European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

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ASSESSMENT REPORT FOR INDUCTOS

International non-proprietary name: dibotermin alfa

Procedure No: EMEA/H/C/000408/II/0036

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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I. INTRODUCTION

InductOs contains dibotermin alfa. The preparation is an integral osteoinductive product for periosseous implantation, consisting of dibotermin alfa, a recombinant human Bone Morphogenetic Protein-2 (rhBMP-2), with the accompanying solvent (sterile water) for reconstitution of dibotermin and matrix. The matrix is an Absorbable Collagen Sponge (ACS).

Dibotermin alfa is an osteoinductive protein that results in the induction of new bone 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 and the matrix is degraded, with vascular invasion being 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.

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. InductOs is also indicated for single-level (L4 – S1) 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.

Following the assessment of the six monthly study progress report on study 400 (A Prospective, Randomised, Controlled, Stratified Study of InductOs in Subjects with Open Diaphyseal Tibia Fractures Treated with Reamed Locked Intramedullary Nail Fixation) and the Marketing Authorisation Holder's (MAH's) notification regarding an increased infection rate observed among rhBMP-2/ACS treated patients compared to the standard of care control group, on 16 August 2007 the CHMP requested the MAH to submit a review of infection risk across all indications and a risk minimisation plan concerning infections. Thus, the MAH submitted a cumulative review of infections with the use of rhBMP-2/ACS in all therapeutic indications and proposed to exclude "reamed nail fixation in tibia fractures" from the therapeutic indications of InductOs as part of its risk minimisation activities. Furthermore, the MAH proposed to update sections 4.4 "Special warnings and precautions for use", 4.8 "Undesirable effects" and 5.1 "Pharmacodynamic properties" of the Summary of Product Characteristics (SPC) to include that in a clinical study in subjects with open tibia fractures and treated with reamed nail fixation, an increased rate of infection was observed in the InductOs-treated group. Finally, the MAH proposed to re-order existing statements concerning nerve compression in sections 4.4 and 4.8 of the SPC and to replace the term *rhBMP-2/ACS* with *InductOs* in sections 4.2 and 4.4 of the SPC.

As part of its risk minimisation activities, the MAH proposed to circulate a Direct Healthcare Professional Communication (DHPC) to inform Health Care Professionals about the increased risk of infection in subjects with open tibial fracture treated with reamed nails and rhBMP-2/ACS.

II. CLINICAL ASPECTS

2.1 Risk of infection in other clinical studies of rhBMP-2/ACS in tibial fractures

Study 3100N8-400-WW (study 400) was a multicentre, multinational, prospective, single-blind (subject only), stratified, randomised, open-label, parallel comparison of standard of care (SOC) versus SOC and InductOs. The study population comprises subjects with open tibia shaft fractures requiring reamed, statically locked intramedullary (IM) nail fixation. Following definitive fracture fixation with a reamed IM nail, 300 subjects will be randomly assigned to receive either InductOs, to be implanted at the time of definitive coverage, or standard of care, routine wound closure. This study showed an increased infection rate associated with the use of the products (19.0% *vs* 9.0%, difference 10% with a 95% CI 2 – 19%).

Three studies of rhBMP-2/ACS have been performed in subjects with open tibial fractures in which unreamed and reamed IM nails for definitive fracture reduction were used. These studies were shortly presented below:

- Studies C9530-11 and C9612-11 were conducted to evaluate the effect of rhBMP-2/ACS in subjects with open tibia fractures using either reamed or unreamed IM nails, compared to standard soft tissue and bone care without rhBMP-2/ACS (SOC). In Study C9530-11, the overall difference in the risk of infection between the SOC and the rhBMP-2/ACS treatment groups (comparing those with reamed nails with the total (reamed + unreamed) was –0.14 (95% CI, -0.30 to 0.03; two-sided Fisher exact test, p=0.0896). In Study C9612-11 the overall difference in the risk of infection between SOC and rhBMP-2/ACS treatment groups was -0.01 (95% CI, -0.25 to 0.22; two-sided Fisher exact test, p=1.0000). Although the risk of infection was lower in the rhBMP-2/ACS groups in both studies, the difference was not statistically significant.
- In study C9828-11, conducted to evaluate external skeletal fixation of open tibia fractures without (SOC) or with rhBMP-2/ACS, the overall difference in the risk of infection between SOC and rhBMP-2/ACS treated subjects was –0.06 (95% CI, -0.26 to 0.13; two-sided Fisher exact test p=0.5459). Again, there was no significant difference in the risk of infection between the SOC and rhBMP-2/ACS treated groups.

The MAH presented a pooled data analysis of the studies described above, including study 400. No significant difference in the rate of infections between patients treated with rhBMP-2/ACS and other treatment groups was observed. The overall difference in the risk of infection between control and rhBMP-2/ACS treated patients was –0.01 (95% CI, -0.06 to 0.05; two-sided Fisher's exact test p=0.8719). The MAH performed an additional analysis, using only data from patients with open tibia fractures treated with IM nails, no difference was found in the rate of infections between treatment groups. The overall difference in the risk of infection between standard of care and rhBMP-2/ACS treated subjects was 0.02 (95% CI, -0.03 to 0.08; two-sided Fisher exact test, p=0.4564).

2.2 Infections with use of rhBMP-2/ACS in tibial fractures, in the MAH pharmacovigilance database

The MAH performed a search in their Pharmacovigilance database up to 8 September 2007. In total, 88 reports of infection in patients with tibial fractures, 77 of which were surgical site infections, were reported in temporal association with InductOs. All reports were received from clinical trials conducted by the MAH, most involving open tibial fractures. A variety of organisms were identified; *Staphylococcus* was the most common genus. Twenty-eight infections were reported within one month of receiving the product, and 48 were reported later.

The MAH stated that in literature (Bowen TR, Widmaier JC. Host classification predicts infection after open fractures. Clin Orthop Relat Res. 2005; 433:205-11) it was shown that the occurrence of infections in open tibial fractures treated without rhBMP-2/ACS was twice that observed for open fractures at other locations, at least partly related to the likelihood of contamination during injury.

2.3 Review of infections with use of rhBMP-2/ACS in other indications

The MAH has reviewed all available information for the spinal indications from clinical studies and from the pharmacovigilace database.

Spinal indications: clinical studies

In 2 of 4 clinical studies of rhBMP-2/ACS use in anterior lumbar interbody fusion and in a single study of posterolateral lumbar fusion, the rate of infections was lower in the rhBMP-2/ACS treated group than in those subjects who did not receive this product. In the remaining 2 studies of rhBMP-2/ACS involving anterior lumbar interbody fusion (ALIF) and in a single study with posterior interbody lumbar fusion (PLIF), there was no significantly increased risk of infection in the rhBMP-

2/ACS treated subjects. A total of 796 patients were treated with rhBMP-2/ACS in these clinical studies. In ALIF, infection rates ranged from 5.9% to 12.7% in rhBMP-2/ACS treated subjects vs. 7.0% to 11.8% of those not treated with this product. In the small (34 subjects, 33 controls) PLIF study, the infection rate was 20.6% in the rhBMP-2/ACS treated group and 15.2% in controls; the Posterolateral Lumbar Fusion Study (25 subjects, 21 controls) demonstrated an infection rate of 16% in the treated group and 23.8% in the controls.

Spinal indications: pharmacovigilance database

A cumulative review was performed of all reports of infection with use of rhBMP-2/ACS submitted to the MAH safety database through 8 September 2007. This review included all reports (spontaneous and study) received by the MAH. A total of 166 reports of infections were received, 117 of which were local (i.e. occurring at the surgical site), 44 non-local, and 5 indeterminable. There were 68 reports of infection when rhBMP-2/ACS was used for spinal surgery; 49 of these were from sponsored clinical studies. Of the 39 surgical site infections, 22 were early-onset, 10 were late-onset, and 7 were indeterminable. Positive bacterial cultures were reported in 13 patients, with Staphylococcus the most common identified organism. Post-operative spinal wound infections occur in approximately 1-12% of patients overall, with Staphylococcus aureus the most commonly identified organism.

Dental-Craniofacial Procedures: clinical studies

In all maxillary sinus studies, sinusitis was reported as an adverse event. The incidence ranged from 11-17% in the rhBMP-2/ACS treatment groups and 13-38% in the bone graft treatment groups. In the 2 comparative studies the difference in incidence of infection between the rhBMP-2/ACS and control treatment groups was not statistically significant.

Dental-Craniofacial Procedures: pharmacovigilance database

Local infection has been reported in one patient, who received rhBMP-2/ACS for dental implantation.

2.4 Proposed Risk Minimisation Activities

The MAH initially halted enrolment in study 400 pending the outcome of Clinical Safety Review Team assessment. When this assessment was unable to explain the difference in infection rates between rhBMP-2/ACS-treated subjects and controls, enrolment in study 400 was terminated.

The MAH proposed to exclude “reamed nail fixation” from the indication to use InductOs in open tibial fractures and to revise the SPC to include information regarding the increased risk of infection observed in study 400.

The MAH also proposed the circulation of a DHPC informing orthopaedic practitioners about the increased risk of infection observed in subjects with open tibial fracture treated with reamed nails and rhBMP-2/ACS in study 400. The DHPC will also highlight the change in indication for treatment of open tibial fractures with rhBMP-2/ACS, for use with unreamed (not reamed) nails.

The MAH will continue to closely monitor reports of infection with use of rhBMP-2/ACS received from both study and spontaneous sources. Monitoring includes review of Individual Case Safety Reports as received as well as weekly review; aggregate review of adverse events is performed monthly to determine trends in reporting. Cumulative reviews of specific adverse events will be performed as appropriate.

2.5 Discussion

From the analysis of the studies in subjects with open tibial fractures, the CHMP noted that the rate of infection between the treatment groups and the standard of care group was comparable (differences in infection rate respectively -0.01 and 0.02; both not significant). The CHMP also noted that the analysis was not stratified according to the nails which were used (reamed or unreamed) and therefore from these data no conclusion about difference in the infection rate between reamed and unreamed nails

could be drawn. Nevertheless, the CHMP stratified the results according to reamed or unreamed nails in the table below and noted that whatever the type of nail, the infection rate was fairly consistent with InductOs (around 20%) whereas it differed with SOC (lower rate for reamed than unreamed). The excess of infections for reamed IM nails with InductOs was only driven by the results of study 400, in which no patients were treated with unreamed IM nails; previously there had been evidence of an excess of infections for reamed IM nails on SOC.

	SOC		InductOs (all doses)	
	Reamed	Unreamed	Reamed	Unreamed
Study C9530-11 (21%)	14/41 (34%)	25/109 (23%)	22/108 (20%)	41/192
Study C9612-11	1/10 (10%)	2/9 (22%)	2/18 (11%)	4/22 (18%)
Study 400-WW	12/135 (9%)		26/135 (19%)	
Pooled data (21%)	27/186 (15%)	27/118 (23%)	50/261 (19%)	45/214

The CHMP highlighted that the MAH has not presented a comprehensive discussion on the plausibility of differences in incidence of infections between reamed and unreamed nails or of the influence of InductOs. As there may be a concern if the data from study 400 indicate absence of efficacy with reamed nails, evidence of efficacy for use with unreamed nails may be questioned. Thus, the CHMP requested the MAH to commit to provide efficacy from study 400 data as soon as available, even if results are preliminary, and to submit a benefit/risk assessment including all data which are currently available.

The CHMP noted that the MAH received spontaneous reports concerning infection and should provide additional information on these cases. The MAH should continue the close monitoring of infections and discuss this on a yearly basis in the PSUR.

Up to 8 September 2007, 88 reports of infections have been reported to the MAH. At the time of the renewal (June 2007 CHMP plenary meeting), 74 spontaneous cases were reported (74 reports / 52 months = 1.4 report per month). In the period from the renewal until 8 September 2007, 14 additional cases were reported (14 / 9 =1.6). This number is in line with the number reported in the period before the renewal. However, no information about these cases has been provided by MAH. Also no information is provided about the nails which have been used in these cases (reamed or unreamed). Thus the CHMP requested that the MAH should discuss the 14 additional cases in the next PSUR.

Based on the review of infections in clinical studies in spinal indication, the rate of infection in the treatment groups compared to the rate of infection in the standard of care group was lower. However, in the analysis of the MAH, a comparison was made between the infection rate of the two treatment groups *vs* the standard of care group.

Up to 8 September 2007, 39 reports of surgical site infections have been reported to the MAH. At the time of the renewal, 38 spontaneous cases were reported. In the period from the renewal until 8 September 2007, 1 additional case was reported (14 / 9 =1.6). This number is in line with the number reported in the period before the renewal. Thus, the CHMP requested that the MAH should discuss this case in the next PSUR.

With regard to the change of the therapeutic indication, the CHMP highlighted that in one of the main studies performed before registration of InductOs (C9530-11), both the protocol defined and post hoc analyses (requested by the CPMP) suggested that the clinical benefit was mainly observed in patients who receive unreamed IM nail. Since this study was not powered for subgroup analyses, the MAH committed to conduct a controlled, randomised clinical trial of InductOs (plus standard care) versus standard care in patients treated with reamed IM nails (study 400). In study 400, an increased infection rate associated with the use of the products, was observed (19.0% *vs* 9.0%, difference 10% with a 95%

CI 2 – 19%). The overall efficacy of patients treated with InductOs in combination with reamed nails, compared to SOC group, was comparable. However, the efficacy was lower among patients with an infection (both treatment and SOC) compared to patients without infection. Already before registration, a clinical trial showed that 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). Thus, the proposed change of the indication to exclude "reamed nail fixation in tibia fractures" was considered acceptable by the CHMP.

Finally, considering that no new data on efficacy and infection rate with unreamed intramedullary nail fixation have become available, the CHMP recommended that the MAH should monitor the infection rate for InductOs used with unreamed intramedullary nail fixation and discuss it on a yearly basis in the PSUR.

2.6 Conclusion

The CHMP concluded that the number of cases regarding infection, received by the MAH since the renewal, was in line with the number of reported cases in the period up to the renewal. No information on the nails which have been used in these cases (reamed or unreamed) has been provided. The CHMP concluded that the MAH should discuss the 14 additional cases in the next PSUR. In addition, the MAH should discuss the additional case of infection in spinal surgery in the next PSUR. Furthermore, the CHMP concluded that the MAH should continue the close monitoring of infections and discuss this on a yearly basis in the PSUR.

The CHMP concluded that the risk minimisation activities were currently considered to be sufficient. Nevertheless, the MAH should continue to closely monitoring infections and discussing this on a yearly basis in the PSUR. The CHMP agreed with the DHPC together with the action plan for its distribution as proposed by the MAH.

The CHMP highlighted that the excess of infections for reamed IM nails with InductOs is only driven by the results of study 400, that the number of patients included in study 400 was higher compared to the numbers in study C9530-11, and that the difference in infection rate between the two groups was found to be significant. Thus, the CHMP concluded that the change of the therapeutic indication of InductOs to exclude "reamed nail fixation in tibia fractures" was adequate.

The CHMP requested the MAH to submit a benefit/risk assessment including all data which are currently available.

Finally the CHMP requested the MAH to provide the efficacy data of study 400 as soon as possible, even if the results are preliminary, to enable a full benefit/risk assessment.

The CHMP agreed to the changes to the Product Information as outlined in section III "CHANGES TO THE PRODUCT INFORMATION" of this discussion.

III. CHANGES TO THE PRODUCT INFORMATION

The CHMP agreed to exclude "reamed nail fixation in tibia fractures" from section 4.1 of the SPC and to include in section 4.4 of the SPC information on the increased rate of infection observed in the InductOs-treated group versus the standard of care control group in reamed nail fixation. The CHMP also agreed with the MAH's proposal to re-order existing statements on nerve compression in sections 4.4 and 4.8 of the SPC and to replace the term "*rhBMP-2/ACS*" with "*InductOs*" in sections 4.2 and 4.4 of the SPC in order to facilitate the translation in different languages.

With regard to section 4.8 of the SPC, the CHMP noted that it was not acceptable to include a statement to describe adverse events "being observed more frequently in the control group than in the InductOs treatment group". Thus, the CHMP recommended the deletion of the sentence related to pain in extremity which was observed more frequently in the control group than in the InductOs treatment group. The CHMP also requested to include a sentence in this section to highlight that for use with unreamed nails, estimated rates of infection were similar between treatment groups in a study (21% versus 23% respectively).

With regard to the MAH's proposal for section 5.1 of the SPC, the CHMP recommended to delete the information on infections in patients with open tibia fracture treated with reamed intramedullary nails. The CHMP agreed with the MAH's proposal to delete the sentence related to patients with Gustilo III fractures treated with InductOs. The CHMP requested to delete the following paragraph from section 5.1 of the SPC: "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)." Finally, the data regarding the infection rate should not be repeated again in section 5.1 of the SPC.

The MAH agreed to amend the SPC as recommended by the CHMP and submitted a revised document.

The MAH took also the opportunity to update the contact details of the German local representative in the Package Leaflet.

IV. CONCLUSION

On 24 April 2008 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics and Package Leaflet.