Nivestim

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/0085	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/02/2025		PL	
IB/0083	B.II.e.z - Change in container closure system of the Finished Product - Other variation	31/10/2024	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).

IB/0082/G	This was an application for a group of variations. B.II.z - Quality change - Finished product - Other variation B.I.z - Quality change - Active substance - Other variation	29/10/2024	n/a		
IB/0080	C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH	15/10/2024		SmPC and PL	
IB/0081	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	07/10/2024	n/a		
IA/0078/G	This was an application for a group of variations. 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.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	11/07/2024	n/a		
IA/0077	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	08/04/2024		SmPC	

IB/0076	C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH	23/02/2024		SmPC	
II/0074/G	This was an application for a group of variations. Grouped application consisting of: C.I.13: Submission of the final report from the non-interventional (NI) post authorization safety study (PASS) study ZOB-NIV-1513/C1121008, listed as a category 3 study in the RMP. This is a multinational, multi-centre, prospective, non-interventional, post-authorisation safety study in Healthy Donors (HDs) exposed to nivestim (biosimilar filgrastim) for Haematopoietic Stem Cell (HSC) Mobilisation (NEST). The RMP version 12.2 has also been submitted. C.I.11: Submission of an updated RMP version 12.2 to remove the important potential risk of cytogenetic abnormalities and development of secondary haematologic malignancies from the list of safety concerns following completion of the category 3 NI PASS study ZOB-NIV-1513/C1121008. The requested group of variations proposed amendments to the Risk Management Plan (RMP). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	11/01/2024	n/a		This variation concerns the final study reports of the post-authorization safety study ZOB-NIV-1513/C1121008, listed as a category 3 study in the Risk Management Plan (RMP), to evaluate long-term safety of Nivestim in healthy donors. Overall, no new safety concerns were observed and were consistent with the known safety profiles of the biosimilar Nivestim and Neupogen reference product. The RMP is updated accordingly (version 12.2) to move reference of study ZOB-NIV-1513 to a completed additional pharmacovigilance study. Additionally, the important potential risk of cytogenetic abnormalities and development of secondary haematologic malignancies were removed from the RMP list of safety concerns since no additional risk minimisation measures nor additional pharmacovigilance activities are proposed.

	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
IB/0073/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.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	09/06/2023	n/a		
IB/0072	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/05/2023	05/01/2024	PL	
IB/0071	C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH	12/01/2023	05/01/2024	SmPC, Labelling and PL	
II/0070/G	This was an application for a group of variations. 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 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	15/12/2022	n/a		

	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer A.7 - Administrative change - Deletion of manufacturing sites				
N/0069	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/09/2022	05/01/2024	PL	
IB/0068	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	15/09/2022	n/a		
PSUSA/1391/ 202109	Periodic Safety Update EU Single assessment - filgrastim	05/05/2022	n/a		PRAC Recommendation - maintenance
IB/0067/G	This was an application for a group of variations. B.II.f.1.e - Stability of FP - Change to an approved stability protocol B.II.f.1.e - Stability of FP - Change to an approved stability protocol 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.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor	05/04/2022	n/a		

	changes to an approved test procedure B.II.f.1.e - Stability of FP - Change to an approved stability protocol				
IA/0066/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	07/02/2022	n/a		
N/0064	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/10/2021	05/01/2024	PL	
II/0063	Submission of an updated RMP version 10.1 in order to update the RMP in accordance with GVP Module V and the Guidance on the format of the RMP in the EU - in integrated format (Rev. 2.0.1) and to propose deletion of selected safety concerns listed as important identified risk, important potential risk and missing information. 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	30/09/2021	n/a		

	by new additional data to be submitted by the MAH where significant assessment is required				
N/0062	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	31/03/2021	05/01/2024	PL	
II/0061	Update of section 6.5 of the SmPC to add a statement on the content of a derivative of natural rubber latex in the needle cover formulation. Section 6 of the Package Leaflet was updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/04/2020	18/11/2020	SmPC and PL	Each pre filled syringe is affixed with a needle closed by a needle cover that contains epoxyprene, a derivative of natural rubber latex which may come into contact with the needle.
II/0059	B.I.e.2 - Introduction of a post approval change management protocol related to the AS	26/03/2020	n/a		
IB/0057	C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH	10/12/2019	18/11/2020	SmPC, Annex II, Labelling and PL	
IB/0058/G	This was an application for a group of variations. 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	09/12/2019	n/a		

	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits 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.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter 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.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter 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.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - 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.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.e - Change in test procedure for the finished product - Update of the test procedure to comply				

	with the updated general monograph in the Ph. Eur.				
N/0060	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/12/2019	18/11/2020	PL	
PSUSA/1391/ 201809	Periodic Safety Update EU Single assessment - filgrastim	16/05/2019	n/a		PRAC Recommendation - maintenance
IA/0056/G	This was an application for a group of variations. B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation 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.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test	02/05/2019	n/a		

	procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure				
N/0055	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/04/2019	16/09/2019	PL	
IB/0053	C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH	13/11/2018	16/09/2019	SmPC, Labelling and PL	
IA/0052/G	This was an application for a group of variations. 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) A.7 - Administrative change - Deletion of manufacturing sites	07/09/2018	16/09/2019	Annex II and PL	

	B.I.c.1.z - Change in immediate packaging of the AS - Other variation B.I.c.2.b - Change in the specification parameters and/or limits of the immediate packaging of the AS - Addition of a new specification parameter to the specification with its corresponding test method B.I.c.2.c - Change in the specification parameters and/or limits of the immediate packaging of the AS - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
T/0051	Transfer of Marketing Authorisation	06/08/2018	23/08/2018	SmPC, Labelling and PL	
IB/0050	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/05/2018	23/08/2018	SmPC and PL	
IB/0049	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	24/10/2017	23/08/2018	SmPC and PL	
IAIN/0048	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	20/07/2017	18/09/2017	Annex II and PL	
N/0047	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/02/2017	18/09/2017	Labelling and PL	
IB/0046	C.I.2.a - Change in the SPC, Labelling or PL of a	11/10/2016	18/09/2017	SmPC and PL	

	generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH				
IB/0045	B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	22/09/2016	n/a		
IB/0044	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	01/08/2016	n/a		
IB/0043/G	This was an application for a group of variations. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	20/06/2016	n/a		

N/0042	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/06/2016	06/07/2016	PL	
IG/0693	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	02/06/2016	n/a		
PSUSA/1391/ 201509	Periodic Safety Update EU Single assessment - filgrastim	13/05/2016	n/a		PRAC Recommendation - maintenance
IB/0040	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	29/02/2016	n/a		
IB/0038	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	07/01/2016	n/a		
IB/0036	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	22/12/2015	n/a		
IG/0645	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	17/12/2015	n/a		
II/0033	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	24/09/2015	n/a		

	by new additional data to be submitted by the MAH where significant assessment is required				
IAIN/0035/G	This was an application for a group of variations. B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	14/08/2015	06/07/2016	SmPC, Labelling and PL	
IAIN/0034	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	14/08/2015	06/07/2016	SmPC, Labelling and PL	
IAIN/0032	A.1 - Administrative change - Change in the name and/or address of the MAH	16/07/2015	06/07/2016	SmPC, Labelling and PL	
II/0029	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	02/07/2015	n/a		
II/0028/G	This was an application for a group of variations. B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting	02/07/2015	n/a		

	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.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				
R/0025	Renewal of the marketing authorisation.	26/03/2015	27/05/2015	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, including all variations introduced since the marketing authorisation was granted, the CHMP considered that the benefit-risk balance of Nivestim in the approved indications remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IG/0555	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	22/05/2015	n/a		
N/0027	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/01/2015	27/05/2015	PL	
IB/0026/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.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor	05/12/2014	n/a		

	changes to an approved test procedure 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				
II/0022	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	25/09/2014	n/a		
IG/0477	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	03/09/2014	n/a		
IA/0023/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 A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	01/08/2014	15/01/2015	Annex II and PL	

IB/0021/G	This was an application for a group of variations. 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 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	16/04/2014	n/a		
IB/0019	C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH	21/01/2014	15/01/2015	SmPC and PL	
IG/0382	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	02/12/2013	n/a		
IB/0018	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	29/10/2013	n/a		
N/0017	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/08/2013	18/12/2013	PL	
IG/0317	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/07/2013	n/a		

II/0014/G	This was an application for a group of variations. B.II.b.1.c - Addition of a new site for manufacture, primary packaging and release testing of the finished product. B.II.b.4.c - Increase in the batch size for the finished product. B.II.e.1.a.3 - Change to the material used for the needle shield. B.II.b.2.a - Addition of a new release and stability testing site for the finished product. A.5.b - Change in the address of a site registered for secondary packaging of the finished product. A.7 - Deletion of a secondary packaging site. 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, batch control, and secondary packaging, for biological/immunological medicinal products. B.II.b.4.c - Change in the batch size (including batch size ranges) of the finished product - The change requires assessment of the comparability of a biological/immunological medicinal product B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products 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	25/04/2013	n/a		

	takes place 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) A.7 - Administrative change - Deletion of manufacturing sites				
II/0013/G	This was an application for a group of variations. B.I.a.1.e – Addition of Hospira Zagreb d.o.o, Prudnička cesta 60, 10291 Prigorje Brdovečko, Croatia, for manufacture and quality control of the active substance. B.I.a.1.f – Registration of new sites for testing of master and working cell banks. B.I.a.2.c – Changes to the manufacturing process of the active substance. B.I.a.3.c – Increase in the batch size of the active substance manufacture. B.I.a.4.a – Tightening of an in-process test specification. B.I.a.4.b – Addition of new in-process tests. B.I.a.4.z – Reclassification of in-process tests. B.I.b.1.d – Deletion of tests from the specifications for the inclusion bodies. B.I.c.1.b – A new container closure system is proposed for storage of the active substance. 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	25/04/2013	18/12/2013	Annex II	

	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.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.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 B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits 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.z - Change to in-process tests or limits applied during the manufacture of the 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.c.1.b - Change in immediate packaging of the AS - Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological ASs				

IG/0286	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	12/04/2013	n/a		
II/0011	Update of section 4.8 of the SmPC as per the reference medicinal product (Neupogen, Amgen Europe BV.) and in accordance with the Hospira global Core Safety Information. Angiopathy and information relating to pseudogout have been added and the term, " decreased glucose" has been amended to "blood glucose decreased" in-line with the reference product. A minor editorial correction was also included. The PL has also been updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the PL. Furthermore, the PI is being brought in line with the latest QRD template version 8.2. C.I.2.b - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Change(s) require to be further substantiated by new additional data to be submitted by the MAH	13/12/2012	18/12/2013	SmPC, Annex II, Labelling and PL	The MAH aligned the product information of Nivestim with the current safety information of the reference medicinal product Neupogen. No cases of pseudogout and angiopathy were retrieved from the safety database.
IB/0012	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	18/10/2012	n/a		

IAIN/0010	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	23/07/2012	n/a		
IB/0009	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	18/07/2012	n/a		
IAIN/0007	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	04/05/2012	n/a		
IAIN/0008/G	This was an application for a group of variations. C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV 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.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 C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities C.I.9.h - Changes to an existing pharmacovigilance	18/04/2012	n/a		

	system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
IB/0006	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	20/01/2012	n/a		
IAIN/0005/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 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)	23/11/2011	14/06/2012	Annex II and PL	
N/0004	Following the CHMP request, the MAH applied to update section 4 of package leaflet to include warnings with respect to reports of graft versus host disease (GvHD) and fatalities. In addition, user instructions in package leaflet have been changed to align with wording used by biological product (Neupogen) and to address concerns around the potential for loss/waste of product. Finally, the MAH took this opportunity to update the contact details for Czech, Estonian, Hungarian, Irish, Latvian, Lithuanian, Polish and Slovenian local representatives.	25/07/2011	14/06/2012	PL	

	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)				
IB/0003	To extend the maximum out of refrigerator storage period for Nivestim from 48 hours to 7 days based on real-time data. B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	19/11/2010	n/a	SmPC and PL	
IB/0002	To extend the shelf-life for the 12 MU/0.2 ml and 30 MU/0.5 ml presentations from 2 years to 30 months based on real-time stability data. The shelf-life for the 48 MU/0.5 ml presentation is currently 30 months and will remain unchanged. B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	19/10/2010	n/a	SmPC	
IA/0001	To change the plunger rods and safety device for Nivestim 30MU and 48MU. 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	14/07/2010	n/a	SmPC and PL	