Apidra

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/0096	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/02/2025		Labelling and PL	
II/0095	B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch	17/10/2024	n/a		

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	control/testing takes place and any of the test method at the site is a biol/immunol method				
N/0094	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/08/2024		PL	
IA/0093/G	This was an application for a group of variations. B.I.c.2.c - Change in the specification parameters and/or limits of the immediate packaging of the AS - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.c.2.b - Change in the specification parameters and/or limits of the immediate packaging of the AS - Addition of a new specification parameter to the specification with its corresponding test method B.I.c.2.a - Change in the specification parameters and/or limits of the immediate packaging of the AS - Tightening of specification limits	13/12/2023	n/a		
PSUSA/1752/ 202304	Periodic Safety Update EU Single assessment - insulin glulisine	30/11/2023	n/a		PRAC Recommendation - maintenance
N/0091	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/06/2023		PL	
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		

II/0088/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	10/03/2022	n/a		
N/0089	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/12/2021		PL	
N/0087	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/11/2020	20/08/2021	PL	
PSUSA/1752/ 202004	Periodic Safety Update EU Single assessment - insulin glulisine	29/10/2020	n/a		PRAC Recommendation - maintenance
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/0085	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/0083	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/02/2020	20/08/2021	PL	

II/0082/G	This was an application for a group of variations. 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.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.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing	16/01/2020	n/a		
PSUSA/1752/ 201904	Periodic Safety Update EU Single assessment - insulin glulisine	31/10/2019	n/a		PRAC Recommendation - maintenance
IAIN/0080	B.IV.1.b - Change of a measuring or administration device - Deletion of a device	15/02/2019	11/04/2019	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 intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name	20/11/2018	n/a		

	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				
PSUSA/1752/ 201804	Periodic Safety Update EU Single assessment - insulin glulisine	31/10/2018	n/a		PRAC Recommendation - maintenance

IB/0077	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	03/04/2018	11/04/2019	SmPC, Labelling and PL	
PSUSA/1752/201704	Periodic Safety Update EU Single assessment - insulin glulisine	26/10/2017	n/a		PRAC Recommendation - maintenance
IAIN/0075	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	16/06/2017	03/08/2017	SmPC, Labelling and PL	
II/0074/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	09/06/2017	n/a		
IA/0073	B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	05/01/2017	03/08/2017	SmPC, Labelling and PL	
IB/0071	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	14/12/2016	n/a		

	an obsolete parameter)				
IA/0070/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	14/12/2016	n/a		
IB/0072	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	06/12/2016	n/a		
PSUSA/1752/ 201604	Periodic Safety Update EU Single assessment - insulin glulisine	27/10/2016	n/a		PRAC Recommendation - maintenance
IB/0069	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	04/10/2016	n/a		
II/0066	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	15/09/2016	03/08/2017	Labelling	
N/0067	Update of the package leaflet with revised contact details of the local representatives for Hungary, Italy and Lithuania. In addition, the MAH took the opportunity to make linguistic amendments to the	28/06/2016	03/08/2017	PL	

	Danish, Finnish, Hungarian, Icelandic, Lithuanian, Spanish and Swedish labelling and package leaflets. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)				
IA/0065/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits 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)	22/12/2015	n/a		
IB/0064	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	09/11/2015	n/a		
PSUSA/1752/ 201504	Periodic Safety Update EU Single assessment - insulin glulisine	06/11/2015	n/a		PRAC Recommendation - maintenance
N/0063	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/08/2015	03/08/2017	PL	

PSUV/0060	Periodic Safety Update	06/11/2014	n/a		PRAC Recommendation - maintenance
IB/0061	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	24/10/2014	n/a		
IB/0057	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)	22/07/2014	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/0054	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	26/06/2014	n/a		
PSUV/0055	Periodic Safety Update	08/05/2014	n/a		PRAC Recommendation - maintenance
N/0056	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/05/2014	01/10/2014	PL	

IB/0053	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	22/11/2013	01/10/2014	SmPC, Labelling and PL	
II/0049	Update of sections 4.2, 4.4, 4.8 and 6.6 of the SmPC following assessment of Apidra Risk Management Plan, to inform healthcare professionals about the causes leading to diabetic ketoacidosis (DKA) when Apidra is administered in continuous subcutaneous insulin infusions (CSII), and to highlight the advice on how to mitigate the risk by correct use of these systems. The package leaflet has been updated accordingly. The amendments to the product information are only applicable to the Apidra 100 Units/ml solution for injection in a vial, as this is the only presentation that can be used in a pump system. The MAH has also submitted data clarifying the stability of Apidra in pump systems for CSII which was also requested in RMP 025.6. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 9.0. The requested variation proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet. C.I.3.b - Implementation of change(s) requested	24/10/2013	01/10/2014	SmPC, Annex II and PL	Following the assessment of the Apidra Risk Management Plan, the MAH was requested to submit a Type II variation to revise the SmPC and PL to make more prominent the risk of Diabetic Ketoacidosis (DKA) associated with pump administration and to include advice on how to manage the condition. In addition, the MAH was asked to respond to a list of questions on the stability of Apidra in pump systems for with continuous subcutaneous insulin infusions (CSII). The amendments to the product information are only applicable to the Apidra 100 Units/ml solution for injection in a vial, as this is the only presentation that can be used in a pump system. The MAH agreed to amend section 4.4 of the SmPC to include information on the risk of DKA occurring in association with CSII. Additionally the MAH included "Hyperglycaemia (potentially leading to Diabetic ketoacidosis)" in section 4.8 with a frequency of "unknown". The MAH also agreed that advice already in section 6.6 should be included in section 4.2. The package leaflet has been amended to highlight this risk to patients (given that patients will self-administer Apidra using CSII). The updated text in sections 4.2 and 4.4 of the SmPC reads as follows: 4.2 Posology and method of administration Method of administration Continuous subcutaneous insulin infusion

	following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				Apidra may be used for Continuous Subcutaneous Insulin Infusion (CSII) in pump systems suitable for insulin infusion with the appropriate catheters and reservoirs. Patients using CSII should be comprehensively instructed on the use of the pump system. The infusion set and reservoir used with Apidra must be changed at least every 48 hours using aseptic technique. These instructions may differ from general pump manual instructions. It is important that patients follow the Apidra specific instructions when using Apidra. Failure to follow Apidra specific instructions may lead to serious adverse events. When used with a subcutaneous insulin infusion pump, Apidra must not be mixed with diluents or any other insulin. Patients administering Apidra by CSII must have an alternative insulin delivery system available in case of pump system failure (see section 4.4 and 4.8). 4.4 Special warnings and precautions for use Continuous subcutaneous insulin infusion Malfunction of the insulin pump or infusion set or handling errors can rapidly lead to hyperglycaemia, ketosis and diabetic ketoacidosis. Prompt identification and correction of the cause of hyperglycaemia or ketosis or diabetic ketoacidosis is necessary. Cases of diabetic ketoacidosis have been reported when Apidra has been given in continuous subcutaneous insulin infusion in pump systems. Most of the cases were related to handling errors or pump system failure. Interim subcutaneous injections with Apidra may be required. Patients using continuous subcutaneous insulin

					infusion pump therapy must be trained to administer insulin by injection and have alternative insulin delivery system available in case of pump system failure (see section 4.2 and 4.8).
IB/0052	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	01/10/2014	SmPC, 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		
II/0046/G	This was an application for a group of variations. This was an application for a group of variations to change in the specification parameters and limits of the finished product. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change	17/01/2013	17/01/2013		

	outside the approved specifications limits range				
II/0047	Update of section 4.6 of the SmPC in order to reflect current post-marketing experience of Apidra use in pregnancy. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	18/10/2012	19/11/2012	SmPC and PL	In this variation the MAH presented a cumulative summary of reports of exposure in pregnancy from the pharmacovigilance safety database up to 16 April 2012. This includes 114 reports of pregnancy exposure reported with or without an adverse event from all sources (spontaneous, clinical trial, and post-marketing surveillance). The limited information provided did not show any new safety concerns.
II/0048	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	20/09/2012	20/09/2012		
II/0044	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	24/05/2012	n/a		
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	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

	presentation for the Insuman, Insuman Human 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				users) and a continued evaluation of possible improvements of the 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/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 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)	29/02/2012	n/a		

	to the DDPS that does not impact on the operation of the pharmacovigilance system				
II/0038	To change in the specification parameters and limits of the immediate packaging of the finished product. B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation	16/02/2012	16/02/2012		
IB/0043	B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)	19/12/2011	n/a		
IB/0039	B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)	19/10/2011	n/a		
IA/0037	B.III.2.a.2 - Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material	26/09/2011	n/a		
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/0036	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/0035	Changes to the cleaning procedure used for the bioreactor during 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	19/05/2011	19/05/2011		
II/0029	Update of product information to reflect the risk of medication errors (insulin mix-up). C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	16/12/2010	24/01/2011	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/0034	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/0033	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/0032	B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g.	23/11/2010	n/a		

	duplication of line)				
IB/0031	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/0030	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	17/09/2010	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 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	06/05/2010	n/a	Annex II	

	system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
X/0023	Annex I_2.(e) Change or addition of a new route of administration	22/10/2009	14/01/2010	SmPC, Annex II, Labelling and PL	Please refer to the scientific discussion: Apidra H-557-X-23-AR.
IB/0027	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)	10/11/2009	n/a		
IB/0026	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	10/11/2009	n/a		
R/0025	Renewal of the marketing authorisation.	29/05/2009	20/08/2009	SmPC and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit-risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Apidra continues to be favourable.
N/0021	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/03/2009	n/a	Labelling	
IB/0022	IB_38_c_Change in test procedure of finished product - other changes	12/02/2009	n/a		

IA/0024	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	21/01/2009	n/a		
II/0019	Update of Summary of Product Characteristics, Labelling and Package Leaflet. Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/04/2008	20/06/2008	SmPC, Labelling and PL	Update of the Product Information to harmonise the SPC, Labelling and PL of the sanofi-aventis insulin containing products (insuline glargine, insulin glulisine and insulin human). Particularly, the package leaflet has been updated to reflect the results of Readability User Testing. The PL has also been updated to reflect the outcome of the user consultation study performed to demonstrate the readability and usefulness of the PL to patients.
II/0017	Extension of Indication To include use of the product in a paediatric population of 6 years and above based on the results of the paediatric studies HMR1964D/3001 and HMR1964A/1017. Extension of Indication	24/04/2008	20/06/2008	SmPC, Annex II and PL	Please refer to the scientific discussion: Apidra H-557-II-17-AR
IB/0020	IB_38_c_Change in test procedure of finished product - other changes	20/02/2008	n/a		
IA/0018	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	06/08/2007	n/a		
II/0015	To update section 5.1 and section 5.2 of the SPC following assessment of the documentation concerning "MAH Obligation to submit data not yet submitted to the EMEA". The Package leaflet has	24/05/2007	02/07/2007	SmPC and PL	Post approval, the MAH has performed additional clinical pharmacology studies to further characterise time-concentration and time-action profiles for dose-proportionality in exposure and effect, and across a wide

	been amended to correct a mistake in section 3 and to introduce some improvements in section 4 and in the "Instructions for Use" for Optiset and SoloStar. In addition, minor changes to the list of local representatives have been introduced. The MAH also took the opportunity to update the Annexes in accordance with the QRD template, version 7.2. Update of Summary of Product Characteristics and Package Leaflet				range of body mass indices, to explore the effect on endogenous glucose production, and to study the diurnal post-prandial blood glucose profile. An in vitro study was performed to add information on protein binding. These data were submitted in the framework of the "MAH obligation to submit data not yet submitted to EMEA". Following the assessment of these data, the CHMP requested the MAH to provide full reports for studies F2003KIN0199, 1019, 1501, 1502, 1505 and synopses of studies 3005 and 3502. The MAH amended sections 5.1 and 5.2 of the SPC, to include some of the results that were considered of special interest for the prescribing physician.
II/0016	Quality changes	21/06/2007	25/06/2007		
N/0014	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/03/2007	n/a	PL	
IB/0013	IB_25_a_02_Change to comply with Ph. - compliance with EU Ph. - excipient	06/12/2006	n/a		
II/0012	Update of Summary of Product Characteristics and Package Leaflet of the Optiset presentations to reflect a revision of the Optiset Instructions for Use. Update of Summary of Product Characteristics and Package Leaflet	21/09/2006	24/10/2006	SmPC and PL	After the experience gained from user surveys and outside experts consultation, the MAH has proposed to revise the Optiset Instructions for Use and the Summary of Product Characteristics of the Optiset presentations for Apidra. 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).

II/0010	New presentation(s)	27/07/2006	01/09/2006	SmPC, Labelling and PL	
IB/0011	IB_25_a_02_Change to comply with Ph. - compliance with EU Ph. - excipient	31/07/2006	n/a		
II/0008	Modifications to the OptiSet pen and imprinting the name of the insulin on the pen for identification. Change(s) to (an) ancillary medical device(s)	23/03/2006	05/05/2006	SmPC, Labelling and PL	The purpose of the change is to implement a technical improvement 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.
IA/0009	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	03/03/2006	n/a	SmPC, Annex II, Labelling and PL	
II/0005	Change(s) to the manufacturing process for the active substance	13/10/2005	19/10/2005		
N/0006	The Marketing Authorisation Holder (MAH) applied for an update of the list of local representatives in the Package Leaflet. Linguistic and typographic corrections were also introduced in the labelling and Package Leaflet.	16/09/2005	n/a	Labelling and PL	

	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)				
II/0004	Update of sections 4.2, 4.4 and 6.6 of the Summary of Product Characteristics (SPC), labelling and Package Leaflet (PL) for Apidra (OptiSet presentations). In addition, the term "international units" was substituted by "units" in the PL of all the presentations. Update of Summary of Product Characteristics, Labelling and Package Leaflet	26/05/2005	04/07/2005	SmPC, Labelling and PL	This variation concerns the update of sections 4.2, 4.4 and 6.6 of the Summary of Product Characteristics (SPC) for Apidra, 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. These changes include an additional warning statement (in Sections 4.2 and 4.4) that the Instructions for Handling in Section 6.6 should be carefully followed. The handling of OptiSet was updated based on readability test results. Accordingly, the Package Leaflet (PL) has been revised for improved clarity including a revision of the instructions for the use of Apidra (OptiSet presentations). A caution statement has also been added to the outer carton. In addition, the term "international units" was substituted by "units" in all package leaflets (vial, cartridge, cartridge for OptiClik, OptiSet), in line with the CHMP recommendations and the labelling approved for Apidra.
II/0002	This variation was for the addition of a new presentation: cartridge for Opticlick. The package sizes for this presentation introduced with this variation are: 1, 3, 4, 5, 6, 8, 9 and 10 cartridges. New presentation(s)	17/03/2005	13/05/2005	SmPC, Labelling and PL	The new cartridges are identical to cartridges already authorised for the product and are irreversibly integrated in a disposible module for use with the pen delivery device Opticlick., which has already been approved and is also being used with other centrally authorised products. The quality data provided in support of this variation were satisfactory. A separate Summary of Product

					Characteristics (SPC) was developed with specific text for Opticlick in sections 6.5 and 6.6.
II/0001	Change(s) to container	16/03/2005	23/03/2005		
N/0003	The Marketing Authorisation Holder applied for changes to the labelling to add instructions on the aluminium foil used for sealing the transparent plastic tray containing the cartridge. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/03/2005	n/a	Labelling	