EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Insulin Human Winthrop

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/0081	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/04/2016		PL	
IA/0079/G	This was an application for a group of variations 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	02/10/2015	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).

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	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/0078/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/0077/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 and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	11/08/2015	n/a		

N/0076	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/08/2015		PL	
PSUSA/1753/ 201410	Periodic Safety Update EU Single assessment - INSULIN HUMAN, ISOPHANE INSULIN	11/06/2015	n/a		PRAC Recommendation - maintenance
N/0074	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/01/2015		PL	
IB/0073	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		
IB/0070	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		
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/0068	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	11/09/2014	SmPC, Labelling and PL	
IB/0067	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	11/09/2014	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/0063/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	15/11/2012	15/11/2012		

	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 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	28/06/2012	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	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

	Whintrop, Apidra, Lantus and Optisulin to reinforce the appropriate use of SoloStar. The Package Leaflet 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				Product Information. During this period a number of product technical complaints 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				
R/0055	Renewal of the marketing authorisation.	22/09/2011	21/11/2011	SmPC, Annex II, Labelling and PL	Insulin Human Winthrop is a duplicate of Insuman and has been registered in 2007 under Informed Consent Application with cross-reference to the authorized product Insuman. The CHMP granted a renewal with unlimited validity for Insuman on 16 November 2006. The clinical efficacy of recombinant human insulin is well established. The post-marketing surveillance of Insuman has not revealed unexpected safety concern. The data provided in the PSURs submitted with this renewal application do not raise any new safety signal. Consequently, the benefit risk balance remains unchanged. The CHMP recommended the renewal of the Marketing Authorisation for Insulin Human Winthrop with unlimited validity.
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/0054	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a	01/06/2011	n/a		

	non-significant specification parameter (e.g. deletion of an obsolete parameter)				
II/0053	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 product and is not related to a protocol	19/05/2011	19/05/2011		
II/0049	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 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/0052	Update of the Product Information (SmPC section 4.4 and Package Leaflet section 2) to add a warning on an increased incidence of heart failure when pioglitazone is used in combination with insulin, especially in patients with predisposing factors 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/0051	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/0050	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/0047/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 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)	18/08/2010	n/a		
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	06/05/2010	n/a	Annex II	

	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				
IA/0046	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		
IB/0045	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/0044	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		
II/0043	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	24/09/2009	30/10/2009	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

	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				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/0040	IB_38_c_Change in test procedure of finished product - other changes	04/08/2009	n/a		
IB/0042	IB_30_b_Change in supplier of packaging components - replacement/addition	28/07/2009	n/a		
II/0039	Addition of new presentations New presentation(s)	23/04/2009	28/05/2009	SmPC, Labelling and PL	
X/0004	Annex I_2.(c) Change or addition of a new strength/potency	23/10/2008	19/02/2009	SmPC, Labelling and PL	
IB/0038	IB_38_c_Change in test procedure of finished product - other changes	12/02/2009	n/a		
II/0037	To extend the shelf-life of the active substance human insulin. Change(s) to shelf-life or storage conditions	22/01/2009	28/01/2009		
II/0033	Replacement of reagents and minor adjustments of the manufacturing process of the drug substance.	20/11/2008	25/11/2008		

	Change(s) to the manufacturing process for the active substance				
II/0007	Addition of new presentation including the disposable pen injector system Solostar. New presentation(s)	25/09/2008	31/10/2008	SmPC, Labelling and PL	
IB/0036	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	26/09/2008	n/a		
IB/0035	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	24/09/2008	n/a		
IA/0034	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	12/09/2008	n/a		
IB/0012	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	16/07/2008	16/07/2008	SmPC, Labelling and PL	
IB/0011	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	16/07/2008	16/07/2008	SmPC, Labelling and PL	
IB/0010	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	16/07/2008	16/07/2008	SmPC, Labelling and PL	
IB/0009	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	16/07/2008	16/07/2008	SmPC, Labelling and PL	

IB/0008	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	16/07/2008	16/07/2008	SmPC, Labelling and PL	
IA/0032	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	16/07/2008	16/07/2008	SmPC, Labelling and PL	
IA/0031	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	16/07/2008	16/07/2008	SmPC, Labelling and PL	
IA/0030	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	16/07/2008	16/07/2008	SmPC, Labelling and PL	
IA/0029	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	16/07/2008	16/07/2008	SmPC, Labelling and PL	
IA/0028	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	16/07/2008	16/07/2008	SmPC, Labelling and PL	
IA/0027	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	16/07/2008	16/07/2008	SmPC, Labelling and PL	
IA/0026	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	16/07/2008	16/07/2008	SmPC, Labelling and PL	
IA/0025	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	16/07/2008	16/07/2008	SmPC, Labelling and PL	
IA/0024	IA_41_a_01_Change in pack size - change in no. of	16/07/2008	16/07/2008	SmPC,	

	units within range of appr. pack size			Labelling and PL	
IA/0023	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	16/07/2008	16/07/2008	SmPC, Labelling and PL	
IA/0022	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	16/07/2008	16/07/2008	SmPC, Labelling and PL	
IA/0021	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	16/07/2008	16/07/2008	SmPC, Labelling and PL	
IA/0020	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	16/07/2008	16/07/2008	SmPC, Labelling and PL	
IA/0019	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	16/07/2008	16/07/2008	SmPC, Labelling and PL	
IA/0018	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	16/07/2008	16/07/2008	SmPC, Labelling and PL	
IA/0017	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	16/07/2008	16/07/2008	SmPC, Labelling and PL	
IA/0016	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	16/07/2008	16/07/2008	SmPC, Labelling and PL	
IA/0015	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	16/07/2008	16/07/2008	SmPC, Labelling and	

				PL	
IA/0014	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	16/07/2008	16/07/2008	SmPC, Labelling and PL	
IA/0013	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	16/07/2008	16/07/2008	SmPC, Labelling and PL	
II/0005	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 Winthrop, 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/0006	IB_38_c_Change in test procedure of finished product - other changes	26/02/2008	n/a		
II/0001	Change(s) to the test method(s) and/or specifications for the active substance	24/01/2008	06/02/2008		
II/0003	The Marketing Authorisation Holder applied for the addition of a new presentation: cartridge for Opticlick. New presentation(s)	15/11/2007	20/12/2007	SmPC, Labelling and PL	
IA/0002	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	06/08/2007	n/a		