InductOs

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
II/0100	C.I.11.b - Submission of an updated RMP version 2.1 in order to submit the final study report from study EUPAS32916 listed as category 3 study in the RMP. This is an observational study to evaluate the effectiveness of additional Risk Minimisation Measures for InductOs.	02/09/2021		SmPC	Study EUPAS32916 is a cross-sectional study to evaluate the effectiveness of additional Risk Minimisation Measures: A survey among 55 physicians to assess their knowledge and understanding of selected risks of InductOs in Europe. Based on the results of this study and having the limitation of the study in mind, it has been concluded that physicians

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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	In addition, the MAH took the opportunity to submit study protocol for study EUPAS32916 that was agreed by PRAC and to update section 4.4 of the SmPC to add the traceability statement for biological medicinal products. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				are not fully aware of the risk of medication errors, incorrect use, and heterotopic ossification and the risk minimization measures to prevent these risks. In addition, the majority of the physicians did not use dibotermin alfa on a regular basis, and did use (always, frequently or sometimes) the educational material (82%) to obtain information on these risks. Therefore, it has been concluded that the educational material should remain in place and actions taken to increase awareness with physicians on the existence of the educational materials and simplify the access to the materials. In addition, the study status of EUPAS32916 to evaluate the effectiveness of additional Risk Minimisation Measures in the RMP has been changed from ongoing to completed. The Annex IID text and the reference to the educational materials in section 10 have been maintained. For more information, please refer to the Summary of Product Characteristics.
PSUSA/1034/ 202009	Periodic Safety Update EU Single assessment - dibotermin alfa	06/05/2021	n/a		PRAC Recommendation - maintenance
IB/0098	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	06/12/2019	n/a		
IB/0097	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	18/06/2019	n/a		

II/0093	B.I.a.3.c - Change in batch size (including batch size ranges) of AS or intermediate - The change requires assessment of the comparability of a biological/immunological AS	24/01/2019	n/a		
IB/0096	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	20/11/2018	n/a		
IA/0095	B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits	09/11/2018	n/a		
IB/0094	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	05/11/2018	n/a		
IA/0092/G	This was an application for a group of variations. B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test	05/10/2018	n/a		
IA/0090	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or	17/08/2018	08/08/2019	Annex II	

	manufacturer of a novel excipient				
IB/0091	B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation	15/08/2018	n/a		
PSUSA/1034/ 201709	Periodic Safety Update EU Single assessment - dibotermin alfa	12/04/2018	n/a		PRAC Recommendation - maintenance
IA/0089	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	21/02/2018	n/a		
IA/0087	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	10/08/2017	n/a		
IA/0086/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch	23/06/2017	n/a		

	control/testing takes place				
IB/0085	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	06/04/2017	31/05/2017		
A20/0082	Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 23 July 2015 the opinion of the European Medicines Agency further to the statement of GMP non-compliance for the manufacturing site of the absorbable collagen sponge. The CHMP was requested to assess the impact thereof on the benefit-risk balance of InductOs and to give its recommendation whether the marketing authorisation of this product should be maintained, varied, suspended or revoked.	22/10/2015	20/11/2015		Please refer to the assessment report: InductOs EMEA/H/A-20/1422/C/0408/0082
IB/0083	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	08/10/2015	n/a		
II/0079	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	23/07/2015	n/a		
IAIN/0081	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV	16/07/2015	n/a		

	(including contact details) and/or changes in the PSMF location				
II/0078/G	This was an application for a group of variations. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	25/06/2015	n/a		
II/0077	B.II.e.5.c - Change in pack size of the finished product - Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/immunological medicinal products	25/06/2015	10/11/2015	SmPC, Labelling and PL	
IB/0080	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	13/04/2015	n/a		
PSUSA/1034/ 201409	Periodic Safety Update EU Single assessment - dibotermin alfa	10/04/2015	n/a		PRAC Recommendation - maintenance
II/0071	Extension of the indication to broaden (anatomically)	20/11/2014	19/12/2014	SmPC, Annex	Please refer to the scientific discussion

	the use of InductOs in 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 in the treatment of adults. Consequently, sections 4.1, 4.2, 4.8, 4.9 and 5.1 of the SmPC have been updated. Further, SmPC section 4.4 has been updated with warnings related to type of surgery, device and spinal level, and sections 4.4, 4.5, 4.6, 5.1 and 5.3 of the SmPC based on supportive non-clinical and clinical data relating to immunogenicity, tumorigenicity or fusion success. The Package Leaflet was updated accordingly. Furthermore, the standard term has been updated from "kit for implant" to "powder, solvent and matrix", and the expression of the strength changed from “12mg” to “1.5 mg/ml” throughout the SmPC, labelling and Package leaflet. In addition, the MAH took the opportunity to implement the latest QRD template (version 9.0) and to make editorial changes throughout the annexes. A revised RMP version 2 was agreed as part of the procedure. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one			II, Labelling and PL	EMA/H/C/0408/II/71 for further information.
IB/0074	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting	17/12/2014	n/a		

	material/intermediate				
IB/0075/G	This was an application for a group of variations. B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	05/12/2014	n/a		
IAIN/0073	C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV and/or QPPV contact details and/or back-up procedure	27/06/2014	n/a		
N/0072	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/04/2014	14/05/2014	PL	
IAIN/0070	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	07/03/2014	n/a		
IB/0069	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	28/01/2014	n/a		
IB/0068	B.I.a.1.z - Change in the manufacturer of AS or of a	08/08/2013	n/a		

	starting material/reagent/intermediate for AS - Other variation				
IB/0067	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	25/06/2013	n/a		
IB/0066	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/04/2013	14/05/2014	SmPC, Annex II and PL	Update of Annex II of the product information to bring in line with the QRD template (version 8.3) and update of Sections 3 and 6 of the Package Leaflet following a recommendation from the CHMP of the PIL user test. The MAH also took the opportunity to correct typographical errors in the EL, EN, DE, FI, FR, and LT product information.
IB/0065	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	31/01/2013	n/a		
IB/0064	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	31/01/2013	n/a		
R/0062	Renewal of the marketing authorisation.	24/05/2012	20/07/2012		Based on the review of the available information, the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers the benefit/risk profile of InductOs continues to be favourable. The CHMP is also of the opinion that the renewal can be granted with unlimited validity.

IAIN/0063	C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV	03/04/2012	n/a		
IB/0060	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	30/01/2012	n/a		
II/0058	Introduction of a new Detailed Description of the Pharmacovigilance System (DDPS). C.I.8.a - Introduction of a new Pharmacovigilance system - which has not been assessed by the relevant NCA/EMA for another product of the same MAH	17/11/2011	17/11/2011		With this variation the MAH submitted a new version of the DDPS (version 3.0) in accordance with the current Pharmacovigilance guideline. After assessing the documentation the CHMP concluded that the submitted DDPS contained all required elements. The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.
IA/0059/G	This was an application for a group of variations. B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	28/10/2011	31/01/2012	Annex II and PL	

T/0057	Transfer of Marketing Authorisation	18/07/2011	05/08/2011	SmPC and PL	
WS/0117	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.8.b - Introduction of a new Pharmacovigilance system - which has been assessed by the relevant NCA/EMA for another product of the same MAH	14/04/2011	15/06/2011	Annex II	
II/0056/G	This was an application for a group of variations. Change in the test method for active substance and finished product. B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS B.II.d.2.c - Change in test procedure for the finished product - Replacement of a biological/ immunological/immunochemical test method or a method using a biological reagent	17/02/2011	07/03/2011		
II/0054/G	This was an application for a group of variations. - Changes in the manufacturing process of the active substance. - Change in source of an excipient or reagent with TSE risk.	16/12/2010	21/12/2010		

	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol B.II.c.3.a.2 - Change in source of an excipient or reagent with TSE risk - From TSE risk material to vegetable or synthetic origin - For excipients or reagents USED in the manufacture of a biol/immunol AS or in a biol/immunol medicinal product				
II/0053	Change in the manufacturing process of the active substance. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol	18/11/2010	29/11/2010		
II/0051/G	This was an application for a group of variations. B.I.b.2.d. Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance. Chenge (replacement) to a biological/immunological/immunochemical test method or a method using a biological reagent for a biological active substance. B.II.d.2.c. Change in test procedure for the finished product. Replacement of a bioligical/immunological//immunochemical test	21/10/2010	29/10/2010		

	method or a method using a biological reagent. B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS B.II.d.2.c - Change in test procedure for the finished product - Replacement of a biological/ immunological/immunochemical test method or a method using a biological reagent				
IB/0052/G	This was an application for a group of variations. Change in the shelf-life or storage conditions of the finished product. Change in the specification parameters and/or limits of the finished product . B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter	24/09/2010	n/a		
II/0044	Update of Section 4.4 of the SmPC to recommend not administering dibotermin alfa in patients with history or clinical suspicion of malignancy at the site	22/07/2010	31/08/2010	SmPC and PL	Dibotermin alfa (rhBMP-2) is a differentiation factor, which functions as an inducer of bone and an effector of bone remodeling. The PK of rhBMP-2 suggests minimal

	of application. In addition the MAH took the opportunity to add the adverse event "radiculitis" in section 4.8 of the SmPC based a cumulative review of cases of radiculitis. The package leaflet is updated accordingly. The contact details of all local representatives are also updated in the package leaflet. Update of Summary of Product Characteristics and Package Leaflet				circulating rhBMP-2 after local application, making a systemic effect unlikely. In vitro and in vivo studies with rhBMP-2 on malignant cell lines have not demonstrated a potentiating effect. Two spontaneous reports of malignancy at or near the site of rhBMP-2implantation have been investigated. In both cases, rhBMP-2 was used for unapproved indications. In one report, the patient had chemotherapy and radiation treatment for malignancy and malignancy recurrence, which are more likely alternative explanations for the development of osteosarcoma. In the second report, incomplete historical information is available making interpretation of causality difficult to establish. There were no other reports of malignancy developing at or near the site of implantation of rhBMP-2. Furthermore, a review of all postmarketing cases of malignancies where a patient with a history of malignancy was treated with rhBMP-2 and subsequently developed a malignancy identified ten reports (including the two reports mentioned before) describing 9 patients who developed cancer after rhBMP-2 treatment and who had a history of cancer. Based on the cases presented the contributory role rhBMP-2 cannot be excluded. InductOs is already contraindicated for patients with any active malignancy or patient undergoing treatment for a malignancy. Nevertheless, as precautionary measure physicians should be advised that InductOs should not be used in patients with history or clinical suspicion of malignancy at the site of application. A cumulative search of the MAH's safety database through 26 June 2009 reported 113 reports (67 spontaneous and 46 study) describing events of radicular pain following rhBMP-2 use in various surgical approaches that included anterior lumbar interbody fusion, cervical

					fusion/laminectomy/decompression, posterior/postero
II/0047	To introduce a change to the viral filtration step of the active substance manufacturing process. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol	20/05/2010	01/06/2010		
IB/0048	C.I.8.b - Introduction of a new Pharmacovigilance system - which has been assessed by the relevant NCA/EMA for another product of the same MAH	06/05/2010	n/a	Annex II	
IB/0049	To change the conditions for the diluent preparation. B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	26/04/2010	n/a		
IB/0046/G	This was an application for a group of variations. B.I.b.z - Change in control of the AS - Other variation B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	13/04/2010	n/a		
II/0041	Update of section 4.4 and 4.8 of the SmPC to include a warning about device migration and its associated risks reported with the use of dibotermin alfa. The	18/02/2010	26/03/2010	SmPC and PL	Reports from the literature, clinical trials (range 0- 1.4%) and postmarketing use (24 cases) of dibotermin alfa (rhBMP-2/ACS) showed that device migration (movement

	Package leaflet was updated accordingly. In the Package leaflet the contact details of the local representative for Austria, Czech Republic, Germany, Greece, Portugal, Slovak Republic and Spain are updated. The MAH also took the opportunity to make minor typographical changes to improve clarity and consistency in the SmPC and Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet				of the metal cage from the initial surgical placement) can occur after the use of rhBMP 2/ACS in spinal fusion surgery. In some cases device migration may necessitate a surgical revision. The vast majority of cases concerned off-label use (including unapproved surgical approach, devices and/or concomitant therapies) nevertheless there is reasonable suspicion that the occurrence of device migration may be causally related to dibotermin alfa. Review of AEs associated with device migration showed that most cases reported were "cyst like structures" and "bone resorption". These undesirable effects, already listed in the current SmPC, could predispose to the device migration. As such, they also have been reported in section 4.8 as being in some cases associated with the device migration.
II/0043	To change the specification and method of analysis for the active substance and the finished product. Update of or change(s) to the pharmaceutical documentation	18/02/2010	01/03/2010		
IB/0042	IB_19_a_Change in specification of an excipient - tightening of specification limits	14/12/2009	n/a		
II/0040	Replacement of the method for identity testing of drug substance and drug product. The specifications remain unchanged. Change(s) to the test method(s) and/or specifications for the active substance Change(s) to the test method(s) and/or	23/07/2009	12/08/2009		

	specifications for the finished product				
II/0039	Change in equipment to manufacture the Absorbable collagen sponge. Update of or change(s) to the pharmaceutical documentation	23/04/2009	07/05/2009		
II/0038	Change to the stability testing protocol of the drug substance reference material. Change(s) to the test method(s) and/or specifications for the active substance	18/12/2008	07/01/2009		
II/0037	Change to the storage conditions of manufacturing equipment used during the purification of the active substance. Change(s) to the manufacturing process for the active substance	20/11/2008	25/11/2008		
II/0036	To exclude "intramedullary reamed nail fixation in tibia fractures" from the therapeutic indication. The Marketing Authorisation Holder took the opportunity to update the contact details of the German local representative in the PL. Update of Summary of Product Characteristics and Package Leaflet	24/04/2008	19/06/2008	SmPC and PL	Please refer to the Scientific Discussion "InductOs/H/C/000408/II/0036" for further information.
II/0035	Change(s) to the manufacturing process for the	21/02/2008	03/03/2008		

	active substance				
II/0034	Update of or change(s) to the pharmaceutical documentation	21/02/2008	03/03/2008		
IA/0033	IA_15_b_02_Submission of Ph. Eur. certificate for active substance - new manuf./other substances	25/10/2007	n/a		
IA/0032	IA_15_a_Submission of Ph. Eur. certificate for active substance - approved manufacturer	25/10/2007	n/a		
R/0030	Renewal of the marketing authorisation.	21/06/2007	30/08/2007	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP was of the opinion that the quality, safety and efficacy of InductOs continued to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of InductOs continued to be favourable. From the data that became available since the granting of the initial Marketing Authorisation for InductOs, no new safety issues were identified except for the formation of antibodies in a clinical trial. Therefore, the CHMP concluded that the MAH should continue to closely monitor the formation of antibodies, immune response and neutralising antibodies. Furthermore, the CHMP recommended that the MAH should continue to monitor fluid collections, bone resorption/osteolysis, bone growth, infections, deep vein thrombosis, neurological disorders, malignancies, anaemia, local hypesthesia and heterotopic calcification. Additionally, the CHMP acknowledged that the exposure of InductOs was

					still limited due to its limited marketing. Thus, based upon the safety profile of InductOs, which required the submission of yearly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.
II/0029	Change(s) to the test method(s) and/or specifications for the active substance Change(s) to the test method(s) and/or specifications for the finished product	26/04/2007	10/05/2007		
II/0028	To update sections 4.4 and 4.8 of the SPC, following the assessment of PSUR n 6, to include information on the formation of fluid collections. To update section 4.2 of the SPC to enforce the message to use the correct posology and to follow the instructions for using InductOs in anterior lumbar spine fusion indication. These changes are also reflected in the PL. The MAH completed the list of local representatives in the PL to include the two new EU Member States (Bulgaria and Romania). Moreover, the MAH updated the product information in line with the latest EMEA/QRD template. In addition the MAH took the opportunity to include the name of the MAH in the labelling of the vial solvent. Update of Summary of Product Characteristics, Labelling and Package Leaflet	22/02/2007	29/03/2007	SmPC, Labelling and PL	DDuring the period covered by PSUR n 6 (covering the period from 9 September 2005 to 8 September 2006) formation of fluid collections (pseudocysts, localised oedema, implant site effusion) sometimes encapsulated, in some cases resulting in nerve compression and pain was reported in patients undergoing spine surgery associated with the use of dibotermin alfa/Absorbable Collagen Sponge (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. None of the fluid collections reported occurred in Europe. Therefore, the CHMP concluded that the 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 intervetebral space.

II/0027	Change(s) to the test method(s) and/or specifications for the finished product	22/02/2007	26/02/2007		
IA/0026	IA_21_a_Submission of Ph. Eur. certificate for excipient - from approved manufacturer	20/09/2006	n/a		
IB/0025	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	29/08/2006	n/a		
II/0020	To remove "pregnancy" from section 4.3 and to update sections 4.6 and 5.3 of the SPC to include additional information on formation of antibodies and on pregnancy following new non clinical data. To update section 2 in the PL to reflect the changes introduced in the SPC. Update of Summary of Product Characteristics and Package Leaflet	27/07/2006	28/08/2006	SmPC and PL	The MAH has studied the effect of anti-dibotermin antibodies in a rabbit developmental toxicity study, where pregnant rabbits have been immunised against dibotermin alfa, the active ingredient for InductOs. The findings of this non clinical study indicated that the potential risk of anti-dibotermin antibodies for embryo-foetal development was limited. 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. Therefore section 5.3 "Preclinical Safety Data" of the SPC was updated to include the findings from this non clinical study. As the basis for a contraindication must be provided by clinical data or strong non clinical data, the CHMP concluded that there was no basis for a contraindication of the use of InductOs during pregnancy. Thus, the contraindication for pregnancy was deleted from section 4.3 "Contraindication" of the SPC and replaced by a labelling expressing an advice against the use of InductOs during pregnancy in section 4.6 "Pregnancy and lactation" unless

					clearly necessary. In addition, as antibodies do not disappear immediately section 4.6 of the SPC was updated to include that women of childbearing potential should be advised to use effective contraception up to at least 12 months after treatment.
II/0023	To update sections 4.4 and 4.8 of the SPC to include information on the occurrence of neurological disorders in patients undergoing spine surgery following the CHMP assessment of PSUR n 5 covering the period from 9 September 2004 to 8 September 2005. To address two editorial changes in section 4.4 and 4.9 of the SPC. To update the Annexes in line with the EMEA QRD template version 7.0. Update of Summary of Product Characteristics, Labelling and Package Leaflet	28/06/2006	04/08/2006	SmPC, Annex II, Labelling and PL	During the period covered by PSUR n 5 (from 9 September 2004 to 8 September 2005), nerve compression associated with exuberant and/or ectopic bone formation has been reported in patients undergoing spine surgery with dibotermin alfa/Absorbable Collagen Sponge. Six (6) cases of nerve compression associated with exuberant and/or ectopic bone formation and/or calcification were identified through the period covered by PSUR n 5. In all of these reports, the patient received dibotermin alfa for augmentation of spine fusion surgery. The patients reported symptoms likely to represent neurological complications of excess bone formation (i.e. regional pain or radiculopathy). Therefore the MAH updated section 4.4 "Special warnings and precautions for use" and 4.8 "Undesirable effects" of the SPC to include information on the occurrence of neurological disorders in patients undergoing spine surgery.
II/0024	The marketing authorisation holder introduced new assays to test the Absorbable Collagen Sponge. Quality changes	27/07/2006	01/08/2006		
II/0022	Update of or change(s) to the pharmaceutical documentation Change to the test procedure and/or specification of	27/04/2006	04/05/2006		

	a raw material				
II/0021	Update of section 4.8 of the SPC to add that placement of InductOs can cause initial resorption of the trabecular bone following the review of cases of osteolysis reported in PSUR n 4 covering the period from 9 March 2004 to 8 September 2004. Update of Summary of Product Characteristics	23/02/2006	29/03/2006	SmPC	From an independent investigation in Germany the MAH has received reports of osteolysis. The investigation concerned a study in which InductOs was substituted for autograft bone during spinal surgery using posterior lumbar interbody fusion (PLIF) technique and Telamon PEEK cages. InductOs is not approved for this indication in the EU, nor is it approved for use with Telamon PEEK cage device. None of the patients concerned were clinically symptomatic; the event was a radiographic finding. There was radiographic evidence of: "questionable osteoclastic activity at the deck plate and floor plate of the adjoining vertebral body". All patients improved, despite these radiographic findings; none of the patients were clinically symptomatic and at the investigations after 6 and 12 months no pathological findings were found. Although none of the event are classified as serious, the investigator halted the study because of the events.
II/0016	Change(s) to the manufacturing process for the active substance	13/10/2005	19/10/2005		
IA/0019	IA_25_b_02_Change to comply with Ph. - compliance with EU Ph. update - excipient	30/09/2005	n/a		
IA/0018	IA_05_Change in the name and/or address of a manufacturer of the finished product	29/09/2005	n/a		
II/0013	Change(s) to the test method(s) and/or specifications for the active substance	28/07/2005	17/08/2005		

	Change(s) to the test method(s) and/or specifications for the finished product				
IA/0015	IA_05_Change in the name and/or address of a manufacturer of the finished product	14/06/2005	n/a	Annex II and PL	
IA/0014	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	14/06/2005	n/a	Annex II	
II/0009	Change(s) to the manufacturing process for the active substance	16/03/2005	30/03/2005		
II/0007	This variation relates to an extention of the therapeutic indications for InductOs. The MAH proposes to amend Sections 4.1, 4.2, 4.3, 4.4 , 4.5, 4.6, 4.8, 5.1 and 5.3 in the SPC. Changes to the PL have been made to reflect the changes to the SPC. Extension of Indication	17/02/2005	29/03/2005	SmPC and PL	The new indication is: InductOs is 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. For this new indication InductOs should not be used alone, but must be used with the LT-CAGE Lumbar Tapered Fusion Device. Please refer to the Scientific Discussion "InductOs-H-C-408-II-07" for further information.
IA/0012	IA_25_b_02_Change to comply with Ph. - compliance with EU Ph. update - excipient	29/03/2005	n/a		
IA/0010	IA_05_Change in the name and/or address of a manufacturer of the finished product	29/11/2004	n/a		
II/0008	The MAH applied for the update of the SPC and PL further to spontaneous reports of localised oedema following unlicensed use of the product in cervical	29/07/2004	24/09/2004	SmPC and PL	The changes to the SPC reflect spontaneous reports from the US of localised oedema following unlicensed use in cervical spine fusion procedures. Although InductOs is not

	spine fusion procedures. The changes affect the SPC sections 4.4 , 4.8 and section 4.9. The PL has been amended accordingly. Update of Summary of Product Characteristics and Package Leaflet				approved in the EU for use in any form of spine fusion the MAH had become aware that a proportion of its use in the EU has been for spine fusion procedures. Seven reports, on 16 patients, of localised cervical oedema coincident with the administration ofdibotemin alfa (rhBMP-2)/ACS were reviewed; in all of the cases the product was used off-label in the cervical spine. In general, the patients had an uneventful post-operative course and presented 1.5-7 days after surgery with neck swelling. Six of the patients recovered, with many receiving corticosteroids. Localised oedema has been noted earlier in patients treated with InductOs although a causal relationship could not be established. Sections 4.4 and 4.8 of the SPC have been updated to reflect this information. The PL was amended accordingly.
N/0006	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/02/2004	23/02/2004	Labelling and PL	
N/0005	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/12/2003	20/01/2004	Labelling and PL	
N/0004	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/07/2003	22/07/2003	PL	
I/0002	20_Extension of shelf-life as foreseen at time of authorisation	25/04/2003	10/06/2003	SmPC	
I/0003	20a_Extension of shelf-life or retest period of the active substance	25/04/2003	02/05/2003		

T/0001	Transfer of the Marketing Authorisation from Genetics Institute of Europe B.V. to Wyeth Europa Ltd. Transfer of Marketing Authorisation	19/12/2002	31/01/2003	SmPC, Labelling and PL	