Prolia

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
IB/0106	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	14/01/2025		SmPC	
II/0100	Submission of the final report from the	03/10/2024		SmPC	For more information, please refer to the Summary of

[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).

	postmarketing observational study 20090522, listed as a category 3 study in the RMP. This is a denosumab global safety assessment among women with postmenopausal osteoporosis (PMO), men with osteoporosis, and men and women who receive Prolia with glucocorticoid exposure in multiple observational databases. Based on the study results, the information regarding osteonecrosis of the jaw in section 4.8 of the SmPC is updated. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				Product Characteristics.
IB/0103/G	This was an application for a group of variations. B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.d.z - Stability of AS - Other variation B.I.d.z - Stability of AS - Other variation B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	27/09/2024	n/a		

	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation				
IB/0104/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	18/09/2024	n/a		
IB/0101/G	This was an application for a group of variations. B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits	16/08/2024	n/a		
IG/1743	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	28/06/2024		Annex II	
II/0099	Update of sections 4.4 and 4.8 of the SmPC in order to update a warning regarding hypocalcaemia and to include reports of life-threatening events and fatal cases occurred in the post marketing setting based on the cumulative review of MAH safety database and literature. The Package Leaflet is updated	11/01/2024		SmPC and PL	Not applicable

	accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0098	Update of sections 4.2, 4.8, 5.1 and 5.2 in order to update efficacy, pharmacokinetic and safety information for paediatric population following the assessment of P46/043 and P46/044 based on final results from study 20130173, listed as a category 3 study in the RMP and study 20170534. The RMP version 31 has also been submitted. In addition, the MAH took this opportunity to introduce minor editorial changes. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	06/07/2023	15/09/2023	SmPC	Not applicable
IAIN/0097	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	05/10/2022	n/a		
PSUSA/954/202109	Periodic Safety Update EU Single assessment - denosumab (indicated for osteoporosis and for bone loss associated with hormone ablation in prostate cancer)	10/06/2022	n/a		PRAC Recommendation - maintenance
WS/2252	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	19/05/2022	n/a		Not applicable

	Please refer to the Recommendations section B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS				
II/0093	Please refer to the Recommendations section C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/03/2022	05/05/2022	SmPC, Labelling and PL	Prolia should not be used in children aged < 18 years because of safety concerns of serious hypercalcaemia. Serious hypercalcaemia has been reported in clinical trials in paediatric patients. Some clinical trial cases were complicated by acute renal injury.
WS/2159/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Please refer to the Recommendations section 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.b.z - Change in control of the AS - Other variation	22/04/2022	15/09/2023	Annex II	The Annex II has been updated to include the name and address of Immunex Rhode Island Corporation as a manufacturer of the biological active substance The PL have been updated to: -add Northern Ireland to the list of local representative at the end of the package leaflet (in compliance with QRG template V10.2 rev.1), and - update the local representatives for Malta and Germany at the end of the package leaflet, in the package leaflet of Xgeva.

II/0092	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	02/12/2021	n/a		
II/0091/G	This was an application for a group of variations. 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 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 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	02/12/2021	n/a		
IAIN/0090	B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information	13/08/2021	25/01/2022	SmPC and PL	
WS/2026	This was an application for a variation following a worksharing procedure according to Article 20 of	08/07/2021	n/a		

	Commission Regulation (EC) No 1234/2008. B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method				
IB/0088	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	18/11/2020	n/a		
IB/0086	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	11/11/2020	n/a		
IA/0087	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	28/09/2020	n/a		
II/0085/G	This was an application for a group of variations. Updates to SmPC section 4.8 adding the adverse reaction "hypersensitivity vasculitis" with a frequency category of very rare, and section 4.4 to introduce QRD traceability statement. The package leaflet has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to	24/09/2020	25/01/2022	SmPC and PL	n/a

	new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
N/0084	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/08/2020	25/01/2022	Labelling and PL	
PSUSA/954/201909	Periodic Safety Update EU Single assessment - denosumab (indicated for osteoporosis and for bone loss associated with hormone ablation in prostate cancer)	17/04/2020	n/a		PRAC Recommendation - maintenance
R/0082	Renewal of the marketing authorisation.	14/11/2019	16/01/2020	SmPC, Annex II and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Prolia in the approved indications remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/954/201809	Periodic Safety Update EU Single assessment - denosumab (indicated for osteoporosis and for bone loss associated with hormone ablation in prostate cancer)	26/04/2019	04/07/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/954/201809.
II/0081	Submission of an updated RMP version 26 in order to amend the study objectives for the category 3 study 20090522 to include the study population 'men and women who receive denosumab with glucocorticoid exposure'. The amended protocol for study 20090522 has also been added to the appropriate annex of the RMP.	11/04/2019	n/a		n/a

	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				
II/0078/G	This was an application for a group of variations. Submission of an updated RMP version 27 in order to add a retrospective cohort database study as a new category 3 study, upon request by PRAC following the assessment of EMEA/H/C/PSUSA/000954/201709, in order to further characterize the potential increased risk of cerebrovascular events (e.g. stroke) and other serious cardiovascular events in subjects with osteoporosis. Further, the important identified and potential risks and missing information in the RMP have been updated in accordance with the Guideline on GVP Module V – Risk management systems (Rev 2). 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 C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing	11/04/2019	n/a		n/a

	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				
IB/0079	B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB	04/01/2019	n/a		
IG/0946	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	04/06/2018	04/07/2019	PL	
II/0068	Extension of Indication to include "Treatment of bone loss associated with long-term systemic glucocorticoid therapy in adult patients at increased risk of fracture (see section 5.1)." for Prolia; as a consequence, sections 4.1, 4.2, 4.6 and 5.1 of the SmPC are updated. In addition, changes related to section 4.4 of the SmPC have been updated with regard to warnings for excipients. The Package Leaflet is updated in accordance. The Risk Management Plan version 19.0 has also been updated. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	26/04/2018	04/06/2018	SmPC and PL	Please refer to the published assessment report Prolia-H-C-1120-II-0068.

IB/0073	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	30/04/2018	n/a		
IB/0075	B.II.z - Quality change - Finished product - Other variation	25/04/2018	n/a		
IB/0074	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	25/04/2018	n/a		
PSUSA/954/201709	Periodic Safety Update EU Single assessment - denosumab (indicated for osteoporosis and for bone loss associated with hormone ablation in prostate cancer)	12/04/2018	n/a		PRAC Recommendation - maintenance
IB/0070	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	08/12/2017	n/a		
IG/0857/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	10/11/2017	04/06/2018	Annex II and PL	
X/0059/G	This was an application for a group of variations.	20/07/2017	18/09/2017	SmPC, Annex II, Labelling	

	Annex I_1.(c) Replacement of a biological AS with one of a slightly different molecular structure B.II.b.5.e - Change to in-process tests or limits applied during the manufacture of the finished product - Widening of the approved IPC limits, which may have a significant effect on overall quality of the finished product B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.3 - Variations related to the introduction of real-time release or parametric release in the manufacture of the finished product B.II.f.1.e - Stability of FP - Change to an approved stability protocol B.II.g.4.b - Changes to an approved change management protocol - Minor changes that do not change the strategy defined in the protocol			and PL	
II/0069	Update of section 4.8 of the SmPC and PL in order to remove cataracts from the list of adverse reaction associated with denosumab therapy based on final data from study 20080560, a category 3 study in the RMP (multicentre, randomized, double blind, placebo-controlled study in men with non-metastatic prostate cancer receiving androgen deprivation therapy cataract development and progression study using a slit-lamp-based evaluation system (Lens Opacities Classification System III (LOCS III).) In addition, the RMP has been updated to remove the important potential risk 'cataract in men with	01/09/2017	04/06/2018	SmPC and PL	

	prostate cancer receiving androgen deprivation therapy'. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/954/201609	Periodic Safety Update EU Single assessment - denosumab (indicated for osteoporosis and for bone loss associated with hormone ablation in prostate cancer)	21/04/2017	23/06/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/954/201609.
II/0063	Update of sections 4.2, 4.4 and 4.8 and 5.1 of the SmPC with information on the long-term use of denosumab in postmenopausal women, including women who had received prior therapy with oral bisphosphonates, based on the results of studies 20110153, 20050234, 20080562, and 2008099 following a PRAC recommendation at the conclusion of the assessment of the PSUR procedure EMA/H/C/PSUSA/00000954/201509. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/06/2017	18/09/2017	SmPC	In patients treated with Prolia for up to 10 years, BMD increased from the pivotal study baseline by 21.7% at the lumbar spine, 9.2% at the total hip, 9.0% at the femoral neck, 13.0% at the trochanter and 2.8% at the distal 1/3 radius. The mean lumbar spine BMD T-score at the end of the study was -1.3 in patients treated for 10 years. Fracture incidence was evaluated as a safety endpoint but efficacy in fracture prevention cannot be estimated due to high number of discontinuations and open-label design. The cumulative incidence of new vertebral and non-vertebral fractures were approximately 6.8% and 13.1% respectively, in patients who remained on denosumab treatment for 10 years (n = 1,278). Patients who did not complete the study of any reason had higher on-treatment fracture rates. Incidence of ONJ was 0.04% at 3 years, 0.06% at 5 years and 0.44% at 10 years of Prolia treatment. The risk of ONJ increased with duration of exposure to Prolia. Overall, long-term antiresorptive treatment (including both denosumab and bisphosphonates) may contribute to an

					increased risk for adverse outcomes such as osteonecrosis of the jaw and atypical femur fractures due to significant suppression of bone remodelling. The optimal total duration of antiresorptive treatment treatment for osteoporosis (including both denosumab and bisphosphonates) has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of denosumab on an individual patient basis, particularly after 5 or more years of use.
IAIN/0067	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	10/03/2017	02/05/2017	Annex II and PL	
II/0057	Update of section 4.6 of the SmPC in order to delete references to the Pregnancy and Lactation Surveillance programs. The Package Leaflet is updated accordingly. The RMP (version 22.0) has been revised to remove all references to the Pregnancy and Lactation Program. In addition, it has been also updated to add to the Pharmacovigilance plan that patients and infants exposed to denosumab during pregnancy or lactation will be followed until the infant is 1 year of age. In addition, the Marketing authorisation holder took the opportunity to make minor editorial updates to the SmPC and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/12/2016	02/05/2017	SmPC and PL	

IB/0061	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	30/11/2016	n/a		
IB/0064	B.II.b.z - Change in manufacture of the Finished Product - Other variation	09/11/2016	n/a		
IA/0060	B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	11/10/2016	02/05/2017	SmPC, Labelling and PL	
IAIN/0058/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.e.1.b.3 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Deletion of an immediate packaging container without a complete deletion of a strength or pharmaceutical form	07/09/2016	02/05/2017	Annex II	
IB/0056	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	21/07/2016	n/a		
II/0055	Update of sections 4.8 and 5.1 of the SmPC based on the final dataset from study 20060289 (treatment for up to 10 years with denosumab in women with	26/05/2016	02/05/2017	SmPC	A total of 2,626 subjects (58% of the women included in the extension study i.e. 34% of the women included in the pivotal study) completed the extension study. In patients

	postmenopausal osteoporosis (PMO)) in fulfilment of the post-authorisation measures MEA 015 and MEA 010. In addition, the MAH took the opportunity to combine the SmPC for Prolia 60 mg solution for injection in a pre-filled syringe and Prolia 60 mg solution for injection in line with the latest QRD template. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				treated with Prolia for up to 10 years, BMD increased from the pivotal study baseline by 21.7% at the lumbar spine, 9.2% at the total hip, 9.0% at the femoral neck, 13.0% at the trochanter and 2.8% at the distal 1/3 radius. Fracture incidence was evaluated as a safety endpoint. In years 4 through 10, the rates of new vertebral and non-vertebral fractures did not increase over time; annualised rates were approximately 1.0% and 1.3%, respectively. Two adjudicated cases of atypical fractures of the femur occurred during the extension study. ONJ has been reported rarely, in 16 patients, in clinical trials in osteoporosis and in breast or prostate cancer patients receiving hormone ablation including a total of 23,148 patients. Thirteen of these ONJ cases occurred in postmenopausal women with osteoporosis during the phase III clinical trial extension following treatment with Prolia for up to 10 years (0.3%; < 0.1 events per 100 subject-years). Fifty nine women participated in the bone biopsy sub-study at month 24 (n = 41) and/or month 84 (n = 22) of the extension study in postmenopausal women with osteoporosis. Bone histology was also evaluated in 17 men with osteoporosis following 1 year treatment with Prolia. Bone biopsy results showed bone of normal architecture and quality with no evidence of mineralisation defects, woven bone or marrow fibrosis. Histomorphometry findings in the extension study in postmenopausal women with osteoporosis showed that the antiresorptive effects of Prolia, as measured by activation frequency and bone formation rates, were maintained over time.

PSUSA/954/201509	Periodic Safety Update EU Single assessment - denosumab (indicated for osteoporosis and for bone loss associated with hormone ablation in prostate cancer)	14/04/2016	n/a		PRAC Recommendation - maintenance
IB/0054	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	08/01/2016	n/a		
II/0051	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	24/09/2015	n/a		
IB/0052/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	18/08/2015	n/a		
II/0049/G	This was an application for a group of variations. B.II.d.3 - Variations related to the introduction of real-time release or parametric release in the manufacture of the finished product B.II.d.1.f - Change in the specification parameters and/or limits of the finished product - Deletion of a	23/07/2015	n/a		

	specification parameter which may have a significant effect on the overall quality of the finished product B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter B.II.f.1.e - Stability of FP - Change to an approved stability protocol				
WS/0666/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.4.e - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of an in-process test which may have a significant effect on the overall quality of the AS B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) 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	23/07/2015	n/a		

	B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol 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				
PSUSA/954/201409	Periodic Safety Update EU Single assessment - denosumab (indicated for osteoporosis and for bone loss associated with hormone ablation in prostate cancer)	23/04/2015	30/06/2015	SmPC, Annex II and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/954/201409.
WS/0660	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	26/03/2015	n/a		
WS/0642/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	26/02/2015	n/a		

	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 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.II.h.1.b.2 - Update to the Adventitious Agents Safety Evaluation information - Replacement of obsolete studies related to manufacturing steps and adventitious agents already reported in the dossier - without modifications of risk assessment				
R/0043	Renewal of the marketing authorisation.	20/11/2014	15/01/2015		Based on the CHMP review of data on quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted, the CHMP considered that the risk-benefit balance of Prolia in the approved indications remains favourable and therefore recommends the renewal of the marketing authorisation. Given that there were several ongoing safety concerns associated with denosumab (Prolia) at the time of this renewal, it was recommended that one additional five-year renewal is asked for on the basis of pharmacovigilance grounds.
IB/0046	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	10/11/2014	n/a		
II/0044	Introduction of a post approval change management protocol related to the finished product	23/10/2014	n/a		Introduction of a post approval change management protocol related to the finished product

	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product				
WS/0589	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To change in-process control limits applied during the manufacture of the AS. B.I.a.4.d - Change to in-process tests or limits applied during the manufacture of the AS - Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the AS	25/09/2014	n/a		To change in-process control limits applied during the manufacture of the AS.
II/0037	Update of the SmPC, upon request by PRAC following the assessment of PSU 027, to refine the warnings on hypocalcaemia including a description of the clinical manifestations of severe symptomatic hypocalcaemia and increases in parathyroid hormone in sections 4.2, 4.4 and 4.8, and to add musculoskeletal pain as an identified risk in section 4.8 further to post-marketing experience. The Package Leaflet and the RMP have been modified accordingly. In addition, the MAH took the opportunity to make editorial changes in the Package Leaflet. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure	24/07/2014	26/08/2014	SmPC and PL	The new information in the SmPC and Package Leaflet informs prescribers of the risk of hypocalcaemia with Prolia, provides information on the nature of these events, and guides physicians in the recognition and management of this risk. Further, a DHPC has also been agreed as an additional risk minimisation measure in order to inform prescribers of this safety concern and the subsequent changes to the SmPC. Denosumab inhibits osteoclast bone resorption, thereby decreasing the release of calcium from bone into the bloodstream. In two phase 3 placebo-controlled clinical trials in postmenopausal women with osteoporosis, there were no reported cases of severe symptomatic hypocalcaemia In the post-marketing setting, rare cases of severe

	concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH				symptomatic hypocalcaemia have been reported. Renal insufficiency was described in the majority of these cases, with most cases occurring in the first weeks of initiating Prolia therapy but it can occur later. Examples of the clinical manifestations of severe symptomatic hypocalcaemia have included QT interval prolongation, tetany, seizures and altered mental status. Symptoms of hypocalcaemia observed in denosumab clinical studies included paresthesias or muscle stiffness, twitching, spasms and muscle cramps. Patients should be encouraged to report symptoms indicative of hypocalcemia.
II/0036	Update of section 4.4 of the SmPC, upon request by PRAC following the assessment of PSU/027, to revise the warnings on osteonecrosis of the jaw (ONJ). The Package Leaflet and the RMP have been updated accordingly. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	24/07/2014	26/08/2014	SmPC and PL	The new information in the SmPC and Package Leaflet informs prescribers of the risk of ONJ with Prolia, provides information on the nature of these events, and guides physicians in the recognition and management of this risk. Further, a DHPC has also been agreed as an additional risk minimisation measure in order to inform prescribers of this safety concern and the subsequent changes to the SmPC. ONJ has been reported rarely in clinical studies and in the post marketing setting in patients receiving Prolia (denosumab at dose 60 mg every 6 months for osteoporosis). ONJ has been reported commonly in patients with advanced cancer treated with denosumab at a dose of 120 mg administered monthly. Known risk factors for ONJ include previous treatment with bisphosphonates, older age, poor oral hygiene, invasive dental procedures (e.g. tooth extractions, dental implants, oral surgery), co-morbid disorders (e.g. pre-existing dental disease, anaemia, coagulopathy, infection), smoking, a

					diagnosis of cancer with bone lesions, and concomitant therapies (e.g., chemotherapy, antiangiogenic biologics, corticosteroids, radiotherapy to head and neck). While on treatment, patients with risk factors should avoid invasive dental procedures if possible. For patients who develop ONJ while on Prolia therapy, doctors should develop a management plan for the individual patient in close collaboration with a dentist or oral surgeon with expertise in ONJ. Temporary interruption of treatment should be considered until the condition resolves and contributing risk factors are mitigated, where possible.
II/0040	The MAH submitted the results of a category 3 PASS - Study 20090695; a post-marketing observational study to estimate off-label use in selected EU member states. The requested variation proposed no amendments to the PI or the RMP. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	24/07/2014	n/a		Not applicable
II/0039	Update of section 5.1 of the SmPC with up to 8-year exposure data, including further information on bone histology (MEA 10), from interim analyses of the ongoing open-label extension study in the treatment of postmenopausal osteoporosis (Study 20060289). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	26/08/2014	SmPC	The CHMP agreed with the MAH's proposal to amend the PI in order to inform prescribers of the long-term exposure results from the study. The data from the first 5 years of the Prolia open-label extension study demonstrated that: - BMD increased at lumbar spine, proximal femur, and radius, in both the long-term and crossover groups. - New vertebral and nonvertebral fracture incidence rates were similar in the long term and crossover groups.

					- Through year 5 of the extension study, bone turnover markers remain reduced in both the long term and crossover groups with a characteristic attenuation at the end of the dosing interval. - The rates of common adverse events or serious adverse events observed through Month 60 have not shown significant increases over time. - Eight events of ONJ and two atypical femoral fractures have been observed. The median time to onset of ONJ was approximately 5 years after the start of denosumab treatment. One case of atypical femoral fracture was reported after 3 years of denosumab treatment and the other case was reported after 7 years of denosumab treatment. Owing to the small number of subjects, no definite conclusion can be drawn on the ONJ rate over time. A longer duration of treatment with Prolia may increase the risk of these adverse events as it does for Xgeva and other antiresorptive treatments. - Bone biopsies at month 24 of the extension study showed bone of normal architecture and quality with no evidence of mineralization defects, woven bone, or marrow fibrosis. The benefit/risk balance of Prolia remains positive.
N/0041	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/06/2014	26/08/2014	PL	
II/0030	Extension of Indication to add the new therapeutic indication: treatment of osteoporosis in men at increased risk of fracture. As a consequence sections 4.1, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly. In addition, the statement in section 5.1 of the SmPC	25/04/2014	03/06/2014	SmPC and PL	For further information, please refer to the scientific discussion: Prolia-H-C-1120-II-30.

	related to the paediatric investigation plan has been updated. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IA/0038	A.7 - Administrative change - Deletion of manufacturing sites	12/05/2014	n/a		
PSUV/0035	Periodic Safety Update	10/04/2014	n/a		PRAC Recommendation - maintenance
II/0033	Changes in the upstream manufacturing process of denosumab. 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	20/02/2014	n/a		
IA/0034	A.7 - Administrative change - Deletion of manufacturing sites	13/11/2013	n/a		
II/0028/G	This was an application for a group of variations. Change in the description and materials of the prefilled syringe container system and changes in the suppliers of some components of the prefilled syringe. B.II.e.1.b.2 - Change in immediate packaging of the	19/09/2013	n/a		

	finished product - Type of container - Sterile medicinal products and biological/immunological medicinal products B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier				
IAIN/0032	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	18/09/2013	n/a		
IA/0031/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	27/08/2013	n/a		
IB/0029	B.IV.1.z - Change of a measuring or administration device - Other variation	02/08/2013	20/12/2013	Labelling and PL	
II/0027	Update of section 4.8 of the SmPC, upon request by the CHMP following the assessment of variation II-20, to reflect a revision and recalculation of all ADR frequencies from events per subject-years to events per total number of subjects. Further, the information in section 4.8 of the SmPC related to osteonecrosis of the jaw (ONJ) and atypical femoral fracture (AFF) was updated to reflect all subjects reporting events through 26 November 2012 per the number of subjects receiving denosumab in	25/07/2013	20/12/2013	SmPC and PL	The scope of this variation was to support a revision and recalculation of all ADR frequencies in the SmPC section 4.8, from events per subject-years to events per total number of subjects. This revision was proposed in response to a request from the PRAC/CHMP following the assessment of variation II/20. Following this recalculation the ADR frequency categories remained the same, with the following exceptions: 'pain in extremity' changed from common to very common and 'eczema' changed from uncommon to common.

	completed and on-going phase 2 and phase 3 bone loss studies. The Package Leaflet has been amended accordingly, and the product information has been aligned with the latest version of the QRD template. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				The results from the pooled analysis regarding 'influenza-like illness' in section 4.8 of the SmPC were updated from event rates (0.006 per subject year for denosumab and 0.003 per subject year for placebo) to subject incidence rates (1.2% for denosumab and 0.7% for placebo). The revised stratified analysis did not identify an imbalance in influenza-like illness. Although the difference is not statistically significant, there was a 2.2% imbalance in Study 20010223 (denosumab: 41 of 314 subjects, placebo: 5 of 46 subjects) using subject incidence. No imbalances were observed in other studies and the numerical imbalances were not directionally consistent across individual studies. In addition, the MAH took the opportunity to update the information in section 4.8 of the SmPC related to osteonecrosis of the jaw (ONJ) and atypical femoral fracture (AFF) to reflect all subjects reporting events through 26 November 2012 per the number of subjects receiving denosumab in completed and on-going phase 2 and phase 3 bone loss studies. The Package Leaflet has been updated accordingly, and the product information has been aligned with the latest version of the QRD template.
II/0026	Transfer of quality control testing methods of drug product B.II.b.2.b.3 - Change to batch release arrangements and quality control testing of the FP - Including batch control/testing for a biol/immunol product and one of the test methods is a biol/immunol/immunochemical method	25/07/2013	n/a		

II/0024	This type II variation concerns an update of section 4.8 of the SmPC with additional information to reflect the fact that anaphylactic reactions have been reported in the post-marketing setting. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update annex II in line with the latest QRD template version 8.3. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/04/2013	20/12/2013	SmPC and PL	Five cases of anaphylactic reaction in the post-marketing setting were assessed as causally related to Prolia. The MAH's proposal to include anaphylactic reaction in the undesirable effects sections of the SmPC for Prolia to inform prescribers is endorsed. The Package Leaflet has been updated accordingly. Changes were also made to the annex II to bring it in line with the current QRD template version 8.3, which were reviewed and accepted by the CHMP. The overall benefit-risk profile of denosumab remains favorable.
IAIN/0025	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/03/2013	n/a		
II/0020	Update of sections 4.4 and 4.8 of the SmPC to include a new warning to reflect rare cases of 'atypical femoral fracture' reported in clinical trials and the post-marketing setting. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to make minor editorial changes to the SmPC. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/01/2013	20/12/2013	SmPC and PL	Atypical femoral fractures have been reported in patients with postmenopausal osteoporosis receiving long-term treatment with Prolia (denosumab). Atypical femoral fractures are subtrochanteric or proximal diaphyseal fractures that occur with little to no trauma. Specific radiographic findings, including a simple transverse or oblique fracture with beaking of the cortex and diffuse cortical thickening of the proximal femoral shaft, characterize these events. They may occur bilaterally. An increased risk of atypical femoral fractures has been reported with bisphosphonates, another class of antiresorptive therapy for postmenopausal osteoporosis. As a result, the MAH has evaluated the potential for atypical femoral fractures in patients treated with Prolia in clinical trials and the post-marketing setting. Cases of atypical femoral fracture have been confirmed in patients receiving

					long-term treatment with Prolia participating in the ongoing open-label extension study of the pivotal phase 3 fracture trial in postmenopausal osteoporosis (FREEDOM). These events have occurred rarely (≥ 1/10,000 to < 1/1,000) based on 8,928 subjects being exposed to Prolia in bone loss studies, corresponding to 31,266 subject-years of exposure. The new information in the SmPC and Package Leaflet informs prescribers of the risk of atypical femoral fracture with Prolia, provides information on the nature of these events, and guides physicians in the recognition and management of this risk. Further, a DHPC has also been agreed as an additional risk minimisation measure in order to inform prescribers of this safety concern and the subsequent changes to the SmPC. During Prolia (denosumab) treatment, patients should be advised to report new or unusual thigh, hip, or groin pain. Patients presenting with such symptoms should be evaluated for an incomplete femoral fracture. The contralateral femur should be examined in denosumab-treated patients who have sustained a femoral shaft fracture. Discontinuation of denosumab therapy in patients suspected to have an atypical femur fracture should be considered while they are evaluated. An individual assessment of the benefits and risks should be performed.
IG/0247	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/12/2012	n/a		
II/0022	To introduce a Post Approval Change Management Protocol to register a new additional manufacturing facility of drug product and an increase in drug	13/12/2012	n/a		

	product batch size. B.II.g.2 - Design Space - Introduction of a post approval change management protocol related to the finished product				
II/0018	Update of sections 4.4 and 4.8 of the SmPC to include information about cases of severe symptomatic hypocalcaemia reported in the post-marketing setting. The Package Leaflet has been updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	18/10/2012	15/11/2012	SmPC and PL	Hypocalcemia is an identified risk for denosumab, and it is already described in the Prolia SmPC. The Prolia SmPC also includes a contraindication for hypocalcemia and steps to mitigate the risk. A review of post-marketing, spontaneous adverse event reports has identified 8 cases of medically confirmed hypocalcemia with severe signs or symptoms, for which a causal association with denosumab could not be ruled out. The majority of these events occurred in patients with severe or end-stage kidney disease who were predisposed to hypocalcemia. The Prolia SmPC currently indicates an increased risk of hypocalcemia in patients with kidney disease and recommends monitoring of calcium levels in patients predisposed to hypocalcemia; adequate intake of calcium and vitamin D is recommended in all patients. The SmPC also indicates that, for all patients, hypocalcemia must be corrected prior to initiating therapy with denosumab. To inform prescribers about the post-marketing experience with Prolia, the SmPC has been updated to report that severe symptomatic hypocalcemia has been observed in patients at increased risk of hypocalcemia.
II/0019	Update of section 4.5 of the SmPC to include results from a PK study with midazolam, a probe substrate for cytochrome P-450 3A4 (CYP3A4), undertaken in women with postmenopausal osteoporosis.	20/09/2012	23/10/2012	SmPC	In this interaction study, Prolia did not affect the pharmacokinetics of midazolam, which is metabolized by cytochrome P450 3A4 (CYP3A4). This indicates that Prolia should not alter the pharmacokinetics of drugs metabolized

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				by CYP3A4.
IAIN/0021/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	03/09/2012	23/10/2012	Annex II and PL	
IB/0017	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	22/06/2012	n/a		
IAIN/0016/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV 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	16/05/2012	n/a		
IB/0015	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	14/05/2012	n/a		

II/0012	Update of SmPC section 5.1 to reflect 2-year clinical data available from study 20060289, an extension study in postmenopausal women who completed the pivotal study 20030216. Further, the MAH has made minor editorial changes to the SmPC. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	15/03/2012	20/04/2012	SmPC	Update of SmPC section 5.1 to reflect 2-year clinical data available from study 20060289. Study 20060289 was an open-label Extension Study in the Treatment of Postmenopausal Osteoporosis. A total of 4550 patients (2343 Prolia & 2207 placebo) who missed no more than one dose of investigational product in the pivotal study (already described in section 5.1 of the SmPC) and completed all study visits agreed to enroll in a 7-year, multinational, multicenter, open label, single-arm extension study to evaluate the long-term safety and efficacy of Prolia. At month 24 of the extension study, after 5 years of denosumab treatment, the long-term group increased BMD by 13.8% at the lumbar spine, 7.0% at the total hip, 6.2% at the femoral neck and 9.7% at the trochanter from the original pivotal study baseline. Fracture incidence was evaluated as a safety endpoint: continued Prolia treatment maintained a low incidence of new vertebral and non-vertebral fractures in years 4 and 5 (annualized rate of new vertebral fracture was 1.4% in both years 4 and 5, while 1.4% and 1.1% of patients had a non-vertebral fracture in years 4 and 5 respectively). Three cases of osteonecrosis of the jaw (ONJ) occurred during the first 25 months in the study, two cases in the de novo treatment group and one case in the long term treatment group, all cases resolved. Information about the 3 ONJ cases in this study have been added to section 5.1 of the Prolia SmPC, and section 4.8 of the SmPC has been updated accordingly as part of variation II/11.
II/0011	This type II variation concerned an update of section	16/02/2012	15/03/2012	SmPC, Annex	The MAH has presented reports of 'hypersensitivity' in 6

	4.8 of the SmPC with information regarding 'hypersensitivity reactions' reported during the post-authorisation phase, a change of the frequency category allocated to the ADR 'hypocalcaemia' from 'very rare' to 'rare', the inclusion of 'osteonecrosis of the jaw' as a rare adverse reaction in the ADR table and the inclusion of text under 'summary of safety profile' in line with the SmPC guideline. The Package Leaflet has been updated accordingly. Further, for increased clarity the MAH has implemented changes to the 'instructions for injecting with the Prolia pre-filled syringe with an automatic needle guard' section of the Package Leaflet. In addition, the MAH took the opportunity to implement editorial changes in the annexes, to update the annexes in line with the latest QRD template (version 8.0) and to update the contact details in the list of local representatives in the Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data			II, Labelling and PL	patients receiving denosumab (60 mg every 6 months) for bone loss. These medically confirmed cases had sufficient information available for review, were not obviously confounded by history or suspect concomitant medication, and although clinical features were variable, drug-related hypersensitivity could not be excluded. Common clinical features among these 6 cases were rash, urticaria, facial oedema, and erythema. None of these cases was fatal and there were no cases featuring bronchospasm or hypotension. The MAH provided data supporting the use of 'Rare' as the appropriate CIOMS frequency category for this ADR. Based on the data from study 20060289 (24 month analysis), an extension study from study 20030216, there were in total 3 cases of ONJ, two cases in the de novo treatment group and one case in the long term treatment group. The MAH provided data supporting the use of 'Rare' as the appropriate CIOMS frequency category for this ADR.
II/0010	Update of sections 4.6 and 5.3 of the SmPC to reflect the outcome of Study 112197 and Study R20090282 with the inclusion of new nonclinical data regarding enhanced pre-postnatal development (ePPND). Further, SmPC section 4.6 has been updated to include information related to the MAH's Pregnancy Surveillance Programme (PSP) and Lactation Surveillance Programme (LSP). The Package Leaflet has been upadated accordingly.	16/02/2012	15/03/2012	SmPC and PL	In a study of cynomolgus monkeys dosed with denosumab during the period equivalent to the first trimester at AUC exposures up to 99-fold higher than the human dose (60 mg every 6 months), there was no evidence of maternal or foetal harm. In this study, foetal lymph nodes were not examined. In another study of cynomolgus monkeys dosed with denosumab throughout pregnancy at AUC exposures 119-fold higher than the human dose (60 mg every 6 months),

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				there were increased stillbirths and postnatal mortality; abnormal bone growth resulting in reduced bone strength, reduced haematopoiesis, and tooth malalignment; absence of peripheral lymph nodes; and decreased neonatal growth. A no observed adverse effect level for reproductive effects was not established. Following a 6 month period after birth, bone related changes showed recovery and there was no effect on tooth eruption. However, the effects on lymph nodes and tooth malalignment persisted, and minimal to moderate mineralisation in multiple tissues was seen in one animal (relation to treatment uncertain). There was no evidence of maternal harm prior to labour; adverse maternal effects occurred infrequently during labour. Maternal mammary gland development was normal. From a clinical viewpoint, women who become pregnant during Prolia treatment are encouraged to enrol in the MAH's Pregnancy Surveillance programme. Contact details are provided in section 6 of the Package Leaflet – Information for the user. Similarly, women who are nursing during Prolia treatment are encouraged to enrol in the MAH's Lactation Surveillance Program. Contact details are provided in section 6 of the Package Leaflet – Information for the user.
II/0009	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/01/2012	27/02/2012	SmPC	
II/0013/G	This was an application for a group of variations. Addition of a new manufacturing site for active substance and a manufacturing site for quality	16/02/2012	n/a		

	control testing, changes in the specification parameters of buffer used in the manufacture of active substance, change in test methods for the finished product and update of TSE certificates. 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.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer 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				
IB/0014	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	27/01/2012	n/a		
IA/0008	A.7 - Administrative change - Deletion of manufacturing sites	12/10/2011	n/a		

IA/0007	C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV	12/08/2011	n/a		
IA/0006/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV 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	28/06/2011	n/a	Annex II	
N/0003	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	31/01/2011	n/a	PL	
IB/0005	B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	06/01/2011	n/a		
IB/0004	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	06/12/2010	n/a		
IA/0002/G	This was an application for a group of variations. C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the	09/11/2010	n/a	Annex II	

	safety database 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/0001	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Extension of storage period of a biological/immunological medicinal product in accordance with an approved stability protocol	20/09/2010	n/a	SmPC	