Privigen

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/0193	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/10/2022		PL	
II/0188	B.II.h.1.b.1 - Update to the Adventitious Agents Safety Evaluation information - Replacement of obsolete studies related to manufacturing steps and	15/09/2022	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).

	adventitious agents already reported in the dossier - with modifications of risk assessment				
IB/0192	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	08/08/2022	n/a		
IB/0190/G	This was an application for a group of variations. B.I.e.4.b - Changes to an approved change management protocol - Minor changes that do not change the strategy defined in the protocol B.I.e.4.b - Changes to an approved change management protocol - Minor changes that do not change the strategy defined in the protocol	26/07/2022	n/a		
IB/0191	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	22/07/2022	n/a		
II/0185	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	14/07/2022	n/a		
IB/0189/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	24/06/2022	n/a		

	B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation				
IA/0187	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	30/03/2022	n/a		
IB/0184/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.I.a.3.e - Change in batch size (including batch size ranges) of AS or intermediate - The scale for a biological/immunological AS is increased/decreased without process change (e.g. duplication of line)	22/03/2022	n/a		
IG/1492	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	18/03/2022	n/a		
IB/0183/G	This was an application for a group of variations. B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	07/03/2022	n/a		

IB/0181/G	This was an application for a group of variations. B.I.e.4.b - Changes to an approved change management protocol - Minor changes that do not change the strategy defined in the protocol B.I.e.4.b - Changes to an approved change management protocol - Minor changes that do not change the strategy defined in the protocol	06/01/2022	n/a		
N/0182	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/12/2021		PL	
IB/0178	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	21/10/2021	n/a		
IB/0176	B.I.a.3.e - Change in batch size (including batch size ranges) of AS or intermediate - The scale for a biological/immunological AS is increased/decreased without process change (e.g. duplication of line)	06/09/2021	n/a		
IG/1429	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	20/08/2021	n/a		
IB/0177/G	This was an application for a group of variations. B.I.z - Quality change - Active substance - Other	03/08/2021	n/a		

	variation B.II.z - Quality change - Finished product - Other variation				
IB/0175/G	This was an application for a group of variations. B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	23/06/2021	n/a		
IB/0174/G	This was an application for a group of variations. B.I.e.4.b - Changes to an approved change management protocol - Minor changes that do not change the strategy defined in the protocol B.I.e.4.b - Changes to an approved change management protocol - Minor changes that do not change the strategy defined in the protocol	27/05/2021	n/a		
II/0170/G	This was an application for a group of variations. B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the	09/04/2021	n/a		

	change requires an assessment of comparability				
IB/0172/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.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	01/03/2021	n/a		
IG/1356	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	16/02/2021	n/a		
II/0169	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	11/02/2021	n/a		
IB/0171/G	This was an application for a group of variations. B.II.z - Quality change - Finished product - Other variation 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	21/01/2021	n/a		

	B.II.e.3.c - Change in test procedure for the immediate packaging of the finished product - Deletion of a test procedure if an alternative test procedure is already authorised				
PSUSA/1633/ 202005	Periodic Safety Update EU Single assessment - human normal immunoglobulin (IgG)	14/01/2021	n/a		PRAC Recommendation - maintenance
II/0161/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to 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	01/10/2020	20/11/2020	SmPC, Annex II, Labelling and PL	Sections 4.8 and 5.1 of the SmPC are updated with results from study IgPro10_5003 showing a statistically significant rate reduction of 89% of haemolytic anaemia (based on an incidence rate ratio of 0.11; adjusted for in-/outpatient setting, age, sex, Privigen dose and indication for Privigen use; one-sided p-value <0.01) after implementation of the IAC step compared to baseline. Additionally, 28 paediatric patients with CIDP <18 years of age were identified throughout the entire study period from 1 January 2008 to 30 April 2019. No paediatric patients with CIDP given a total of 486 Privigen administrations experienced haemolytic anaemia, AMS, acute renal failure, severe anaphylactic reaction or a thromboembolic event. Two patients experienced a moderate anaphylactic reaction, equating to 0.4% of all Privigen administrations. The special warnings and precautions for use in Section 4.4 of the SmPC are also updated to state that the Privigen manufacturing process includes an immunoaffinity chromatography (IAC) step that specifically reduces blood group A and B antibodies (isoagglutinins A and B). Clinical data with Privigen manufactured with the IAC step show statistically significant reductions of haemolytic anaemia Section 5.1 of the SmPC is updated to list the Study

					IgPro10_3004 in Japanese patients with PID and CIPD within the studies on safety and efficacy of Privigen. Safety data from this study were incorporated into the adverse drug reaction database resulting in an updated frequency categorization for 'nausea' (changed from very common to common). In addition, the term 'infusion site discomfort' was added as an ADR and grouped with 'injection site pain with a frequency uncommon in Section 4.8 of the SmPC. The RMP is updated to remove the Category 3 Study IgPro_5003 from the ongoing studies. The additional risk minimization measures for hemolysis are updated with the permanent implementation of an immunoaffinity chromatography step in the manufacturing process of Privigen and the discontinuation of screening of plasma donors. The summary of safety concerns is updated to remove 'safety information pertaining to the paediatric population with CIPD' following the completion of the PASS (IgPro10_5003) study.
IB/0168/G	This was an application for a group of variations. B.I.z - Quality change - Active substance - Other variation B.II.z - Quality change - Finished product - Other variation	19/10/2020	n/a		
II/0163	B.I.e.2 - Introduction of a post approval change management protocol related to the AS	24/09/2020	n/a		
II/0164	B.II.b.3.b - Change in the manufacturing process of the finished or intermediate product - Substantial	17/09/2020	n/a		

	changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product				
II/0160	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	03/09/2020	n/a		
IB/0166/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.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	31/08/2020	n/a		
IG/1269	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	15/07/2020	n/a		
II/0157/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	18/06/2020	n/a		

	of the AS 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				
IB/0162	B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)	14/05/2020	n/a		
II/0159	B.II.b.3.b - Change in the manufacturing process of the finished or intermediate product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product	14/05/2020	n/a		
II/0155	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	02/04/2020	n/a		
IG/1209	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	25/02/2020	n/a		
N/0156	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/02/2020	28/04/2020	PL	

II/0154/G	This was an application for a group of variations. B.I.e.2 - Introduction of a post approval change management protocol related to the AS B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	16/01/2020	n/a		
IB/0153	B.I.z - Quality change - Active substance - Other variation	31/07/2019	n/a		
IB/0152	B.II.z - Quality change - Finished product - Other variation	31/07/2019	n/a		
II/0145	B.II.d.2.c - Change in test procedure for the finished product - Substantial change to or replacement of a biol/immunol/immunochemical test method or a method using a biol. reagent or replacement of a biol. reference preparation not covered by an approved protocol	04/07/2019	n/a		
IB/0150	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	11/06/2019	n/a		
IAIN/0151/G	This was an application for a group of variations. 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 B.II.d.1.b - Change in the specification parameters	06/06/2019	n/a		

	and/or limits of the finished product - Tightening of specification limits for medicinal products subject to OCABR				
II/0147	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	16/05/2019	28/04/2020	SmPC and PL	
II/0146	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	02/05/2019	28/04/2020	SmPC and PL	
IB/0149	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	15/04/2019	n/a		
IG/1074	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	01/04/2019	n/a		
II/0140	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	17/01/2019	n/a		
IB/0144	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/01/2019	31/01/2019	SmPC and PL	

IB/0142	B.I.a.3.e - Change in batch size (including batch size ranges) of AS or intermediate - The scale for a biological/immunological AS is increased/decreased without process change (e.g. duplication of line)	06/12/2018	n/a		
IB/0143	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	20/11/2018	n/a		
II/0136/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.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 B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability	15/11/2018	n/a		
N/0139	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/10/2018	31/01/2019	Labelling and PL	
IA/0141	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/09/2018	31/01/2019	SmPC	
IB/0138	B.II.d.2.a - Change in test procedure for the finished	31/08/2018	n/a		

	product - Minor changes to an approved test procedure				
IB/0137	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	31/08/2018	n/a		
IB/0132	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	18/07/2018	n/a		
IB/0135	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	13/07/2018	n/a		
IB/0133	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	13/07/2018	n/a		
IB/0131/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 of the AS	04/04/2018	n/a		
IG/0885	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes	29/01/2018	n/a		

	do not affect the properties of the FP				
PSUSA/1633/ 201705	Periodic Safety Update EU Single assessment - human normal immunoglobulin (IgG)	11/01/2018	n/a		PRAC Recommendation - maintenance
II/0127	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	14/12/2017	n/a		
IB/0128	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	05/12/2017	n/a		
R/0122	Renewal of the marketing authorisation.	12/10/2017	28/11/2017	PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Privigen in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0126	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	09/11/2017	n/a		
II/0123/G	This was an application for a group of variations. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the	12/10/2017	n/a		

	manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol B.II.z - Quality change - Finished product - Other variation				
IB/0124	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	15/08/2017	n/a		
IA/0121	A.7 - Administrative change - Deletion of manufacturing sites	13/07/2017	n/a		
II/0119	Update of sections 4.8 and 5.1 of the SmPC to include the PATH (IgPro20_3003) study results (safety & efficacy study with chronic inflammatory demyelinating polyneuropathy (CIDP) patients). Minor changes are also introduced to section 4.2 of the SmPC. In addition, the MAH took the opportunity to make some editorial changes to sections 4.3 and 5.2 of the SmPC. The Package leaflet and the RMP (finally agreed version 5.1) were updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	06/07/2017	28/11/2017	SmPC, Labelling and PL	The efficacy and safety profile of Privigen in chronic inflammatory demyelinating polyneuropathy (CIDP) patients in the PATH study was comparable to those seen in the PRIMA study which was pivotal for the approval of the CIDP indication. In terms of safety, no new safety concerns have arisen. With regard to efficacy, the data can be viewed as supplementary to the PRIMA study and to the general knowledge of the beneficial effects of IVIGs in treating CIDP. For more information on safety and efficacy information from the PATH study, please refer to sections 4.8 (Undesirable effects) and 5.1 (pharmacodynamic properties) of the SmPC, respectively.
II/0118	B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the	06/07/2017	n/a		

	change requires an assessment of comparability				
IB/0120	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	19/05/2017	n/a		
II/0114/G	This was an application for a group of variations. 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 B.II.z - Quality change - Finished product - Other variation	11/05/2017	n/a		
IB/0117	B.I.a.z - Change in manufacture of the AS - Other variation	10/05/2017	n/a		
IG/0788	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	12/04/2017	n/a		
IA/0115	B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation	05/04/2017	n/a		
II/0111	To introduce an additional, optional adsorption step (QAE adsorption (C1 esterase inhibitor)) during	09/02/2017	n/a		

	manufacture of the intermediate "Fraction I+II+III Precipitae K3" at the CSL Behring, Kankakee, Illinois (US) (K3) manufacturing site, for the subsequent manufacture of Privigen in IgLAB Bern (Switzerland). 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				
IG/0757	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	26/01/2017	n/a		
PSUSA/1633/ 201605	Periodic Safety Update EU Single assessment - human normal immunoglobulin (IgG)	12/01/2017	n/a		PRAC Recommendation - maintenance
II/0110	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	15/12/2016	n/a		
IB/0108/G	This was an application for a group of variations. B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.5.z - Change to in-process tests or limits	04/10/2016	n/a		

	applied during the manufacture of the finished product - Other variation				
II/0106/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.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.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.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method	22/09/2016	27/10/2016	Annex II	
N/0109	Update of the package leaflet with revised contact details of the local representatives for Cyprus, Estonia, Greece, Latvia and Lithuania.	16/09/2016	27/10/2016	PL	

	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)				
II/0105	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	21/07/2016	n/a		
II/0103	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	09/06/2016	n/a		
II/0101	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	12/05/2016	n/a		
II/0100	Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to include the results of an immune thrombocytopenia study (IgPro10_4001) with a consequential update of the safety information particularly to amend the existing information on haemolysis and to include Transfusion-related acute lung injury (TRALI). The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to amend Annex II of the PI in line with the latest QRD template	28/04/2016	27/10/2016	SmPC, Annex II and PL	The product information was updated to include the following information on a recently completed study: "In the second ITP study, 57 patients with ITP (baseline platelet counts ≤ 30×109 / l) aged between 18 and 65 years were treated with Privigen at 1 g/kg bw. On day 3 patients could receive a second dose of 1 g/ kg bw, for patients with a platelet count of < 50×109 / l on day 3 this second dose was mandatory. Overall, in 42 subjects (74 %) the platelet count increased at least once to ≥ 50×109 / l within 6 days after the first infusion, which was well within

	version 9.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				the expected range. A second dose in subjects with platelet counts ≥ 50×109 /l after the first dose provided a relevant additional benefit in terms of higher and longer-lasting increases in platelet counts compared to a single dose. In subjects with platelet counts < 50×109 / l after the first dose, 30% showed a platelet response of ≥ 50×109 / l after the mandatory second dose." In addition, the safety information was updated with regards to: - Haemolysis: If signs and/or symptoms of haemolysis develop during or after an IVIg infusion, discontinuation of the IVIg treatment should be considered by the treating physician. - Transfusion-related acute lung injury (TRALI): Noncardiogenic pulmonary edema may very rarely occur following treatment with IVIg products, including Privigen. TRALI is characterized by severe respiratory distress, pulmonary edema, hypoxemia, normal left ventricular function, and fever. Symptoms typically appear within 1 to 6 hours following treatment. Monitor patients for pulmonary adverse reactions. TRALI may be managed using oxygen therapy with adequate ventilatory support.
IG/0676/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier	27/04/2016	n/a		

	of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP				
II/0099	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	04/02/2016	n/a		
PSUSA/1633/ 201505	Periodic Safety Update EU Single assessment - human normal immunoglobulin (IgG)	14/01/2016	n/a		PRAC Recommendation - maintenance
II/0096	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/11/2015	27/10/2016	SmPC and PL	
IB/0098	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	23/09/2015	n/a		

II/0092	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	17/09/2015	n/a		
II/0093	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	16/07/2015	n/a		
II/0091	B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes	25/06/2015	n/a		
N/0095	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/05/2015	27/10/2016	PL	
IAIN/0094	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	20/05/2015	n/a		
II/0090	B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing	23/04/2015	n/a		

	process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product				
PSUSA/1633/ 201405	Periodic Safety Update EU Single assessment - human normal immunoglobulin (IgG)	09/01/2015	n/a		PRAC Recommendation - maintenance
II/0088	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	18/12/2014	n/a		
IA/0089	B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	21/11/2014	n/a		
II/0086	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	25/09/2014	n/a		
II/0085	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	25/09/2014	n/a		
IB/0084	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing	12/06/2014	n/a		

	authorisation, including the RMP - Other variation				
N/0083	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/03/2014	22/10/2014	PL	Update of the local representatives contact details for Hungary, Luxembourg and Belgium. The MAH took the opportunity to make minor linguistic amendments to the English, Polish and Slovakian Republic Labelling and Package Leaflets.
IAIN/0082	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	17/02/2014	n/a		
PSUSA/1633/ 201305	Periodic Safety Update EU Single assessment - human normal immunoglobulin (IgG)	09/01/2014	n/a		PRAC Recommendation - maintenance
II/0079	Change in the donor pool in order to reduce the isoagglutinin titre in the final product. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	18/12/2013	n/a		
IB/0080	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	22/11/2013	n/a		
N/0077	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/10/2013	22/10/2014	PL	Update of the local representative's contact details for Bulgaria, Hungary, Poland and Romania in the Package Leaflet. The MAH also included an additional local

					representative for the new Member State, Croatia.
IAIN/0078	C.I.10 - Change in the frequency and/or date of submission of PSURs for human medicinal products	03/10/2013	22/10/2014	Annex II	
II/0075	Changes to the manufacturing process of the active substance. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol	19/09/2013	n/a		
II/0074	To change the manufacturing process of the active substance. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol	25/07/2013	n/a		
II/0073/G	This was an application for a group of variations. Change in the a test procedure for the finished product. In addition, the finished product an in process control limit has been tightened to be in line with the finished product change. B.II.d.2.c - Change in test procedure for the finished product - Replacement of a biological/ immunological/immunochemical test method or a	25/07/2013	n/a		

	method using a biological reagent 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				
II/0072	Changes in the manufacturing process of the active substance B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol	27/06/2013	n/a		
II/0069/G	This was an application for a group of variations. Additional filling size of the finished product. Change in the dimensions of the vial. B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products B.II.e.5.c - Change in pack size of the finished product - Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, and biological/immunological multidose parenteral medicinal products	25/04/2013	22/10/2014	SmPC, Labelling and PL	
II/0068	Change in the manufacturing procedure of the active substance.	25/04/2013	n/a		

	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				
II/0063	Extension of indication to immunomodulation in adults, and children and adolescents (0-18 years) in Chronic inflammatory demyelinating polyneuropathy. SmPC sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 have been amended and the PL has been updated accordingly. In addition Annex II has been updated in line with version 8.3 of the QRD template. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	21/02/2013	26/03/2013	SmPC, Annex II and PL	Please refer to the Scientific Discussion Privigen/H/C/000831/II/63 for further information
IB/0070	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	18/03/2013	n/a		
R/0065	Renewal of the marketing authorisation.	17/01/2013	13/03/2013	SmPC, Annex II, Labelling and PL	Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Privigen remains positive, but considers that its safety profile is to be closely monitored for the following reasons: Haemolysis is a well known risk of IVIgs (included in the core SmPC). As a higher rate of mild and severe haemolytic reactions has been reported with Privigen (a number of risk factors have been identified: higher doses (off-label use), non O blood type, inflammatory conditions, kidney damage

					and nephrotoxic concomitant medication), the CHMP concluded that this risk needs to be further investigate. As detailed in the Risk Management Plan, the MAH will be searching for additional possible causative factors of haemolysis in the ongoing post-authorisation study IgPro10_4001. The MAH will also change its donor pool and the manufacturing process in order to reduce the isoagglutinine titers in the final product and conduct a non-interventional post-authorisation study to compare the rate of haemolysis before and after implementation of these two measures. Therefore, on the justified grounds relating to Pharmacovigilance that the risk of haemolysis associated with Privigen should be further characterised, the CHMP concluded that the MAH should submit an additional five-year renewal.
IAIN/0071	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	31/01/2013	n/a		
II/0064	Submitted data to support Ph. Eur monograph compliance on procoagulant activity B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation	17/01/2013	n/a		
II/0066	Changes in the manufacturing process of the drug substance	18/10/2012	n/a		

	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				
IA/0067	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)	04/10/2012	n/a		
IB/0061	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	19/06/2012	n/a		
IAIN/0062	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	01/06/2012	n/a		
II/0058	Update of the warning on the risk of haemolysis in SmPC section 4.4, with regard to the risk factors of blood groups and high doses and with regard to the rare complications of haemolysis-related renal failure and disseminated intravascular coagulation. In addition, the SmPC, Annex II, Labelling and the PL are updated according to the latest versions of QRD template, Guideline on SmPC and Core SmPC for Human Normal Immunoglobulin for Intravenous Administration. Also editorial changes have been introduced in the Product Information and the list of	16/02/2012	19/03/2012	SmPC, Annex II, Labelling and PL	The SmPC warning on risk of haemolytic anaemia was expanded with information on the following risk factors: high doses, non-0 blood group (both based on analysis of the received case reports with haemolytic reactions in association with Privigen) and underlying inflammatory state (based on scientific literature). Furthermore, of 104 patients reported to have 'Haemolytic disorders' there were 4 reports of secondary acute renal failure and 2 reports of disseminated intravascular coagulation. A corresponding warning has also been included in the SmPC.

	local representatives in the PL has been updated. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
II/0060	B.II.b.3.c - Change in the manufacturing process of the finished product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability	15/03/2012	n/a		
IB/0059	B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation	19/01/2012	n/a		
II/0057	Changes in the manufacturing of the active substance B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol	19/01/2012	19/01/2012		
II/0054	Change in the manufacturing process of the active substance. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol	17/11/2011	17/11/2011		
II/0051	Change in the manufacturing of the active substance.	17/11/2011	17/11/2011		

	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				
IA/0056	C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV	14/11/2011	19/03/2012	Annex II	
IA/0055	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	07/09/2011	n/a		
N/0053	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/07/2011	n/a	PL	Update of the Dutch local representative's contact details and reduction of address details for all local representatives in the Package Leaflet.
IA/0052	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	27/05/2011	n/a		
N/0050	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/03/2011	n/a	PL	Update of the contact details of the Romanian local representative.
IA/0049	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) -	22/02/2011	n/a		

	Inclusion of an updated/amended PMF when changes do not affect the properties of the FP				
II/0046	Changes in the manufacturing process of the active substance. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol	20/01/2011	01/02/2011		
N/0048	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/01/2011	n/a	PL	Change to the contact details of the Bulgarian, French, Italian and Polish local representatives. The MAH also took the opportunity to make minor amendments to the Maltese, Romanian, Austrian, German and Irish local representatives contact details.
II/0045	To introduce an alternative manufacturing site for intermediates 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 material [-] used in the manufacture of a biological/immunological product	16/12/2010	04/01/2011		
II/0042	Change in the primary packaging material; addition of alternative infusion stoppers for closure of Privigen glass bottles. B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative	23/09/2010	29/09/2010		

	composition - Sterile medicinal products and biological/immunological medicinal products				
IB/0043	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	10/09/2010	n/a		
II/0041	Update of the SmPC sections 4.4 and 4.8 with information on the risk of haemolysis / haemolytic anaemia. Additionally, SmPC sections 5.1 and 5.2 were updated with data that was already assessed in Variation II/13. Furthermore, editorial changes have been introduced in section 4.4 and 4.5 of 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	22/07/2010	26/08/2010	SmPC and PL	The MAH has proposed changes to section 4.4 and 4.8 of the SmPC with regard to the risk of haemolysis / haemolytic anaemia. As plasma pools from >1000 donors will contain antibodies to A, B (and thus to AB) antigens on the red blood cells it is logical that patients with these blood groups may be affected by haemolytic reactions. In published scientific literature, haemolytic reactions were associated with a non-O blood group and frequently with high doses of IVIg (> 2 g/kg). Such warning describes a possible class effect/adverse reaction of IVIg products in general. This update of the safety information, editorial changes of the SmPC as well as update appropriate wording in sections 5.1 and 5.2 of the SmPC are acceptable and do not affect the overall positive benefit-risk balance of this product.
II/0040	Modification of the SmPC on the basis on new quality data. The MAH changes the product information including information about dilution of IgPro10 in 5% glucose solution, when dilution is needed before infusion, is added in sections 4.2, 6.3 and 6.6 of the SmPC, and in the section for healthcare professionals in the PIL C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-	22/07/2010	26/08/2010	SmPC, Labelling and PL	

	clinical, clinical or pharmacovigilance data				
IA/0044	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	19/08/2010	n/a		
IB/0039	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	06/05/2010	n/a		
IB/0036	To add a section to the Package Leaflet for Healthcare professionals on the handling and posology. Furthermore, a minor revision to the wording of section 6.2 of the SPC was made to align it with the patient leaflet and minor linguistic changes were introduced to the Bulgarian, Danish, German, Greek, English, Spanish, Icelandic, Latvian, Lithuanian, Maltese, Portuguese, Romanian, French, Norwegian, Hungarian, Dutch, Slovakian, Italian and Polish annexes. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/04/2010	n/a	SmPC, Labelling and PL	
IB/0038	To change a test process control for Proline detection in an optimezed method. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test	15/04/2010	n/a		

	procedure				
IA/0037	To submit the PMF 2nd step documentation for PMF Annual Update 2009. The updated PMF has been granted a certificate of complaince no EMEA/H/PMF/000001/04/AU/007 issued the 18 February 2010. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	07/04/2010	n/a		
II/0034	Change in a test procedure for the finished product. Change(s) to the test method(s) and/or specifications for the finished product	18/02/2010	05/03/2010		
II/0033	Change to the manufacturing process of the active substance. Change(s) to the manufacturing process for the active substance	21/01/2010	27/01/2010		
II/0032	Deletion of a test in the manufacturing process of the finished product, which is not part of the requirements listed in the Ph. Eur. monograph on Human normal immunoglobulin for intravenous administration (Ph. Eur. 6th edition, 2009)	21/01/2010	27/01/2010		

	Change(s) to the test method(s) and/or specifications for the finished product				
II/0031	Change in the self-life of the finished product from 2 to 3 years. Change(s) to shelf-life or storage conditions	17/12/2009	27/01/2010	SmPC	
II/0029	Change to the manufacturing process of an intermediate of the active substance. Change(s) to the manufacturing process for the active substance	17/12/2009	06/01/2010		
II/0028	Addition of alternative container for the storage of intermediates. Change(s) to container	17/12/2009	06/01/2010		
II/0023	Changes to the purification process of the active substance. Change(s) to the manufacturing process for the active substance	19/11/2009	25/11/2009		
IB/0027	IB_31_b_Change to in-process tests/limits during manufacture - addition of new tests/limits	02/10/2009	n/a		
IB/0030	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	01/10/2009	n/a		

II/0017	Deletion of the declaration of the average IgA content from SPC. Update of Summary of Product Characteristics	23/07/2009	21/08/2009	SmPC	The declaration of the average IgA content in the SPC only provides additional information but does not enhance the safety of the patient. The patient information leaflet is not affected. The specified maximum content of IgA (0.025 mg/ml) does not change and will remain in the SPC.
II/0013	Update of Summary of Product Characteristics and Package Leaflet Update of Summary of Product Characteristics and Package Leaflet	23/07/2009	21/08/2009	SmPC and PL	The SPC of Privigen has been updated with information from clinical study ZLB05_006CR. The data provided by this clinical trial updated the efficacy and safety profile of IgPro10. This study utilised a very similar study design as the pivotal Primary Immunodeficiency disease (PID) study ZLB03_002CR. The new study tested a higher increased infusion rate of up to 12 mg/kg/min for patients that previously participated in the pivotal clinical study. The infusion rate of Privigen may therefore be increased up to (but not more than) 7.2 mL/kg of body weight (bw) per hour in patients who tolerate well the drug. The list of Adverse Drug Reactions of Privigen was updated with the safety results of this clinical study.
IB/0025	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	05/08/2009	n/a		
IB/0024	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	05/08/2009	n/a		
II/0016	Change in the manufacturing process of the drug product	23/07/2009	31/07/2009		

	Change(s) to the manufacturing process for the finished product				
II/0015	Changes to the manufacturing process of the drug substance. Change(s) to the manufacturing process for the active substance	23/07/2009	31/07/2009		
II/0014	Approval of alternative testing site for finished product. Quality changes	23/07/2009	31/07/2009		Approval of alternative testing site for finished product.
N/0026	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/07/2009	n/a	PL	
IB/0021	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	09/07/2009	n/a		
IB/0020	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	30/06/2009	30/06/2009	SmPC, Labelling and PL	
IB/0019	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	30/06/2009	30/06/2009	SmPC, Labelling and PL	
IA/0022	IA_13_a_Change in test proc. for active substance - minor change	25/06/2009	n/a		

IB/0018	IB_31_b_Change to in-process tests/limits during manufacture - addition of new tests/limits	18/06/2009	n/a		
II/0011	Introduction of an additional filling size of 25 ml for Privigen (2.5 g/25 ml).This change affects SPC, labelling and package leaflet. In addition CSL Behring has applied to introduce minor linguistic amendments in the Product information. Quality changes	19/03/2009	07/05/2009	SmPC, Labelling and PL	
II/0010	Optional two-fold increase in the batch size of the finished product with a consequential addition of a manufacturing facility for the Active substance and the finish product Quality changes	19/03/2009	30/03/2009		
2PMF/0012	2PMF (2nd step of PMF certification procedure)	17/02/2009	n/a		
II/0006	Change(s) to the manufacturing process of Igpro10 bulk solution Change(s) to the manufacturing process for the active substance	25/09/2008	01/10/2008		
IA/0009	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	24/09/2008	n/a		
MF/0008	2PMF (2nd step of PMF certification procedure)	02/09/2008	n/a		

N/0005	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/08/2008	n/a	PL	
IB/0007	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	18/07/2008	n/a		
IB/0004	IB_31_a_Change to in-process tests/limits during manufacture - tightening of in-process limits	18/07/2008	n/a		
IB/0003	IB_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening	18/07/2008	n/a		
IA/0002	IA_23_b_Change in source of excip./reagent to veg./synthetic material - other cases	07/07/2008	n/a		
MF/0001	2PMF (2nd step of PMF certification procedure)	03/06/2008	n/a		