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IMPORTANT SAFETY INFORMATION
29 March 2007

Direct Healthcare Professional Communication on the association of InductOs™ (dibotermin alfa) with reports of fluid collections (e.g. pseudocysts, localised oedema, implant site effusion) sometimes encapsulated, in patients receiving InductOs™ for spinal procedures, regularly requiring intervention.

Dear Health Care Provider:

Following discussions with the Irish Medicines Board, Wyeth Pharmaceuticals would like to make you aware of the following important safety information regarding InductOs (dibotermin alfa):

Summary

The unapproved use of InductOs in posterior lumbar spine surgery or inappropriate use (e.g. overfilling of the implant/cage) has resulted in a limited number of cases of localised fluid collection (e.g. pseudocysts, localised oedema, implant site effusion) sometimes encapsulated, regularly requiring intervention.

Healthcare professionals are reminded to use InductOs according to the instructions in the Summary of Product Characteristics (SPC), paying attention to the correct dosage and proper placement of the product within the LT-CAGE.

This information has also been approved for distribution by the European Medicines Agency (EMEA).

Further information on the safety concern

Information on Fluid Collection (e.g. pseudocysts, localised oedema, implant site effusion).

The formation of fluid collection, which is sometimes encapsulated, has been reported in some patients undergoing spine surgery with InductOs within days or months after application. The majority of these reports have occurred when InductOs was used in unapproved posterior lumbar approaches, and/or in a manner inconsistent with the instructions for use, such as placing the sponge in places outside the cage and/or in overfilling of the implant/cage.

In more than 50% of the reported cases, this fluid collection sometimes encapsulated, resulted in nerve compression, neurological deficit or pain. Clinical intervention, such as aspiration or surgical removal of the fluid collection sometimes encapsulated, has been required where symptoms persisted.

InductOs is approved for use in anterior spine fusion surgery as an alternative to autologous bone graft, resulting in non-inferior rates of radiographic fusion and clinical improvement. This potential post-operative adverse event needs to be placed in the context of reducing the need for autologous bone graft harvest.

Wyeth identified this emerging adverse event and proposed to the EMEA and national agencies that relevant healthcare professionals should be notified. Wyeth will continue to monitor this phenomenon.

Further information on recommendations to healthcare professionals

Healthcare professionals are reminded:

- to use InductOs in appropriate indications
- to read carefully the SPC instructions for the product preparation and implantation instructions, paying attention to the calculation of the area of wetted sponge to be placed in each cage (LT Cage),
- and to not use the remaining sponge elsewhere in the operative field.

Call for reporting

Healthcare professionals are requested to be alert to adverse events following the implantation of InductOs and to report them to the IMB or Wyeth Pharmacovigilance UK on + 44 1628 414966 or via e-mail to WATWADR@wyeth.com

Communication information

This letter is being sent to all relevant surgeons who perform neurological spine operations as well as to hospital pharmacists.

For more information please contact Wyeth Ireland Medical Information Department 01-4493524 or 01-4493584

Sincerely,

Dr Declan O'Callaghan
Medical Director
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Annex

The SPC approved at the February 2007 CHMP meeting

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

InductOs 12 mg kit for implant

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 12 mg 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.

Excipients:
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Kit for implant.

The kit consists of dibotermin alfa white powder for solution, a clear colourless solvent and a white matrix.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

InductOs is indicated for single-level (L_4 - S_1) anterior lumbar spine fusion as a substitute for autogenous bone graft in adults with degenerative disc disease who have had at least 6 months of non-operative treatment for this condition.

InductOs is indicated for the treatment of acute tibia fractures in adults, as an adjunct to standard care using open fracture reduction and intramedullary nail fixation.

See section 5.1.

4.2 Posology and method of administration

InductOs should be used by an appropriately qualified surgeon.

Follow exactly the directions for preparation for each kit and use the appropriate amount of rhBMP-2/ACS for the intended indication.

InductOs is prepared immediately prior to use from a kit containing all necessary components. Once prepared, InductOs contains dibotermin alfa at a concentration of 1.5 mg/ml (12 mg per vial).

InductOs should not be used in concentrations higher than 1.5 mg/ml (see section 4.9).

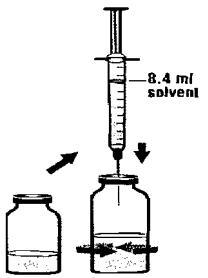
There is very limited experience of the efficacy and safety of the medicinal product in the elderly (>65 years of age).

Experience in children is limited.

Product preparation

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 kit, 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.

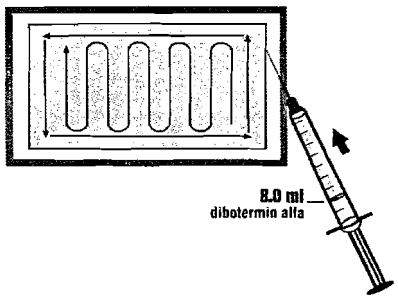


4. Disinfect the stopper of the reconstituted dibotermin alfa vial.

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 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.

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

9. Follow instructions relevant to the planned surgery – anterior lumbar spine fusion or acute tibia fracture repair.

Instructions for use in anterior lumbar spine fusion surgery

InductOs should not be used alone for this indication, but must be used with the LT-CAGE Lumbar Tapered Fusion Device.

Failure to follow the product preparation instructions for rhBMP-2/ACS may compromise its safety and effectiveness. Care and caution should be used to prevent overfilling of the construct and/or intervertebral space. (see section 4.4)

Pre-Implantation

Cut the wetted matrix of InductOs into 6 equal (approximately 2.5 x 5 cm) pieces. During cutting and handling, avoid excessive fluid loss from InductOs. Do not squeeze.

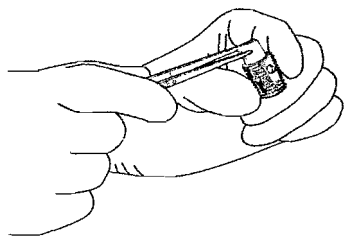
The number of pieces of InductOs required is determined by the size of the LT-CAGE Lumbar Tapered Fusion Device being used. Using the table below, identify the number of 2.5 x 5 cm pieces of InductOs required for the size of LT-CAGE Lumbar Tapered Fusion Device.

LT-CAGE Lumbar Tapered Fusion Device size (lead diameter x length)	**Number of 2.5 x 5 cm pieces of InductOs per LT-CAGE Lumbar Tapered Fusion Device**
14 mm x 20 mm	1
14 mm x 23 mm	1
16 mm x 20 mm	1
16 mm x 23 mm	2
16 mm x 26 mm	2
18 mm x 23 mm	2
18 mm x 26 mm	2

Implantation

Using forceps to avoid excessive squeezing, carefully roll the required number of InductOs pieces for each LT-CAGE device and insert each roll into the matching LT-CAGE Lumbar Tapered Fusion Device, as shown in the figure below.

For instructions of implantation of the LT-CAGE Lumbar Tapered Fusion Device, please refer to the package leaflet for the LT-CAGE device.



Post-Implantation

Once InductOs and the LT-CAGE device are implanted, do not irrigate the wound region.
If a surgical drain is required, place the drain remote from the implantation site or, preferably, one layer superficial to the implantation site.

Instructions for use in acute tibia fractures

Pre-Implantation

- Achieve definitive fracture reduction, fixation, and hemostasis prior to InductOs implantation.
- InductOs does not provide mechanical stability and should not be used to fill spaces in the presence of compressive forces.
- Fold or cut InductOs as needed prior to implantation. During handling, avoid excessive fluid loss from InductOs. Do not squeeze. If the surgical setting requires that only a portion of the product is needed, first prepare the entire InductOs product (following steps 1-8 above), and then cut the product to the desired size and discard the unused portion.

Implantation

InductOs is implanted after the completion of standard fracture and wound management, i.e. at the time of soft-tissue closure. The number of InductOs kits to use and the volume of InductOs to be implanted are 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 kit. The maximum dosage of InductOs is limited to 2 kits. To the extent possible, the accessible surface area of the fracture (fracture lines and defects) should be covered with InductOs. Place InductOs so that it bridges the fracture region and makes good contact with the major proximal and distal fragments. It is not necessary to overlay the contents of multiple kits to achieve the desired effect.

During implantation, use forceps to handle InductOs to avoid excessive loss of fluid.

InductOs may be placed into a void (loosely packed), folded, rolled, or wrapped, as the geometry of the fracture requires. Do not squeeze.

Post-Implantation

Once InductOs is implanted, do not irrigate the wound.

If a surgical drain is required, place the drain remote from the implantation site or, preferably, one layer superficial to the implantation site.

In order to achieve maximum potential efficacy, it is important to achieve 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
- 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 for rhBMP-2/ACS may compromise its safety and effectiveness. Care and caution should be used to prevent overfilling of the construct and/or intervertebral space.

Localised oedema associated with the use of InductOs has been reported in patients undergoing cervical spine surgery. The oedema was delayed in onset and, in some cases, severe enough to result in airway compromise. The safety and efficacy of InductOs in cervical spine surgery have not been established and InductOs should not be used in this condition.

Formation of fluid collections (pseudocysts, localised oedema, implant site effusion), sometimes encapsulated, in some cases resulting in nerve compression and pain has been reported in patients undergoing spine surgery associated with the use of rhBMP-2/ACS. Many of these reports have occurred when rhBMP-2/ACS was used in unapproved approaches/devices or in a manner inconsistent with the instructions for use. Clinical intervention (aspiration and/or surgical removal) may be required if symptoms persist (see section 4.8).

There are no data on the efficacy and safety of the product in concomitant use with bone graft. In the absence of any experience, the repeated use of the medicinal product is not recommended.

InductOs can cause initial resorption of surrounding trabecular bone. Therefore, in the absence of clinical data, the product should not be used for direct applications to trabecular bone when transient bone resorption may create a risk of bone fragility. When InductOs was used with the LT-CAGE device (section 4.2) in clinical trials for anterior lumbar spine fusion, the frequency and severity of resorption of bone as evidenced by radiolucencies and/or device migration was similar to that observed for patients treated with autogenous bone graft.

Use of InductOs may cause heterotopic ossification in the surrounding tissues, which can result in complications. Exuberant bone formation at the site of implantation and ectopic bone formation have been observed.

The safety and efficacy of the use of InductOs in patients with known autoimmune disease, including rheumatoid arthritis, systemic lupus erythematosus, scleroderma, Sjögren's syndrome and dermatomyositis/polymyositis have not been established.

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 or renal impairment.

Both dibotermin alfa and bovine Type I collagen have been found to elicit immune responses in patients.

Anti-dibotermin alfa antibodies: In anterior lumbar spine fusion studies, 0.7% of patients receiving InductOs developed antibodies vs 0.8% of patients receiving autogenous bone graft. In acute tibia fracture studies, 4.4% of patients receiving InductOs developed antibodies vs 0.6% in the control group.

Anti-bovine Type I collagen antibodies: In anterior lumbar spine fusion studies, 19% of patients receiving InductOs developed antibodies to bovine Type I collagen vs. 13% of patients receiving autogenous bone graft. In acute tibia fracture studies,15.7% of patients receiving InductOs developed antibodies to bovine Type I collagen vs. 11.8% of control patients. In either of the 2 indications, no patients who tested positive for anti-bovine Type I collagen antibodies developed antibodies to human Type I collagen.

Although no clear 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. Special consideration of risks and benefits should be given for patients who have previously received injectable collagen (see section 4.3). The possibility of an immune response to the product should be evaluated in cases where an undesirable effect with immunological background is suspected.

Special warnings and precautions for use specific to anterior lumbar spine fusion

The safety and efficacy of InductOs used with spinal implants other than the LT-CAGE device, implanted at locations other than L_4-S_1 in the lower lumbar spine, or used in surgical techniques other than anterior open or anterior laparoscopic approaches have not been established. When degenerative disc disease was treated by a posterior lumbar interbody fusion procedure with cylindrical threaded cages and dibotermin alfa, posterior bone formation was observed in some instances.

Nerve compression associated with ectopic bone formation and InductOs use has been reported. Additional surgical intervention may be required.

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 hemostasis (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).

InductOs does not provide mechanical stability and should not be used to fill space 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.

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 effect. In preclinical studies, concurrent administration of glucocorticoids depressed bone repair (measured as a % change from control), but the effects of InductOs were not altered.

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.

4.6 Pregnancy and lactation

Pregnancy
There are no adequate data from the use of dibotermin alfa in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

Animal studies have been conducted that cannot rule out effects of anti-dibotermin alfa antibodies on embryo-foetal development (see section 5.3). Due to the unknown risks to the fetus associated with the potential development of neutralising antibodies to dibotermin alfa, InductOs should not be used during pregnancy unless clearly necessary (see section 4.4). Women of childbearing potential should be advised to use effective contraception up to at least 12 months after treatment.

Lactation

It is unknown whether dibotermin alfa is excreted in human breast milk. The excretion of dibotermin alfa has not been studied in animals. Lactation is not recommended during treatment with InductOs.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed, but since InductOs has no systemic effect, it is not likely to interfere with the ability to drive or use machinery.

4.8 Undesirable effects

Over 1490 patients have been evaluated in clinical studies, of which more than 955 received InductOs treatment. In the long bone fracture studies, over 418 patients received InductOs. In the anterior lumber spine fusion studies, over 288 patients received InductOs.

There have been post-marketing reports of localised oedema in patients undergoing cervical spine surgery associated with the use of InductOs. The oedema was delayed in onset and, in some cases, severe enough to result in airway compromise (see section 4.4).

There have been post-marketing reports of formation of fluid collections (pseudocysts, localised oedema, implant site effusion), sometimes encapsulated, in some cases resulting in nerve compression and pain in patients undergoing spine surgery with rhBMP-2/ACS (see section 4.4).

Placement of InductOs can cause initial resorption of trabecular bone (see section 4.4 and section 5.1).

Undesirable effects specific to use in anterior lumbar spine fusion
The undesirable effects observed in anterior lumbar spine fusion patients were generally representative of the morbidity associated with spine fusion using autogenous bone graft taken from the iliac crest.

Very common (≥1/10) undesirable effects: accidental injury, neuralgia, back pain and bone disorder, were similar in both control and InductOs treatment groups.

Nerve compression associated with ectopic bone formation has been reported in patients undergoing spine surgery with InductOs (see section 4.4).

Undesirable effects specific to use in acute tibia fractures

The undesirable effects observed in long bone fracture patients were generally representative of the morbidity associated with either orthopaedic trauma or the surgical procedure.

Very common (≥1/10) undesirable effects were similar in both control and InductOs treatment groups, with two exceptions: localised infection and pain in extremity (both specific to the fractured limb) were observed more frequently in the control group than in the InductOs treatment group.

Common (≥1/100 to <1/10) undesirable effects were observed with equal incidence in control and InductOs treatment groups, with four exceptions: blood amylase increased (without overt signs of pancreatitis in InductOs treated patients), tachycardia, hypomagnesemia and headache were observed significantly more frequently in the InductOs treatment group than in the control group.

4.9 Overdose

Use of InductOs in patients undergoing cervical spine surgery in concentrations or amounts greater than those recommended in section 4.2 for the approved indications has been associated with reports of localised oedema (see section 4.4).

In the case of patients receiving concentrations or amounts greater than those recommended, treatment should be supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 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 center until the entire InductOs implant is replaced by trabecular bone.

Remodeling of the surrounding trabecular bone occurs in a manner that is consistent with the biomechanical forces placed on it. Placement of InductOs into trabecular bone resulted in transient resorption of the bone surrounding the implant, followed by replacement with new, more dense bone. 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, preclinical studies have indicated that the bone induced by InductOs, if fractured, can repair itself in a manner indistinguishable from native bone.

Preclinical 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 preclinical studies indicate that there is a negative feedback mechanism at the molecular level that limits bone induction by BMPs.

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.

<u>Pharmacodynamic information specific to anterior lumbar spine fusion studies</u>

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 the LT-CAGE Lumbar Tapered 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. The success rate for radiologically determined fusion was 94.4% versus 88.9% (95% two-sided CI of the difference: -1.53, 12.46) for InductOs and autogenous bone graft, respectively. For pain and disability (Oswestry score), the success rate was 72.9% versus 72.5% (95% two-sided CI of the difference: -11.2, 12.0). A single, multi-component endpoint, known as overall success was the primary variable of the study. Overall success consists of the following primary efficacy and safety considerations:

1. Radiographically demonstrated fusion
2. Oswestry pain/disability improvement
3. Maintenance or improvement in neurological status
4. No Grade 3 or 4 adverse event classified as implant-associated or implant-/surgical procedure associated
5. No additional surgical procedure performed that was classified as a "failure"

At 24 months post-operation, the overall success rate was 57.5% versus 55.8% (95% two-sided CI of the difference: -10.72, 14.01) for InductOs and autogenous bone graft, respectively.

An additional, non-comparative study of 134 patients who received anterior lumbar interbody fusion procedures via a laparoscopic surgical technique yielded similar success rates of 92.9%, 85.6% and 90.3% for fusion, pain and disability, and neurological status, respectively. The study confirmed the applicability of anterior lumbar spine fusion using InductOs via laparoscopic surgical implantation techniques.

<u>Pharmacodynamic information specific to acute tibia fracture studies</u>

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).

In the subgroup of patients who received reamed IM nail fixation, InductOs was not observed to reduce the rate of secondary intervention. However, statistically significant differences in favour of InductOs were observed for some of the secondary efficacy variables (i.e. acceleration of the rate of fracture and soft tissue healing, and reduction of the rate of hardware failure).

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). Moreover, patients with Gustilo III fractures treated with InductOs 1.5 mg/ml had significantly less infections of the limb studied.

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% vs. 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% vs. 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 on conventional studies of pharmacology, acute and repeat exposure toxicity.

In reproductive toxicity studies in rats, where dibotermin alfa was administered intravenously to maximize systemic exposure, increased fetal weight and increased fetal 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-BMP-2 antibodies. In some fetuses with decreased body weights there were decreases in ossification of frontal and parietal bones (4 out of 151 fetuses), which is generally considered to be reversible, and antibody related effects could not be ruled out. There were no other alterations in fetal external, visceral, or skeletal morphology. Other animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, maternal toxicity, embryolethality, or fetotoxicity.

InductOs has not been tested for in vivo carcinogenicity. Dibotermin alfa has demonstrated variable effects on human tumour cell lines in vitro. Although the available in vitro data suggest a low potential for promotion of tumour growth, the use of InductOs is contraindicated in patients with an active malignancy or in patients undergoing treatment for a malignancy (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. The significance of these data for humans is not known.

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

InductOs must not be mixed with other medicinal products except those listed in section 6.6.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at 15°C to 30°C. Store in the original package.

6.5 Nature and contents of container

Each kit of InductOs is provided with:

- 12 mg sterile dibotermin alfa powder in a 20 ml vial (Type I glass) stoppered with a bromobutyl rubber closure sealed with an aluminum flip-off seal and plastic cap.
- solvent for reconstitution in 10 ml vial (Type I glass) stoppered with a bromobutyl rubber closure sealed with an aluminum flip-off seal and plastic cap.
- one sterile matrix in a polyvinyl chloride (PVC) blister package sealed with a Tyvek lid.
- 2 sterile 10 ml disposable polypropylene syringes.
- 2 sterile needles (stainless steel).

6.6 Special precautions for disposal

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

Dibotermin alfa must be used only with the accompanying solvent and matrix provided in the InductOs kit. See section 4.2.

7 MARKETING AUTHORISATION HOLDER

Wyeth Europa Ltd.
Huntercombe Lane South
Taplow, Maidenhead
Berkshire, SL6 0PH
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

EU/1/02/226/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9 September 2002

10 DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency (EMEA) http://www.emea.europa.eu