Insuman

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/0151	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/08/2024		PL	
PSUSA/1753/ 202310	Periodic Safety Update EU Single assessment - insulin human, insulin human / insulin isophane (subcutaneous and intravenous routes of	13/06/2024	n/a		PRAC Recommendation - maintenance

[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).

	administration)				
PSUSA/10107 /202309	Periodic Safety Update EU Single assessment - insulin human (Intraperitoneal use only)	16/05/2024	n/a		PRAC Recommendation - maintenance
II/0146	Please refer to the Recommendations section 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	11/04/2024	n/a		
IB/0148/G	This was an application for a group of variations. B.I.c.2.z - Change in the specification parameters and/or limits of the immediate packaging of the AS - Other variation B.I.c.2.z - Change in the specification parameters and/or limits of the immediate packaging of the AS - Other variation	30/01/2024	n/a		
IA/0144	B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	11/07/2023	11/09/2023	SmPC, Labelling and PL	
II/0142	Submission of the final report from study HUBIN-C-06380 listed as a category 3 study in the RMP. This is an observational prospective PASS designed to gain additional longitudinal and long term safety data related to the use of Insuman Implantable 400 IU/mL via an IP implantable pump in a European	09/02/2023	n/a		Not applicable

	observational cohort of patients with type 1 diabetes. The updated RMP version 5.0 was agreed during the procedure. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IG/1551	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)	02/12/2022	n/a		
IB/0141	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	01/09/2022	11/09/2023	SmPC	
N/0140	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/12/2021	11/09/2023	PL	
PSUSA/1753/202010	Periodic Safety Update EU Single assessment - insulin human, insulin human / insulin isophane (subcutaneous and intravenous routes of administration)	10/06/2021	n/a		PRAC Recommendation - maintenance
IB/0139	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	26/05/2021	n/a		
PSUSA/10107/202009	Periodic Safety Update EU Single assessment - insulin human (Intraperitoneal use only)	06/05/2021	n/a		PRAC Recommendation - maintenance

N/0135	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/10/2020	20/08/2021	PL	
IA/0136	B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test	20/10/2020	n/a		
IG/1282	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	15/09/2020	n/a		
IAIN/0133	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/08/2020	20/08/2021	SmPC, Annex II and PL	
N/0132	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/03/2020	20/08/2021	PL	
II/0130	Submission of the final report from a completed Phase 3 study, HUBIN-L-05335, listed as a category 3 post-authorisation efficacy / safety study in the RMP. This study covers the evaluation of Insuman Implantable 400 IU/mL in patients with Type 1 diabetes treated with the Medtronic MiniMed Implantable Pump System using Insuplant 400 IU/mL, addressing the Post-Authorisation Measure MEA040. In this application, the RMP v4.1 combines the updates related to HUBIN-L-05335 study final results and the approval of amended protocol V2 of the ongoing Post Authorization Safety Study HUBIN-C-06380 (MEA/047.4 & MEA/047.5, concerning PRAC decision: EMA/PRAC/256519/2018 dated 17-May-	03/10/2019	n/a		

	2018; updates are limited to Annex 3 of Part VII). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IA/0131	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	11/09/2019	n/a		
II/0128/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.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	16/05/2019	n/a		
IAIN/0129	B.IV.1.b - Change of a measuring or administration device - Deletion of a device	23/04/2019	08/04/2020	SmPC, Labelling and PL	
IG/0999/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or	20/11/2018	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient				

IB/0125	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	02/08/2018	n/a		
PSUSA/1753/201710	Periodic Safety Update EU Single assessment - insulin human, insulin human / insulin isophane (subcutaneous and intravenous routes of administration)	14/06/2018	n/a		PRAC Recommendation - maintenance
II/0124	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	31/05/2018	n/a		
IB/0123	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	24/04/2018	n/a		
PSUSA/10107/201709	Periodic Safety Update EU Single assessment - insulin human (Intraperitoneal use only)	12/04/2018	n/a		PRAC Recommendation - maintenance
IB/0122	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	03/04/2018	14/06/2018	SmPC, Labelling and PL	
IB/0119	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/02/2018	14/06/2018	SmPC, Labelling and PL	
IB/0118/G	This was an application for a group of variations. B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s) B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is	29/06/2017	14/06/2018	SmPC, Labelling and PL	

	not an integrated part of the primary packaging - Device with CE marking C.I.7.b - Deletion of - a strength				
II/0117/G	This was an application for a group of variations. 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 B.II.b.4.d - Change in the batch size (including batch size ranges) of the finished product - The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes	22/06/2017	n/a		
PSUSA/10107 /201609	Periodic Safety Update EU Single assessment - insulin human (Intraperitoneal use only)	06/04/2017	n/a		PRAC Recommendation - maintenance
IB/0116	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	24/01/2017	n/a		
IA/0115	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)	14/12/2016	n/a		
II/0112/G	This was an application for a group of variations. B.II.b.1.c - Replacement or addition of a	19/05/2016	n/a		

	manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place 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				
N/0113	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/04/2016	14/06/2018	PL	
PSUSA/10107 /201509	Periodic Safety Update EU Single assessment - insulin human (Intraperitoneal use only)	14/04/2016	n/a		PRAC Recommendation - maintenance
IB/0111/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	11/01/2016	n/a		
IA/0109/G	This was an application for a group of variations.	02/10/2015	n/a		

	B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure				
IA/0108/G	This was an application for a group of variations. B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure	02/10/2015	n/a		
IA/0107/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.d - Change in the specification parameters	11/08/2015	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
N/0106	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/07/2015	14/06/2018	PL	
PSUSA/1753/201410	Periodic Safety Update EU Single assessment - insulin human, insulin human / insulin isophane (subcutaneous and intravenous routes of administration)	11/06/2015	n/a		PRAC Recommendation - maintenance
PSUSA/10107/201409	Periodic Safety Update EU Single assessment - insulin human (Intraperitoneal use only)	10/04/2015	n/a		PRAC Recommendation - maintenance
IB/0103	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	16/12/2014	n/a		
II/0102	Update of the Risk Management Plan (RMP) for Insuman Implantable 400 IU/ml version 2.0 dated 16 July 2014. 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	20/11/2014	n/a		

IB/0099	B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition)	18/07/2014	n/a		
IG/0454	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	17/07/2014	n/a		
IG/0453	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	27/06/2014	n/a		
II/0097	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/04/2014	n/a		
IG/0427	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	16/04/2014	n/a		
IB/0096	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	05/12/2013	03/10/2014	SmPC, Labelling and PL	
X/0091	Annex I_2.(d) Change or addition of a new pharmaceutical form	25/07/2013	19/09/2013	SmPC, Annex II, Labelling and PL	

IB/0095	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	17/09/2013	03/10/2014	SmPC, Annex II, Labelling and PL	
IG/0314	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/07/2013	n/a		
IG/0300	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	03/05/2013	n/a		
IG/0246/G	This was an application for a group of variations. B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new tests and limits B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test	13/12/2012	n/a		
II/0090/G	This was an application for a group of variations. - To introduce changes in the manufacturing process of the active substance. - To change the immediate packaging of the active substance. - To delete a non-significant in-process test applied during the manufacture 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	15/11/2012	n/a		

	manufacture of a biological/immunological medicinal product and is not related to a protocol B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test				
IG/0198	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	27/07/2012	n/a		
WS/0229	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	24/05/2012	03/07/2012	SmPC, Labelling and PL	
WS/0208	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 6.6 for SoloStar pre-filled pen presentation for the Insuman, Insuman Human Whintrop, Apidra, Lantus and Optisulin to reinforce the appropriate use of SoloStar. The Package Leaflet	15/03/2012	20/04/2012	SmPC, Annex II, Labelling and PL	Update of the labelling documents for three sanofi-aventis insulins is proposed in this type II variation to reinforce the appropriate use of Solostar prefilled pen. This update is based on the experience gained since 2006 (e.g. following reports and questions raised by the pen users) and a continued evaluation of possible improvements of the Product Information. During this period a number of product technical complaints

	was proposed to be updated in accordance. Furthermore, the MAH proposed this opportunity to bring the PI in line with latest QRD template version 8.0 for Insuman, Apidra, Lantus and Optisulin. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				were received concerning the functionality of the pen, namely a blocked pen, where it is impossible to dial or inject a dose. The cause was identified that when dialling a dose and pushing the dose button without a needle attached to the pen, a mechanical pressure within the system builds, leading to a blockage of the pen mechanism. For this reason the Instructions for Use are updated to make the patient aware not to dial a dose or push the dose button without having a needle attached. There was no technical change made to the Solostar prefilled pen.
IG/0158/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	28/03/2012	n/a		
IG/0147/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.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	29/02/2012	n/a		

	DD C.I.9.f - Changes to an existing pharmacovigilance system as described in the DDPS - Deletion of topics covered by written procedure(s) describing pharmacovigilance activities 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				
IG/0091	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	05/07/2011	n/a		
IA/0082	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)	01/06/2011	n/a		
II/0081	Changes to the cleaning procedure of the bioreactor used at Step 3 (main fermentation) of the manufacturing process of the active substance (lower the temperature and incubation time (from >/=121ºC for >/= 45 min to >/= 60 ºC for >/= 30 min) for the treatment with sodium hydroxide solution). Minor editorial corrections in Module S.2 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	19/05/2011	19/05/2011		

	product and is not related to a protocol				
II/0077	Update of product information to reflect the risk of medication errors (insulin mix-up). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	16/12/2010	01/02/2011	SmPC, Annex II, Labelling and PL	The portfolio of the MAH contains several different insulins with several insulin delivery devices (IDD), including the re-usable devices (OptiPen Pro and OptiClik) and the device/drug combinations (pre-filled disposable pens OptiSet and SoloStar). The complexity regarding the various insulin treatments used in a single diabetic patient, (i.e. long acting, rapid acting; with the latter needing to be administered multiple times a day) in order to achieve optimal glycaemia control has created a situation wherein product differentiation becomes increasingly important. Adverse events associated with insulins mix-ups, often result in massive overdose of the rapid-acting insulin which may subsequently lead to hypoglycaemia, which if left untreated may be life-threatening, or result in death. In most cases, however, the patients noticed the mistake and took measures to avoid hypoglycaemia, which may explain the large number of cases with no AE or non-serious cases. In order to mitigate the risk of medication errors, the MAH has focused its efforts up to now on educational activities to ensure the safe administration of their insulins. The MAH has also focused on differentiation strategies for insulin products to mitigate the potential risk of administering the wrong insulin to a person with diabetes. The product information for all the insulins from this MAH has been updated through the present variation to include warnings on the risk of insulin mix-up. Additionally, the MAH will incorporate changes to the existing insulins packaging. The aim of these changes is to better differentiate the different products and to increase

					readability for the pharmacist, Health Care Professional or patient in order to reduce potential mix-ups.
IB/0080	C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	19/01/2011	n/a	SmPC and PL	
IA/0079	B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	20/12/2010	n/a		
IB/0078	Change in the Product Information (SmPC, L and PL) to include the name of the re-usable pens to be used with the cartridge presentations. B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	19/11/2010	n/a	SmPC, Labelling and PL	
IA/0075/G	This was an application for a group of variations. 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 B.I.a.4.a - Change to in-process tests or limits	18/08/2010	n/a		

	applied during the manufacture of the AS - Tightening of in-process limits 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)				
IG/0004/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.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of 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.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the 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	06/05/2010	n/a	Annex II	
IA/0074	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	23/04/2010	n/a		

II/0070	Update and transfer of the existing information on switching patients between different Sanofi-Aventis Deutschland GmbH insulins from section 4.2 to section 4.4 of the SPC. Update of the pharmacotherapeutic group in section 5.1 of the SPC to comply with the latest QRD template. Minor wording changes introduced in annex IIIA (for the presentations cartridge, cartridge for Opticlick, pre-filled pen Optiset and pre-filled pen SoloStar). Update to the instructions for use of the Optiset pre-filled pen presentations in the Package Leaflet. Update of the contact details of the local representatives for Poland and Italy in the Package Leaflet for all presentations. Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/09/2009	11/11/2009	SmPC, Labelling and PL	Section 4.4 of the SPC was updated in order to harmonise the information between all Sanofi-Aventis Deutschland GmbH insulins regarding the transfer of patients from one insulin to another in order to improve the information given to the prescriber and to answer questions raised concerning the adjustment of the dose needed this specific transition period. Section 5.1 of the SPC was updated to comply with the latest version of the QRD template for the SPC. Minor changes were introduced in the Labelling to harmonise the information between all Sanofi-Aventis Deutschland GmbH insulins and in the wording of the OptiSet User Manual (located at the end of the Package Leaflet) for quality purposes.
IB/0073	Change to a test procedure of the immediate packaging of the finished product. IB_27_b_Change to test proc. of immediate packaging - other changes (incl. replacement/addition)	11/11/2009	n/a		
IB/0072	Change in a test procedure of the finished product IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	11/11/2009	n/a		
IB/0067	IB_38_c_Change in test procedure of finished product - other changes	04/08/2009	n/a		

IB/0069	IB_30_b_Change in supplier of packaging components - replacement/addition	29/06/2009	n/a		
II/0066	Addition of new presentations New presentation(s)	23/04/2009	29/05/2009	SmPC, Labelling and PL	
X/0057	Annex I_2.(c) Change or addition of a new strength/potency	23/10/2008	19/02/2009	SmPC, Labelling and PL	
IB/0065	IB_38_c_Change in test procedure of finished product - other changes	12/02/2009	n/a		
II/0064	Extension of shelf-life of the drug substance. Change(s) to shelf-life or storage conditions	22/01/2009	28/01/2009		
II/0060	Replacement of reagents and minor adjustments of the manufacturing process of the drug substance. Change(s) to the manufacturing process for the active substance	20/11/2008	26/11/2008		
II/0059	Addtion of new presentations New presentation(s)	25/09/2008	04/11/2008	SmPC, Labelling and PL	
IB/0063	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	26/09/2008	n/a		

IB/0062	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	24/09/2008	n/a		
IA/0061	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	12/09/2008	n/a		
II/0056	Update of Summary of Product Characteristics and Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	24/04/2008	18/06/2008	SmPC and PL	Update of the Product Information (PI) to harmonise the SPC and PL of the sanofi-aventis insulin containing products (insuline glargine, insulin glulisine and insulin human). Particularly for Insulin human, the SPC has been revised and the Package Leaflet has been updated to reflect the outcome of the user Readability User Testing performed to demonstrate the readability and usefulness of the PL to patients.
IB/0058	IB_38_c_Change in test procedure of finished product - other changes	26/02/2008	n/a		
II/0053	Change(s) to the test method(s) and/or specifications for the active substance	24/01/2008	30/01/2008		
II/0055	The Marketing Authorisation Holder applied for the addition of a new presentation: cartridge for Opticlick. New presentation(s)	15/11/2007	18/12/2007	SmPC, Labelling and PL	
IA/0054	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	06/08/2007	n/a		
IB/0032	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	25/07/2007	25/07/2007	SmPC, Labelling and	

				PL	
IB/0031	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	25/07/2007	25/07/2007	SmPC, Labelling and PL	
IB/0030	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	25/07/2007	25/07/2007	SmPC, Labelling and PL	
IB/0029	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	25/07/2007	25/07/2007	SmPC, Labelling and PL	
IB/0028	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	25/07/2007	25/07/2007	SmPC, Labelling and PL	
IA/0052	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	25/07/2007	10/10/2007	SmPC, Labelling and PL	
IA/0051	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	25/07/2007	25/07/2007	SmPC, Labelling and PL	
IA/0050	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	25/07/2007	25/07/2007	SmPC, Labelling and PL	
IA/0049	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	25/07/2007	25/07/2007	SmPC, Labelling and PL	
IA/0048	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	25/07/2007	25/07/2007	SmPC, Labelling and	

				PL	
IA/0047	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	25/07/2007	25/07/2007	SmPC, Labelling and PL	
IA/0046	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	25/07/2007	25/07/2007	SmPC, Labelling and PL	
IA/0045	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	25/07/2007	25/07/2007	SmPC, Labelling and PL	
IA/0044	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	25/07/2007	25/07/2007	SmPC, Labelling and PL	
IA/0043	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	25/07/2007	25/07/2007	SmPC, Labelling and PL	
IA/0042	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	25/07/2007	25/07/2007	SmPC, Labelling and PL	
IA/0041	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	25/07/2007	25/07/2007	SmPC, Labelling and PL	
IA/0040	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	25/07/2007	25/07/2007	SmPC, Labelling and PL	
IA/0039	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	25/07/2007	25/07/2007	SmPC, Labelling and	

				PL	
IA/0038	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	25/07/2007	25/07/2007	SmPC, Labelling and PL	
IA/0037	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	25/07/2007	25/07/2007	SmPC, Labelling and PL	
IA/0036	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	25/07/2007	25/07/2007	SmPC, Labelling and PL	
IA/0035	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	25/07/2007	25/07/2007	SmPC, Labelling and PL	
IA/0034	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	25/07/2007	25/07/2007	SmPC, Labelling and PL	
IA/0033	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	25/07/2007	25/07/2007	SmPC, Labelling and PL	
R/0025	Renewal of the marketing authorisation.	16/11/2006	16/01/2007	SmPC, Annex II, Labelling and PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of Insuman continues to be favourable. The CHMP was also of the opinion that the renewal can be granted with unlimited validity.
II/0027	Update of Summary of Product Characteristics and Package Leaflet of the Optiset presentations to	21/09/2006	31/10/2006	SmPC and PL	After the experience gained from the users through user surveys and outside experts consultation, the MAH has

	reflect a revision of the Optiset Instructions for Use. Update of Summary of Product Characteristics and Package Leaflet				proposed to revise the Optiset Instructions for Use and the Summary of Product Characteristics of the Optiset presentations for Insuman. The MAH has performed a readability test that shows that the revised manual complies with the standard acceptance criteria (80% of participants were able to find the information requested in the PL and instructions for use manual and could show that they understand it).
IB/0026	IB_25_a_02_Change to comply with Ph. - compliance with EU Ph. - excipient	27/07/2006	n/a		
IA/0024	IA_01_Change in the name and/or address of the marketing authorisation holder IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.) IA_05_Change in the name and/or address of a manufacturer of the finished product	01/06/2006	n/a	SmPC, Annex II, Labelling and PL	
II/0023	Change(s) to (an) ancillary medical device(s) Change(s) to (an) ancillary medical device(s)	23/03/2006	05/05/2006	SmPC, Labelling and PL	Modifications to the OptiSet pen and imprinting the name of the insulin on the pen for identification. The purpose of this change is to implement technical improvements to OptiSet in order to prevent mishandling of the pen and thus to improve the safety of the device, particularly when it is wrongly used. In addition, the trade name of the insulin will be printed on the pen, to enable a complete differentiation from other insulins provided with the OptiSet pen. The data provided was adequate and satisfactory and the proposed changes were acceptable. The instructions for use of the pen have been updated accordingly.

II/0022	Change(s) to container	26/01/2006	14/02/2006	SmPC	
II/0021	The Marketing Authorisation Holder applied for changes at steps 8 (folding and precipitation of by-products), 9 (tryptic cleavage) and 12 (carboxypeptidase B cleavage) of the manufacturing process of the active substance. Change(s) to the manufacturing process for the active substance	23/06/2005	30/06/2005		
II/0020	Update of sections 4.2, 4.4, 6.6 of the Summary of Product Characteristics to include additional warnings for the use of the OptiSet device and update of the Package Leaflet including a complete revision of the instructions for the use of Insuman OptiSet. Addition of a caution statement to the outer carton. In addition the MAH applied to include a storage precaution with regard to the first use of Insuman Optiset in section 6.4 of the SPC and to include minor linguistic changes in the SPC, Labelling and Package Leaflet. Update of Summary of Product Characteristics, Labelling and Package Leaflet	29/07/2004	24/09/2004	SmPC, Labelling and PL	The MAH applied for this variation to update sections 4.2, 4.4 and 6.6 of the SPC to include additional warnings for the use of the OptiSet device and to highlight the most important handling steps for the use of the OptiSet in a more prominent way. In the SPC it was highlighted in sections 4.2 (paragraph administration) and in section 4.4 (addition of specific paragraph "handling of the pen") that the instructions for use included in the package leaflet must be read carefully before use and that Optiset has to be used as recommended in these instructions. More details about the use of the pen have been introduced in section 6.6. The Package Leaflet has been revised accordingly to improve clarity. The instructions for the use of Insuman OptiSet has been completely revised. A caution statement has been added to the outer carton.
II/0019	Update of section 6.6 of the Summary of Product Characteristics to include instructions and warnings for handling the OptiPen in case of mechanical defects.	23/06/2004	04/08/2004	SmPC, Labelling and PL	Following reports received from patients who had experienced difficulties with insulin administration by OptiPen the CHMP concluded at the March 2004 plenary meeting that the Product Information for Insuman cartridges should be amended to include a warning in the

	Update of Summary of Product Characteristics, Labelling and Package Leaflet				Product Information describing that Optipen should not be used in case of mechanical defects. Some devices were investigated after the reported failure and the manufacturer's reports conclude in a suspected user's failure rather than a device failure. Information was added to section 6.6 of the SPC (cartridge presentations). This information was also added to the labelling the outer packaging as well as clarification that the cartridges are to be used in conjunction with an insulin pen such as OptiPen and other pens suitable for Insuman cartridges. To section 3 of the Package Leaflet was added the advice to follow the manufacturer's instructions for using the pen carefully for loading the cartridge, attaching the needle, and administering the insulin injection, to see instructions for using the pen and not to use OptiPen if it is damaged.
II/0018	The Marketing Authorisation Holder applied for the omission of routine sterility testing of the container closure system for Insuman Infusat cartridges. Change(s) to the test method(s) and/or specifications for the finished product	22/04/2004	27/04/2004		
II/0015	Update of section 4.4 of the Summary of Product Characteristics (SPC) and section 4 of the Package Leaflet to include a class warning regarding hypoglycaemic reactions after transfer from animal source insulin to human insulins. In addition the MAH applied to update the local representatives in the Package Leaflet.	24/07/2003	24/10/2003	SmPC and PL	The CHMP requested an update of section 4.4 of the SPC to include a class labelling for all centrally authorised human insulins relating to hypoglycaemic reactions after transfer from animal source insulin to human insulin. This information was added to section 4.4. of the SPC and section 4 of the Package Leaflet.

	Update of Summary of Product Characteristics and Package Leaflet				
I/0016	12_Minor change of manufacturing process of the active substance	25/09/2003	02/10/2003		
I/0017	11b_Change in supplier of an intermediate compound used in manufacture of the active substance	01/08/2003	05/09/2003		
II/0014	Change(s) to the test method(s) and/or specifications for the finished product	25/04/2002	30/04/2002		
R/0013	Renewal of the marketing authorisation.	13/12/2001	22/03/2002	SmPC, Annex II, Labelling and PL	
I/0012	17_Change in specification of the medicinal product	12/12/2001	n/a		
II/0009	Update of Summary of Product Characteristics and Package Leaflet	14/12/2000	14/06/2001	SmPC, Labelling and PL	
I/0010	Change of the name of the Marketing Authorisation Holder from Hoechst Marion Roussel Deutschland GmbH to Aventis Pharma Deutschland GmbH. This name change results in two consequential changes (i) in the name of the manufacturer of the active substance and ii) in the name of the manufacturer of the medicinal product. 03_Change in the name and/or address of the	21/12/2000	14/06/2001	SmPC, Annex II, Labelling and PL	

	marketing authorisation holder 01_Change following modification(s) of the manufacturing authorisation(s) 11a_Change in the name of a manufacturer of the active substance				
II/0011	Update of or change(s) to the pharmaceutical documentation	26/04/2001	04/05/2001		
II/0008	Quality changes	19/10/2000	15/11/2000		
I/0007	24_Change in test procedure of active substance	19/10/2000	15/11/2000		
X/0003	X-3-v_Addition of a new route of administration	20/01/2000	01/08/2000	SmPC, Annex II, Labelling and PL	
II/0006	Quality changes	13/04/2000	28/04/2000		
II/0004	New presentation(s)	18/11/1999	20/03/2000	SmPC, Labelling and PL	
II/0005	Change(s) to the manufacturing process for the finished product	20/01/2000	22/02/2000		
II/0002	New presentation(s)	16/12/1999	18/02/1999	SmPC, Labelling and PL	
II/0001	New presentation(s)	16/12/1998	18/02/1999	SmPC, Labelling and PL	