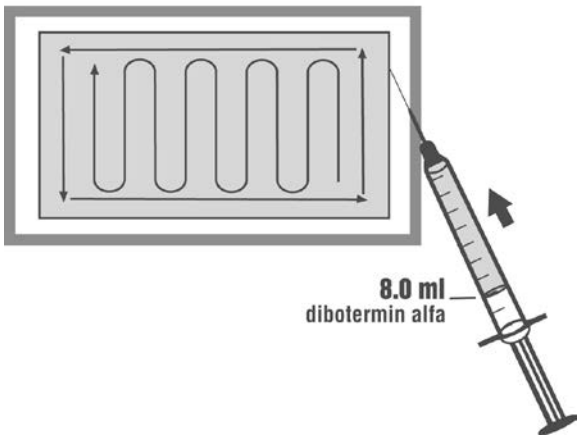
4. Disinfect the stopper of the reconstituted dibotermin alfa vial.

In the sterile field

5. Peel open the interior package of the matrix and leave the matrix in its tray.

6. Using aseptic transfer technique and the syringe and needle from step 1, withdraw 8.0 ml of the reconstituted dibotermin alfa solution from the vial in the non-sterile field, holding up the inverted vial to facilitate withdrawal.

7. Leaving the matrix in its tray, UNIFORMLY distribute the dibotermin alfa solution on the matrix, following the pattern in the figure below.



8. Wait a MINIMUM of 15 minutes before using the prepared InductOs product. The product must be used within 2 hours after preparation.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Medtronic BioPharma B.V.
Earl Bakkenstraat 10
6422 PJ Heerlen
The Netherlands
tel +31 (0) 45 566 8000
fax +31 (0) 45 566 8012

8 MARKETING AUTHORISATION NUMBER(S)

EU/1/02/226/001
EU/1/02/226/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9 September 2002
Date of latest renewal: 20 July 2012

10 DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

Additional educational materials for healthcare professionals are available on the following URL: [URL to be included] <and the <Member State> website>.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Wyeth BioPharma Division of Wyeth Pharmaceuticals LLC
One Burtt Road
Andover
Massachusetts 01810
USA

Name and address of the manufacturer responsible for batch release

Medtronic BioPharma B.V.
Earl Bakkenstraat 10
6422 PJ Heerlen
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2)

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder (MAH) must agree the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed:

- at increasing awareness about the risk of heterotopic ossification and the potential risk of medication errors and incorrect use of InductOs and providing guidance on how to manage these risks.

The MAH shall ensure that in each Member State where InductOs is marketed, all healthcare professionals who are expected to use InductOs are provided with the following educational package:

- Healthcare professionals educational material

The healthcare professional educational material should contain:

- The Summary of Product Characteristics
- Healthcare professionals training material
  The healthcare professionals training material shall contain the following key elements:
  - Detailed description from the SmPC of the administration procedures of InductOs and of the measures that need to be taken to prevent medication errors, incorrect use, and minimise the risk of heterotopic ossification.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR 4 MG PACK

1. NAME OF THE MEDICINAL PRODUCT

InductOs 1.5 mg/ml powder, solvent and matrix for implantation matrix
Dibotermin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 4 mg dibotermin alfa. When reconstituted, InductOs contains 1.5 mg/ml dibotermin alfa.

3. LIST OF EXCIPIENTS

Excipients
Powder: sucrose, glycine, glutamic acid, sodium chloride, sodium hydroxide and polysorbate 80
Solvent: water for injections
Matrix: bovine Type I collagen

4. PHARMACEUTICAL FORM AND CONTENTS

Powder, solvent and matrix for implantation matrix contain:

1 vial with 4 mg dibotermin alfa
1 vial with 10 ml water for injections
2 sterile matrices (2.5 x 5 cm)
2 syringes (5 ml)
2 needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Implantation. Read the Summary of Product Characteristics before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C. Do not freeze. Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Medtronic BioPharma B.V.
Earl Bakkenstraat 10
6422 PJ Heerlen
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/226/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

TRAY TOP LID LABEL FOR 4 MG PACK

1. NAME OF THE MEDICINAL PRODUCT

InductOs 1.5 mg/ml powder, solvent and matrix for implantation matrix
Dibotermin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 4 mg dibotermin alfa. When reconstituted, contains 1.5 mg/ml dibotermin alfa.

3. LIST OF EXCIPIENTS

Excipients
Powder: sucrose, glycine, glutamic acid, sodium chloride, sodium hydroxide and polysorbate 80
Solvent: water for injections
Matrix: bovine Type I collagen

4. PHARMACEUTICAL FORM AND CONTENTS

Powder, solvent and matrix for implantation matrix contain:

1 vial with 4 mg dibotermin alfa
1 vial with 10 ml water for injections
2 sterile matrices (2.5 x 5 cm)
2 syringes (5 ml)
2 needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Implantation. Read the Summary of Product Characteristics before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C. Do not freeze. Store in original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/226/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

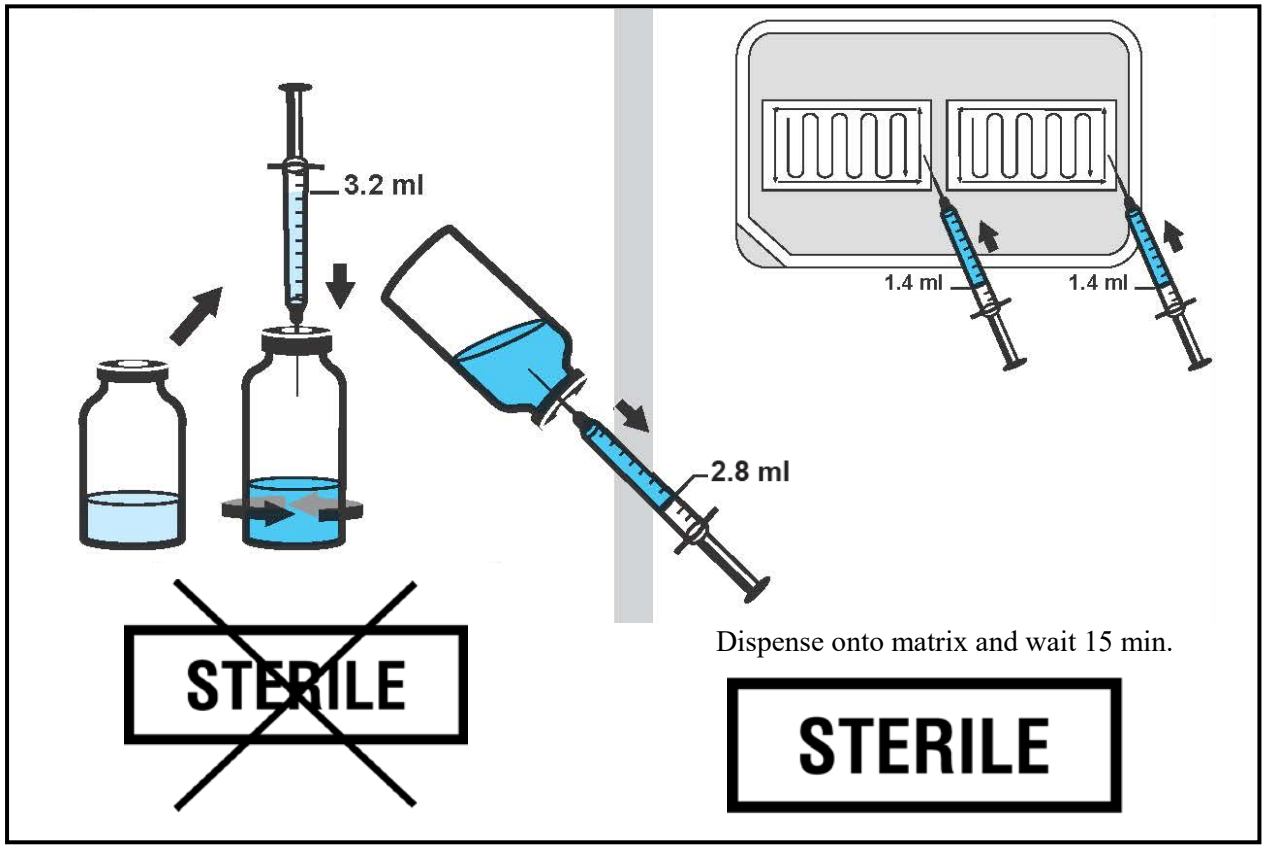
15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

TRAY UNDERSIDE OF LID STICKER FOR 4 MG PACK



MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL PROTEIN LABEL FOR 4 MG PACK

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Powder for InductOs 1.5 mg/ml
Dibotermin alfa
Implantation

2. METHOD OF ADMINISTRATION

Read the Summary of Product Characteristics before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

4 mg dibotermin alfa

6. OTHER

Medtronic BioPharma B.V.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL SOLVENT LABEL FOR 4 MG PACK

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for InductOs
Water for injections

2. METHOD OF ADMINISTRATION

Read the Summary of Product Characteristics before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

Medtronic BioPharma B.V.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

MATRIX LABEL FOR 4 MG PACK

1. NAME OF THE MEDICINAL PRODUCT

Matrix for InductOs 1.5 mg/ml
Bovine Type I collagen

2. METHOD OF ADMINISTRATION

Implantation. Read the Summary of Product Characteristics before use.

3. EXPIRY DATE

EXP: see reverse

4. BATCH NUMBER

Lot: see reverse

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 sterile matrices (2.5 x 5 cm)

6. OTHER

7. REVERSE

{number}

{YYYY MM}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR 12 MG PACK

1. NAME OF THE MEDICINAL PRODUCT

InductOs 1.5 mg/ml powder, solvent and matrix for implantation matrix
Dibotermin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 12 mg dibotermin alfa. When reconstituted, InductOs contains 1.5 mg/ml dibotermin alfa.

3. LIST OF EXCIPIENTS

Excipients
Powder: sucrose, glycine, glutamic acid, sodium chloride, sodium hydroxide and polysorbate 80
Solvent: water for injections
Matrix: bovine Type I collagen

4. PHARMACEUTICAL FORM AND CONTENTS

Powder, solvent and matrix for implantation matrix contain:

1 vial with12 mg dibotermin alfa
1 vial with 10 ml water for injections
1 sterile matrix (7.5 x 10 cm)
2 syringes (10 ml)
2 needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Implantation. Read the Summary of Product Characteristics before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C. Do not freeze. Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Medtronic BioPharma B.V.
Earl Bakkenstraat 10
6422 PJ Heerlen
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/226/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

TRAY TOP LID LABEL FOR 12 MG PACK

1. NAME OF THE MEDICINAL PRODUCT

InductOs 1.5 mg/ml powder, solvent and matrix for implantation matrix
Dibotermin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 12 mg dibotermin alfa. When reconstituted, contains 1.5 mg/ml dibotermin alfa.

3. LIST OF EXCIPIENTS

Excipients
Powder: sucrose, glycine, glutamic acid, sodium chloride, sodium hydroxide and polysorbate 80
Solvent: water for injections
Matrix: bovine Type I collagen

4. PHARMACEUTICAL FORM AND CONTENTS

Powder, solvent and matrix for implantation matrix contain:
1 vial with 12 mg dibotermin alfa
1 vial with 10 ml water for injections
1 sterile matrix (7.5 x 10 cm)
2 syringes (10 ml)
2 needles

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Implantation. Read the Summary of Product Characteristics before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30°C. Do not freeze.
Store in original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Medtronic BioPharma B.V.
Earl Bakkenstraat 10
6422 PJ Heerlen
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/02/226/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

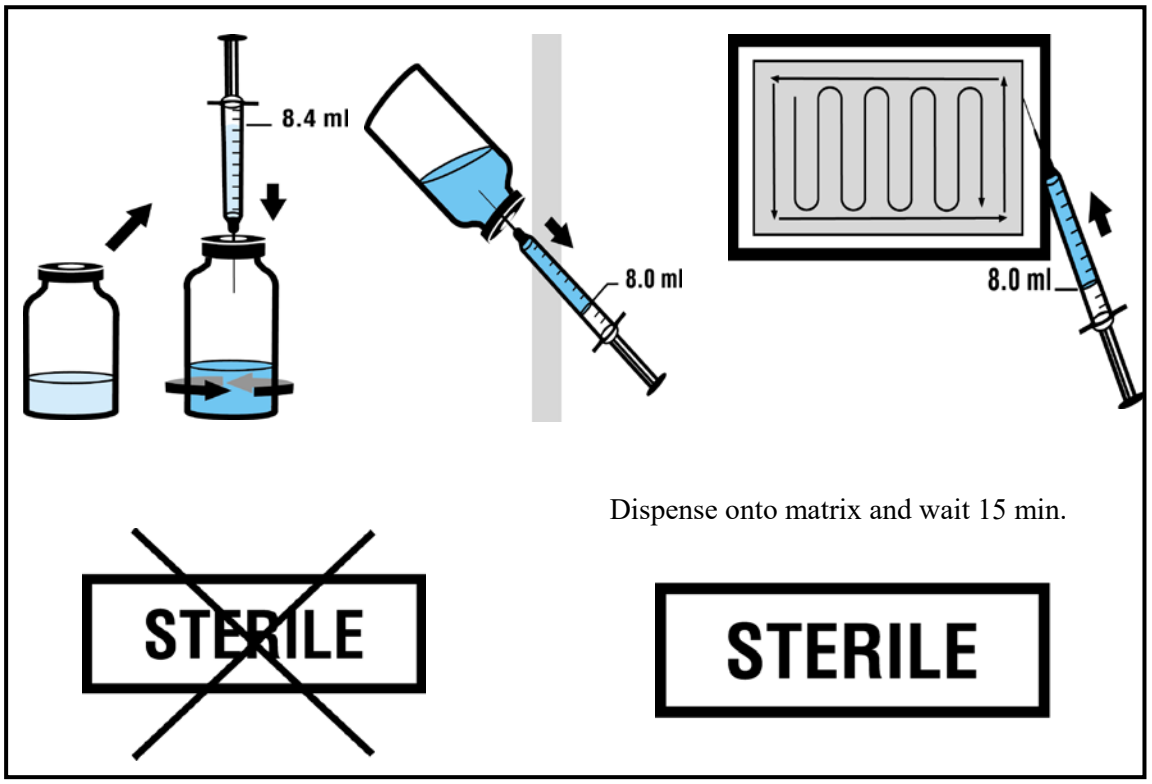
15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

TRAY UNDERSIDE OF LID STICKER FOR 12 MG PACK



MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL PROTEIN LABEL FOR 12 MG PACK

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Powder for InductOs 1.5 mg/ml
dibotermin alfa
Implantation

2. METHOD OF ADMINISTRATION

Read the Summary of Product Characteristics before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

12 mg dibotermin alfa

6. OTHER

Medtronic BioPharma B.V.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL SOLVENT LABEL FOR 12 MG PACK

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for InductOs
Water for injections

2. METHOD OF ADMINISTRATION

Read the Summary of Product Characteristics before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

10 ml

6. OTHER

Medtronic BioPharma B.V.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

MATRIX LABEL FOR 12 MG PACK

1. NAME OF THE MEDICINAL PRODUCT

Matrix for InductOs 1.5 mg/ml
Bovine Type I collagen

2. METHOD OF ADMINISTRATION

Implantation. Read the Summary of Product Characteristics before use.

3. EXPIRY DATE

EXP: see reverse

4. BATCH NUMBER

LOT: see reverse

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 sterile matrix (7.5 x 10 cm)

6. OTHER

7. REVERSE

{number}

{YYYY MM}

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

InductOs 1.5 mg/ml powder, solvent and matrix for implantation matrix
Dibotermin alfa

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What InductOs is and what it is used for

InductOs contains the active substance, dibotermin alfa. It is a copy of a protein called bone morphogenetic protein 2 (BMP-2), which is produced naturally by the body and helps with the formation of new bone tissue.

InductOs may be used either in lower back spine fusion surgery or to repair fractures of the shin bone.

Lower back spine fusion surgery
If you have a lot of pain from a damaged disc in your lower back, and other treatments have not proven effective, you may be considered for lower back spine fusion surgery. InductOs is used instead of taking a bone graft from your hip; this avoids the problems and pain that can be caused by an operation to collect the bone graft.

When used in lower back fusion surgery, InductOs is used in combination with a medical device, which corrects the position of your spine. If you have any question about the medical device, please ask your doctor.

Fractures of the shin bone
If you have broken your shin bone, InductOs is used, to help your fracture heal and to reduce the need for additional surgeries. It is used in addition to standard treatment and care of shin bone fractures.

2. What you need to know before you receive InductOs

You should not receive InductOs
- if you are allergic to dibotermin alfa or bovine collagen or any of the other ingredients of this medicine (listed in section 6).
- if you are still growing (skeletally immature).
- if you have an active infection at the surgery site.

- if the doctor treating you decides that you have inadequate blood supply at the fracture site.
- for treating a fracture that is disease-related (e.g., fractures due to Paget's disease or cancer).
- if you have been diagnosed with or are being treated for cancer.

Warnings and precautions to be discussed with your doctor
- You should inform your doctor if you have an autoimmune disease, such as rheumatoid arthritis, systemic lupus erythematosus, scleroderma, Sjögren's syndrome or dermatomyositis/polymyositis.
- You should inform your doctor if you have any bone disease.
- You should inform your doctor of any history of cancer.
- The product should not be placed in direct contact with certain types of bones. Your surgeon will know which bones to avoid.
- Use of InductOs may cause bone formation (heterotopic ossification) in the surrounding tissues, which can result in complications.
- Some patients may develop nerve pain due to localised fluid collection, which would require drainage or a surgical procedure to remove the fluid.
- Some patients may develop antibodies (made by your body to fight a foreign protein) to InductOs. While no harmful effects have been noted, the long-term effects are unknown.
- You should inform your doctor if you have kidney or liver disease.
- Localised swelling, in some cases resulting in breathing difficulty, has been reported in patients when InductOs has been used in surgery of the upper (neck) region of the spine. The safety and effectiveness of InductOs in spine surgery in the neck have not been established, and InductOs should not be used in this situation.

Other medicines and InductOs
Tell your doctor if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
The effects of InductOs on pregnancy are not known. The use of the product in pregnant women is not advised.

It is not known if InductOs passes into breast milk.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before receiving this medicine.

Driving and using machines
InductOs will not affect your ability to drive or operate machines.

InductOs contains bovine collagen, a protein obtained from cattle
Some patients may develop antibodies (made by your body to fight a foreign protein) against the collagen in the medicine. In clinical studies, the presence of antibodies to collagen was not associated with side effects, such as allergies, nor was it shown to decrease the effectiveness of InductOs. If you think you have an allergic reaction to collagen, contact your doctor.

InductOs contains sodium
This medicine contains less than 1 mmol (23 mg) sodium per maximum dose (two 12 mg packs), i.e. it is essentially 'sodium-free'.

3. How InductOs is given

The doctor treating you will implant InductOs during surgery. The medical staff will prepare InductOs in the operating room. The powder is dissolved in the sterile water to form a solution that is used to

soak the sponge. The soaked sponge is then implanted where bone growth is needed. Over time, the sponge will gradually disappear as new bone is formed.

If you are receiving InductOs for lower back spine fusion, your surgeon will remove the damaged disc that is causing the pain and replace it with a medical device filled with InductOs. The medical device corrects the position of your spine, and InductOs encourages bone to grow between the two vertebrae to fix them permanently in the correct position.

If you are receiving InductOs for a broken shin bone, your doctor will place InductOs around your broken bone when your fracture is treated. The doctor will determine how much InductOs you will receive, depending on the size and number of fractures. Generally, one 12 mg pack is used; however, a maximum of two 12 mg packs may be used.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Tell your doctor immediately, or go immediately to the emergency department of your nearest hospital if you have localised swelling, which may result in breathing difficulties, after InductOs has been used in surgery of the upper (neck) region of your spine. The frequency of this side effect is unknown and cannot be estimated from the available data.

Other side effects

Lower back spine fusion surgery
Talk to your doctor if you have any of the following:
- Common (may affect up to 1 in 10 people):
  Additional bone growth, movement of the implanted medical device, localised fluid build-up and pain radiating from your back to your leg (sciatica)
- Unknown (cannot be estimated from available data):
  Increased breakdown of the bone

Fractures of the shin bone
Talk to your doctor if you have any of the following:
- Very common (may affect more than 1 in 10 people):
  Localised infection
- Common (may affect up to 1 in 10 people):
  Localised fluid build-up
- Unknown (cannot be estimated from available data):
  Increased breakdown of the bone

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store InductOs

You will not be required to store this product.

6. Contents of the pack and other information

What InductOs contains

- The active substance in InductOs is dibotermin alfa (also called recombinant human Bone Morphogenetic Protein-2), 4 mg (4 mg pack) or 12 mg (12 mg pack).
- The other ingredients are sucrose, glycine, glutamic acid, sodium chloride, sodium hydroxide and polysorbate 80, water for injections, and bovine Type I collagen.

What InductOs looks like and contents of the pack

InductOs is supplied to your doctor as a kit for implanting during surgery.

- Dibotermin alfa is a white powder presented in a glass vial.
- Water for injections is a clear colourless liquid presented in a glass vial.
- The sponge is white and it is presented in a plastic blister.

Marketing Authorisation Holder and Manufacturer

Medtronic BioPharma B.V.
Earl Bakkenstraat 10
6422 PJ Heerlen
The Netherlands

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site http://www.ema.europa.eu