Forsteo

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
N/0060	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/01/2022		PL	
IB/0058	B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which	10/08/2021	n/a		

[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).

	does not have a significant effect on the overall quality of the AS				
II/0056	B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product	18/03/2021	n/a		
II/0057/G	This was an application for a group of variations. B.II.e.1.z - Change in immediate packaging of the finished product - Other variation B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products	11/02/2021	n/a		
II/0054	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	29/10/2020	n/a		n/a
IB/0055	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/10/2020	19/10/2021	SmPC, Annex II, Labelling and PL	
N/0053	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/04/2020	19/10/2021	PL	
IA/0052	B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new	13/12/2019	n/a		

	specification parameter to the specification with its corresponding test method				
PSUSA/2903/ 201809	Periodic Safety Update EU Single assessment - teriparatide	16/05/2019	n/a		PRAC Recommendation - maintenance
II/0050/G	This was an application for a group of variations. Submission of the final study reports of the European Union (EU) components of two post-authorisation safety studies (PASS); Study B3DMC-GHBX(2.2) and Study B3D-MC-GHBX(2.3b) both US population-based comparative cohort studies undertaken to evaluate a potential association between teriparatide and adult Osteosarcoma. An updated RMP version 7.0 was submitted as part of the application. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	16/05/2019	n/a		Based on the data provided as part of this application, teriparatide treatment does not seem to increase the risk of osteosarcoma, and no difference in the incidence rate of osteosarcoma was observed between the study cohorts. The risk of osteosarcoma will continue to be closely monitored. The benefit-risk balance of Forsteo, remains positive.
N/0049	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/06/2018	18/10/2018	PL	
IB/0048	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	29/11/2017	n/a		

II/0046	Update of section 5.1 of the SmPC of the SmPC based on the results of study B3D-EW-GHDW (VERO), a phase 4 multi-centre, prospective, randomized, parallel, double-blind, double-dummy, active controlled study comparing the effect of teriparatide for injection versus risedronate on the incidence of fractures and low bone mass. In addition, the Marketing authorisation holder (MAH) took the opportunity to correct the formatting throughout the Product Information and to bring Annex II in line with the latest QRD template version 10. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/11/2017	18/10/2018	SmPC, Annex II, Labelling and PL	The MAH submitted the final results of study B3D-EW-GHDW (VERO): a 24-month, randomized, double-blind, comparator-controlled Phase 4 study included 1,360 postmenopausal women with established osteoporosis. 680 subjects were randomised to Forsteo and 680 subjects were randomised to oral risedronate 35 mg/week. At baseline, the women had a mean age of 72.1 years and a median of 2 prevalent vertebral fractures; 57.9% of patients had received previous bisphosphonate therapy and 18.8% took concomitant glucocorticoids during the study. 1,013 (74.5%) patients completed the 24-month follow-up. The mean (median) cumulative dose of glucocorticoid was 474.3 (66.2) mg in the teriparatide arm and 898.0 (100.0) mg in the risedronate arm. The mean (median) vitamin D intake for the teriparatide arm was 1433 IU/day (1400 IU/day) and for the risedronate arm was 1191 IU/day (900 IU/day). For those subjects who had baseline and follow-up spine radiographs, the incidence of new vertebral fractures was 28/516 (5.4%) in Forsteo- and 64/533 (12.0%) in risedronate-treated patients, relative risk (95% CI) = 0.44 (0.29-0.68), P<0.0001. The cumulative incidence of pooled clinical fractures (clinical vertebral and non-vertebral fractures) was 4.8% in Forsteo and 9.8% in risedronate-treated patients, hazard ratio (95% CI) = 0.48 (0.32-0.74), P=0.0009.
IAIN/0047	B.III.2.a.1 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS	19/06/2017	n/a		

N/0045	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/10/2016	16/02/2017	PL	
PSUSA/2903/ 201509	Periodic Safety Update EU Single assessment - teriparatide	14/04/2016	n/a		PRAC Recommendation - maintenance
II/0042/G	This was an application for a group of variations. Submission of an updated RMP v.5 including amendments of the post-authorisation safety study (PASS), B3D-MC-GHBX (GHBX); in addition, non-uraemic calciphylaxis is included in the RMP as a potential important risk as requested by PRAC. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	01/04/2016	n/a		
IG/0662	A.1 - Administrative change - Change in the name and/or address of the MAH	23/02/2016	16/02/2017	SmPC, Labelling and PL	
IB/0043/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process	15/02/2016	n/a		

	of the AS				
PSUSA/2903/ 201409	Periodic Safety Update EU Single assessment - teriparatide	12/03/2015	n/a		PRAC Recommendation - maintenance
II/0039/G	This was an application for a group of variations. The MAH submitted the final report of the European component of the post-authorisation safety study (PASS) B3D-MC-GHBX(1) and the relevant update to the Risk Management Plan (RMP) of Forsteo. The RMP was also updated to remove "Limited Clinical Trial Experience in Pre-Menopausal Women" from the list of missing information elements. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority 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	25/09/2014	n/a		
IB/0038/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process	12/06/2014	n/a		

	of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS				
II/0037	Update of section 4.8 of the SmPC to add 'anaphylaxis' as a rare ADR. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC and Package Leaflet in line with the latest QRD templates. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/04/2014	09/04/2015	SmPC and PL	An assessment of all spontaneous cases reporting anaphylactic reaction with teriparatide revealed 13 cases in which a causal association could not be excluded (including 1 fatality). Overall, the causal association demonstrated in these cases support the recommendation to update section 4.8 of the SmPC and section 4 of the Package Leaflet. Based on the guidance on the estimation of frequency of adverse reactions from spontaneous reporting in the European Commission's SmPC Guideline the calculated frequency of anaphylaxis is "rare". This calculation has been verified and is considered acceptable. Furthermore, it is agreed that the addition of this adverse events to the RMP at present is not warranted. Having considered all the data presented, anaphylaxis in association with teriparatide is at present not considered to have an impact on the benefit-risk balance of Forsteo or any implications for public health. The addition of the event anaphylaxis to the RMP as a safety

					concern would not change the ongoing active surveillance on anaphylaxis. The proposed product information changes along with active surveillance are considered adequate risk minimisation for teriparatide and the adverse event of anaphylaxis.
PSUV/0035	Periodic Safety Update	10/04/2014	n/a		PRAC Recommendation - maintenance
N/0036	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/02/2014	09/04/2015	PL	
IB/0034	B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product	09/09/2013	n/a		
R/0031	Renewal of the marketing authorisation.	13/12/2012	13/02/2013	SmPC, Annex II, Labelling and PL	Based on the CHMP review of data on quality, safety and efficacy, including all variations introduced since the 1st renewal of the marketing authorisation, the CHMP considered that the benefit-risk balance of Forsteo in the authorised indications remains favourable and therefore recommended the renewal of the marketing authorisation, subject to the conditions as laid down in Annex II to the Opinion. The CHMP decided that the PSUR cycle for the product will follow the yearly cycle until otherwise agreed by the CHMP. The CHMP considered that the Marketing Authorisation could be granted with unlimited validity. The CHMP recommended amendments to the Annexes I, II, IIIA and IIIB to align the product information with the latest QRD template version 8.1. These changes do not

					affect the benefit-risk balance of the product, which remains positive.
IB/0032	B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition	30/11/2012	n/a		
N/0030	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/03/2012	13/02/2013	Labelling	
II/0029	Update of Summary of Product Characteristics and Package Leaflet. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	23/06/2011	26/07/2011	SmPC and PL	Update of section 4.8 of the SmPC, following the CHMP assessment of the PSURs 13 and 14, to add the ADR 'nephrolithiasis' and to revise the frequencies of currently listed ADRs. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to revise section 4 of the Package Leaflet to bring it in line with the SmPC, and to implement some minor editorial changes in the product information.
II/0025/G	This was an application for a group of variations. Transfer of one step of the teriparatide active substance manufacturing process to a new manufactruring site. Transfer of the analytical testing of the active substance, the in-process testing and the stability testing to the new manufacturing site. Minor changes to the manufacturing process to support the manufacturing site tranfer. Update of raw materials specifications to be in compliance with European Pharmacopeia.	14/04/2011	27/05/2011	Annex II	

	B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product 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 B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.III.2.a.2 - Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material				
II/0027/G	This was an application for a group of variations. Changes to the control of the drug substance and drug product. 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 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	14/04/2011	20/04/2011		

	biological reagent for a biological AS 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				
II/0024/G	This was an application for a group of variations. - Change in the manufacturing process of the finished product - Change to in-process tests or limits applied to the manufacture of the finished product B.II.b.3.b - Change in the manufacturing process of the finished product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits	20/01/2011	27/01/2011		
IA/0026/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD	20/12/2010	n/a	Annex II	

	C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
IB/0023	C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	18/03/2010	n/a	SmPC and PL	
IA/0022	To change the name of a manufacturer of the finished product. IA_05_Change in the name and/or address of a manufacturer of the finished product	11/01/2010	n/a		
II/0021	Update of section 4.8 of the SPC (addition of "renal failure/impairment") as requested by the CHMP further to the review of PSUR 9 and 10. The Package leaflet is updated accordingly. Section 4.3 has been amended to clarify that Forsteo is contraindicated in metabolic bone diseases other than glucocorticoid-induced osteoporosis. The ATC code of the product has also been corrected. The MAH has also taken the opportunity to update the contact details of the Icelandic local representative in the PIL and to correct mistakes in the Package Leaflet and Pen User Manual.	23/07/2009	28/08/2009	SmPC and PL	Following the review of Forsteo PSUR 09 and 10, the CHMP proposed that the Forsteo SPC section 4.8 be updated with addition of renal failure/impairment with an unknown frequency. The Package leaflet was updated accordingly. In addition section 4.3 of the SPC was updated to clarify that Forsteo is contraindicated in metabolic bone diseases other than glucocorticoid-induced osteoporosis. Finally the ATC code of the product has been corrected.

	Update of Summary of Product Characteristics and Package Leaflet				
II/0020	Addition of manufacturing site for fermentation Quality changes	29/05/2009	05/06/2009		
II/0019	Update of section 4.2, 4.4, 5.1 and 5.3 of the product information with information supporting continuous treatment with Forsteo for up to 24 months. The PL is updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	22/01/2009	25/02/2009	SmPC and PL	The 24-month efficacy data on 538 postmenopausal women (Study B3D-EW-GHCA) and on 214 patients on systemic glucocorticoid therapy (Study B3D-US-GHBZ) provided by the MAH showed that further bone mineral density gain is achieved when continuing treatment with FORSTEO from 18 to 24 months. Based on safety data from these trials and from post-marketing experience, it is not expected that 6 additional months of treatment would significantly change the safety profile of the product. Therefore, the benefit/risk balance of FORSTEO is considered favourable up to 24 months of treatment.
R/0018	Renewal of the marketing authorisation.	19/03/2008	20/05/2008	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 is of the opinion that the quality, safety and efficacy of Forsteo was adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Forsteo continues to be favourable. Nevertheless, the CHMP requested an additional five-year renewal due to the limited use in two recently approved extensions of indications: osteoporosis in men at increased risk of fracture and treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture. The CHMP concluded

					that the Marketing Authorisation Holder should continue to submit yearly PSURs.
II/0016	Quality changes	19/03/2008	21/04/2008	SmPC, Labelling and PL	
II/0017	To include in section 4.8 of the SPC the adverse drug reaction "alkaline phosphatase increase". Consequently, changes are proposed to section 4 of the PL. Update of Summary of Product Characteristics and Package Leaflet	21/02/2008	02/04/2008	SmPC and PL	The MAH provided a cumulative review on "increased alkaline phosphatase" within the submission of PSURs n. 7 and 8. In the period covered by the cumulative review (from 26 November 2002 to 31 March 2007) there have been 175 (8 serious) medically confirmed spontaneous cases of increased alkaline phosphatase (ALP). Of the 175 cases, 39 cases reported concurrent disease states associated with increased ALP levels and in 38 cases concomitant medication has been reported that may be associated with hepatotoxicity. Many cases did not contain sufficient information to assess for confounding factors. The ALP value was provided in 117 cases. The majority of cases had no elevation or mild elevation of ALP. ALP was considered to be moderately to severely increase in 14 cases. Of these 14 cases, 5 patients recovered after stopping teriparatide and 3 patients recovered or were recovering while continuing teriparatide therapy. Thus, section 4.8 of the SPC was updated to include "Alkaline phosphatase increase". In line with the draft revision of the SPC guideline (December 2007) in case of an unexpected adverse reaction detected from spontaneous reporting, each adequately designed study where this reaction could have been detected should be reviewed to choose a frequency category. Thus, based on the estimated incidence of elevated serum alkaline

					phosphatase in clinical trials, "alkaline phosphatase increase" corresponded to a frequency category of "uncommon".
II/0013	To extend the therapeutic indications to include the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at increased risk for fracture. Extension of Indication	21/02/2008	02/04/2008	SmPC, Annex II and PL	Please refer to the Scientific Discussion "Forsteo/H/C/000425/II/0013" for further information.
II/0015	Change(s) to the manufacturing process for the active substance	21/02/2008	26/02/2008		
II/0014	To include in section 4.8 of the SPC the rare adverse reaction "oedema (mainly peripheral)". Consequently, changes are proposed to section 4 of the PL. Update of Summary of Product Characteristics and Package Leaflet	19/07/2007	21/08/2007	SmPC and PL	During the assessment of PSURs n. 5 and 6, covering the period from 27 May 2005 to 26 May 2006, a total of 64 cases of oedema have been reported from the post marketing surveillance. Reports related to oedema were commonly reported with a reporting rate of 0.02% (64/303 000). Furthermore, a positive rechallenge has been reported in 4 cases. The majority of cases of oedema associated with Forsteo were "peripheral oedema". Although there were cases which were not indicative of a causal relationship, the CHMP concluded that overall the cases of oedema suggested a causal role of Forsteo. Thus, section 4.8 of the SPC was updated to include the rare adverse reaction "oedema (mainly peripheral)".
II/0012	Change(s) to the manufacturing process for the active substance	21/06/2007	27/06/2007		
II/0011	Section 4.1 of the SPC has been revised to include	24/05/2007	21/06/2007	SmPC, Annex	Please refer to the Scientific Discussion

	osteoporosis "at increased risk of fracture" and to include a statement on reduction in non-vertebral fractures in women. Furthermore, the therapeutic indications have been extended to include the treatment of osteoporosis in men. Section 5.1 of the SPC has been updated to include information on non-vertebral fractures and osteoporosis in men. Section 1 "What Forsteo is and what it is used for" of the PL has been updated accordingly. The Annexes were updated in line with the EMEA/QRD template version 7.2, including the addition of the two new EU Member States (Bulgaria and Romania) in the list of local representative in the PL. Finally, the contact details of the local representatives in Estonia, Slovakia and Spain were updated and some pictures in the user manual of the PL were replaced. Extension of Indication			II, Labelling and PL	"Forsteo/H/C/000425/II/0011" for further information.
II/0007	Update of section 4.8 and section 4.3 in the SPC. Consequent changes are proposed in section 2 and 4 of the PL. Update of Summary of Product Characteristics and Package Leaflet	27/07/2005	05/09/2005	SmPC and PL	In line with the CHMP recommendations following the review of PSUR n. 3, covering the period from 27 May 2004 to 26 November 2004, the MAH has proposed to update section 4.8 "Undesirable effects" in the SPC with adverse events based on post-marketing spontaneous reports (mild and transient injection site events; arthralgia and myalgia). Section 4.3 "Contraindications" in the SPC has been updated to include that patients with skeletal malignancies or bone metastases should be excluded from treatment with teriparatide.

					Consequent changes are proposed in section 2 "Before You Use Forsteo" and 4 "Possible Side Effects" of the PL.
IB/0010	IB_25_a_02_Change to comply with Ph. - compliance with EU Ph. - excipient	31/08/2005	n/a		
IA/0009	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	21/07/2005	n/a	PL	
IA/0008	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	31/05/2005	n/a		
II/0006	Change(s) to shelf-life or storage conditions	21/04/2005	12/05/2005		
II/0005	Change(s) to shelf-life or storage conditions	21/04/2005	12/05/2005		
II/0004	Update of section 4.8 of the SPC with adverse events based on post-marketing spontaneous reports of hypercalcemia and possible allergic events soon after injection. Update of section 4.9 of the SPC with information on overdose based on post-marketing spontaneous reports. Consequent changes are proposed in section 4 of the PL. Additionally the MAH has proposed to clarify the contraindication "Prior radiation therapy to the skeleton" in section 4.3 of the SPC. Update of Summary of Product Characteristics and Package Leaflet	16/03/2005	27/04/2005	SmPC and PL	As requested by the CHMP following the assessment of the 2nd PSUR for Forsteo, covering the period from 27 November 2003 to 26 May 2004 the MAH has proposed to update section 4.8 of the SPC with adverse events based on post-marketing spontaneous reports of hypercalcemia greater than 2.76 mmol/l (11mg/dl), hypercalcemia greater than 3.25 mmol/l (13mg/dl) and possible allergic events soon after injection (acute dyspnoea, oro/facial oedema, generalized urticaria, chest pain). As requested by the CHMP following the assessment of the 2nd PSUR for Forsteo, the MAH has also proposed to update section 4.9 of the SPC with information on overdose based on post-marketing spontaneous reports. Consequent changes are proposed in section 4 of the PL. Additionally the MAH has proposed to clarify in Section 4.3

					of the SPC the contraindication "Prior radiation therapy to the skeleton" in order to clearly specify the sources of radiation therapy. Therefore the MAH has proposed to change the current wording of the contraindication "Prior radiation therapy to the skeleton" to "Prior external beam or implant radiation therapy to the skeleton". Finally, contact details on local representatives in Spain, Portugal and Slovenia in the PL have been updated.
N/0003	The Marketing Authorisation Holder applied for an update of the list of the local representatives in order to include the contact details of the Marketing Authorisations Holder in the new Member States. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/07/2004	n/a	PL	
N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/12/2003	20/01/2004	PL	
I/0001	14_Change in specifications of active substance	14/11/2003	21/11/2003		