Lantus

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/0137	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/02/2025		Labelling and PL	
IB/0136	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	16/01/2025	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).

	corresponding test method				
WS/2732	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method	17/10/2024	n/a		
N/0134	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/08/2024		PL	
IB/0133/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	13/02/2024	n/a		
WS/2570	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	18/01/2024	n/a		

	material/intermediate				
IB/0130/G	This was an application for a group of variations. 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.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	16/11/2023	n/a		
WS/2539	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	07/09/2023	n/a		
WS/2491	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	20/07/2023	n/a		
N/0129	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/07/2023		PL	

PSUSA/1751/202204	Periodic Safety Update EU Single assessment - insulin glargine	01/12/2022	n/a		PRAC Recommendation - maintenance
IB/0124	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	02/12/2021	n/a		
IA/0125	A.7 - Administrative change - Deletion of manufacturing sites	24/11/2021	25/01/2022	Annex II and PL	
PSUSA/1751/202004	Periodic Safety Update EU Single assessment - insulin glargine	26/11/2020	n/a		PRAC Recommendation - maintenance
N/0123	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/10/2020	25/01/2022	PL	
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/0121	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/08/2020	25/01/2022	SmPC, Annex II and PL	
WS/1819/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	05/06/2020	n/a		

	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation				
PSUSA/1751/201904	Periodic Safety Update EU Single assessment - insulin glargine	14/11/2019	16/01/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1751/201904.
IAIN/0117	B.IV.1.b - Change of a measuring or administration device - Deletion of a device	15/02/2019	08/04/2019	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 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				
PSUSA/1751/ 201804	Periodic Safety Update EU Single assessment - insulin glargine	31/10/2018	n/a		PRAC Recommendation - maintenance
PSUSA/1751/ 201710	Periodic Safety Update EU Single assessment - insulin glargine	17/05/2018	n/a		PRAC Recommendation - maintenance

IB/0114	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	03/04/2018	08/04/2019	SmPC, Labelling and PL	
PSUSA/1751/201704	Periodic Safety Update EU Single assessment - insulin glargine	30/11/2017	n/a		PRAC Recommendation - maintenance
IB/0112/G	This was an application for a group of variations. B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation A.7 - Administrative change - Deletion of manufacturing sites	13/11/2017	n/a		
IAIN/0110	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	03/10/2017	SmPC, Labelling and PL	
PSUSA/1751/201610	Periodic Safety Update EU Single assessment - insulin glargine	05/05/2017	n/a		PRAC Recommendation - maintenance
II/0107/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.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	16/02/2017	n/a		

IAIN/0108/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	05/01/2017	03/10/2017	SmPC, Annex II, Labelling and PL	
II/0105	Submission of the study results of the PASS entitled: "UK SoloStar® Differentiation Study: Study in patients with Type 1 or Type 2 diabetes in the UK, to evaluate the ease of differentiating between SoloStar® pens containing different types of insulin with the current and new labels." This submission addresses MEA 051. As a consequence the mock-ups are revised. 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	03/10/2017	Labelling	
PSUSA/1751/ 201602	Periodic Safety Update EU Single assessment - insulin glargine	02/09/2016	n/a		PRAC Recommendation - maintenance
IG/0661	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)	28/01/2016	n/a		

N/0103	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/12/2015	03/10/2017	PL	
II/0102	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	26/11/2015	n/a		
IB/0101	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	03/09/2015	n/a		
IG/0593/G	This was an application for a group of variations. B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test 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)	05/08/2015	n/a		

II/0098	Update of section 4.2 of the SmPC in order to provide dosing instructions for switching from Toujeo (insulin glargine 300 U/mL) to Lantus (insulin glargine 100 U/mL).The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to correct some minor mistakes in the Product Information, to include the latest renewal date in section 9 of the SmPC and to amend local representative information for Romania in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/06/2015	28/07/2015	SmPC, Labelling and PL	Lantus and Toujeo (insulin glargine 300 units/ml) are not bioequivalent and are not directly interchangeable. To reduce the risk of hypoglycaemia, patients who are changing their basal insulin regimen from an insulin regimen with once daily insulin glargine 300 units/ml to a once daily regimen with Lantus should reduce their dose by approximately 20%.
IB/0099/G	This was an application for a group of variations. B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS 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)	06/07/2015	n/a		
IB/0097/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name	17/06/2015	28/07/2015	SmPC, Annex II, Labelling	

	and/or address of a manufacturer/importer responsible for batch release B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product			and PL	
R/0096	Renewal of the marketing authorisation.	18/12/2014	17/02/2015	SmPC, Labelling 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 Lantus continues to be favourable. The CHMP was also of the opinion that the renewal can be granted with unlimited validity.
IG/0475/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	01/09/2014	n/a		
IG/0463	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for	01/09/2014	n/a		

	the AS -replacement or addition of a site where batch control/testing takes place				
IB/0090	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)	05/08/2014	n/a		
IB/0091	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	18/07/2014	15/12/2014	SmPC and PL	
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/0397/G	This was an application for a group of variations. B.III.2.a.1 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - AS B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	27/01/2014	n/a		

II/0087	Update of section 4.6 of the SmPC based on results of a meta-analysis of published data and a review of other published and post-marketing data of insulin glargine use during pregnancy. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/12/2013	15/12/2014	SmPC and PL	Within this variation the Marketing Authorisation Holder (MAH) updated section 4.6 of the SmPC with information of the use of insulin glargine in pregnancy. In support of the application, the MAH presented results of a meta-analysis of published data on the use of insulin glargine compared to NPH in pregnancy, as well as additional available clinical data published up to 20 May 2013 and post-marketing data. The meta-analysis comprised 8 observational cohort studies with a total of 702 women with pregestational or gestational diabetes, of whom 331 received insulin glargine and 371 received NPH insulin. The meta-analysis examined maternal outcomes for efficacy and safety, and neonatal outcomes. The results of the meta-analysis did not reveal any significant increased risk associated with the use of insulin glargine compared with NPH insulin for any of the maternal or neonatal outcomes reported. With regard to the safety of insulin glargine use during pregnancy, in comparison to NPH insulin, there was no increased risk to the mother for weight gain, severe hypoglycemia, gestational/new-onset hypertension, preeclampsia, or cesarean section. While individual studies did inconsistently report differences, many of the individual findings were favourable to insulin glargine. Glycaemic control as measured by first and third trimester HbA1c was not different between the pregnant women using insulin glargine and those using NPH insulin. The CHMP conclusion on the meta-analysis was that it supports the overall insulin glargine program results, but could not constitute a stand-alone demonstration of glargine efficacy and safety in pregnant women with diabetes due to the limitations of the observational non-

					randomized design of the published reports. In addition to the meta-analysis the MAH also submitted a cumulative summary of exposure reports since the launch of the product and provided information received during the current 6-month reporting period through 21 October 2012. Pregnancy outcomes reported to date in this diabetic patient population do not suggest a new risk for patients treated with insulin glargine. This conclusion was endorsed by the CHMP.
IB/0088	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	15/12/2014	SmPC, Labelling and PL	
IB/0085	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	20/12/2013	SmPC, Labelling and PL	
IG/0323	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	25/07/2013	n/a		
IG/0314	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/07/2013	n/a		
II/0082	Update of section 5.1 of the SmPC in order to include the results from the ORIGIN trial. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.	30/05/2013	20/12/2013	SmPC, Annex II and PL	This variation was submitted to support an update of the Lantus prescribing information based on data from the ORIGIN trial (Outcomes Reduction with an Initial Glargine INtervention). This was a multinational 7-year randomized clinical study that investigated the effect of Lantus on

	Furthermore, the PI is being brought in line with the latest QRD template version 9.0, and some typographical errors were corrected in the SmPC. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				cardiovascular (CV) morbidity and mortality in patients with prediabetes (impaired fasting glucose [IFG], impaired glucose tolerance [IGT]) or early Type 2 diabetes mellitus (T2DM) who had evidence of CV disease. The first coprimary endpoint (composite of the first occurrence of CV death, nonfatal myocardial infarction, or nonfatal stroke) did not show any difference between insulin glargine and standard care. Also, the second coprimary endpoint (hospitalization for heart failure or revascularization procedure added to the first three components), did not show any difference. In addition, analysis by various subgroups did not reveal significant differences. Outcomes of secondary and tertiary endpoints were consistent. Therefore, it is concluded that early treatment with insulin glargine had no effect (beneficial or detrimental) on CV morbidity or cardiovascular and over-all mortality. This is an important finding that has been included in section 5.1 of the SmPC. In subjects with prediabetes, there was a numeric reduction in the percentage of subjects developing diabetes at the first post-EUF OGTT, but this effect declined after 3 months and was not clinically relevant. Cancer relationship to insulin glargine was not demonstrated in any cancer subtype (e.g. breast, colon, prostate, lung), or for new or recurrent cancers, or deaths from cancer, over 6.2 years of median follow-up. Kaplan-Meier curves for the first cancer diagnosed during the trial, the first new cancer diagnosed, and death due to cancer were practically superimposable between the insulin glargine and standard care groups. Although this is important information, it has not been included in the

					SmPC because, (i) the design of the ORIGIN study was not anticipated in order to assess the risks of cancer (ii) it is questionable whether these results could be extrapolated to long-standing diabetes with high doses of insulin (iii) available epidemiological results regarding the risk of breast cancer for longer exposures to glargine are not fully consistent across different studies. No unexpected safety issues were seen in this trial. As was expected weight did increase, and hypoglycaemia was still the major adverse event seen in association with treatment with insulin glargine. Rates of hypoglycemia in ORIGIN might be lower than those seen in other CV intervention trials in diabetes; however, as no beneficial effect of insulin glargine could be detected in this trial, an increase in the incidence of hypoglycaemia is a disadvantage. In summary, any benefit of early treatment with insulin on lower levels of HbA1 without improvement in CV outcome is outweighed by its side effects and applicability. The following text was included in section 5.1 of the SmPC to describe the design and results of this study: "The ORIGIN (Outcome Reduction with Initial Glargine INtervention) study was a multicenter, randomized, 2x2 factorial design study conducted in 12,537 participants at high cardiovascular (CV) risk with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) (12% of participants) or type 2 diabetes mellitus treated with ≤1 antidiabetic oral agent (88% of participants). Participants were randomized (1:1) to receive insulin glargine (n=6264), titrated to reach FPG ≤95 mg/dL (5.3 mM), or standard care (n=6273). The first co primary efficacy outcome was the time to the first occurrence of CV death, nonfatal myocardial infarction

					(MI), or nonfatal stroke, and the second co primary efficacy outcome was the time to the first occurrence of any of the first co primary events, or revascularisation procedure (coronary, carotid, or peripheral), or hospitalisation for heart failure. Secondary endpoints included all cause mortality and a composite microvascular outcome. Insulin glargine did not alter the relative risk for CV disease and CV mortality when compared to standard of care. There were no differences between insulin glargine and standard care for the two co primary outcomes; for any component endpoint comprising these outcomes; for all cause mortality; or for the composite microvascular outcome. Mean dose of insulin glargine by study end was 0.42 U/kg. At baseline, participants had a median HbA1c value of 6.4% and median on-treatment HbA1c values ranged from 5.9 to 6.4% in the insulin glargine group, and 6.2% to 6.6% in the standard care group throughout the duration of follow up. The rates of severe hypoglycaemia (affected participants per 100 participant years of exposure) were 1.05 for insulin glargine and 0.30 for standard care group and the rates of confirmed non severe hypoglycaemia were 7.71 for insulin glargine and 2.44 for standard care group. Over the course of this 6 year study, 42% of the insulin glargine group did not experience any hypoglycaemia. At the last on treatment visit, there was a mean increase in body weight from baseline of 1.4 kg in the insulin glargine group and a mean decrease of 0.8 kg in the standard care group.”

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/0243	A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release	19/12/2012	20/12/2013	Annex II and PL	
WS/0332	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	13/12/2012	n/a		
IG/0227	A.7 - Administrative change - Deletion of manufacturing sites	13/11/2012	n/a		
IG/0192	C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	06/07/2012	n/a		
II/0075	Extension of indication for the use of Lantus in children aged 2 to less than 6 years affecting sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC. The Package Leaflet was proposed to be updated in accordance. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.	19/04/2012	25/05/2012	SmPC and PL	For further information please refer to the scientific conclusion: H-284-VAR-II-75-en

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
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 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	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 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.
II/0077/G	This was an application for a group of variations. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological 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	19/04/2012	19/04/2012		

II/0072	Update of sections 5.1 and 5.2 of the Summary of Products Characteristics (SmPC) to reflect new data on insulin glargine metabolites. In addition a minor change has been done to the Package Leaflet following the latest QRD template. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/07/2011	24/08/2011	SmPC and PL	Insulin glargine is metabolized in the subcutaneous (SC) tissue at the carboxyl terminus of the B chain to form the two active metabolites, M1 and M2. With the availability of a new specific and quantitative bioanalytical method, pharmacokinetic (PK) samples collected in a euglycaemic clamp study were used to further explore the systemic exposure to unchanged insulin glargine and the two metabolites M1 and M2 in patients with Type 1 diabetes mellitus (T1DM) and the correlation to the established glucodynamic effect. In this clinical study insulin glargine was used as a reference at single SC doses of 0.3, 0.6, and 1.2 U/kg. The results of this study demonstrated that M1 was the principle circulating compound whereas unchanged insulin glargine and metabolite M2 were detected in only very few individual patients at few time points. The glucodynamic response correlated with metabolite M1 exposure. The CHMP agreed that this new data on insulin glargine metabolites was added to the SmPC.
IB/0074	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	28/07/2011	n/a		
IA/0073	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/0070	Changes to the cleaning procedure used for the bioreactor during the manufacturing process of the	19/05/2011	19/05/2011		

	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				
IA/0071	A.7 - Administrative change - Deletion of manufacturing sites	11/04/2011	n/a	Annex II and PL	
II/0065	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	24/01/2011	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/0069	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/0068	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/0067	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.	22/10/2010	n/a	SmPC, Labelling and PL	

	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				
IA/0066/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	17/09/2010	n/a		
II/0063	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	24/06/2010	07/07/2010		
R/0062	Renewal of the marketing authorisation.	18/02/2010	05/05/2010	SmPC, Labelling and PL	Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Lantus remains positive, but considers that its safety profile is to be closely monitored for the following reasons: - Following the publication of four epidemiological studies

					on the risk of (breast) cancer with the use of insulin glargine in the journal Diabetologia, concerns were raised about the safety of insulin glargine in this respect. At this moment, three post-marketing pharmacoepidemiology studies are initiated by the MAH to further investigate the possible increased risk of cancer associated with the use of insulin glargine. These studies are planned to be finished within the next three years. Based on this, and according to Article 14.3 of Regulation EC(N0) 726/2004, the CHMP is of the opinion that one additional five-year renewal on the basis of Pharmacovigilance grounds is required. - The CHMP decided that the MAH should continue to submit yearly PSURs. Therefore, based upon the safety profile of Lantus, which requires the submission of yearly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.
II/0057	Update of the warning on switching between different insulins in 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. Section 6 of the Package Leaflet is also updated with an additional telephone number for Italy. Update of Summary of Product Characteristics and Package Leaflet	24/09/2009	04/11/2009	SmPC and PL	Section 4.4 of the SPC was updated in order to harmonize the information between all Sanofi-Aventis Deutschland GmbH insulins regarding the transfer from one insulin to another. The information given to the prescriber has been made clearer. Section 5.1 of the SPC was updated to comply with the latest version of the QRD template for the SPC. Only the lowest available level of this pharmacotherapeutic group is now provided.

					Finally, Section 6 of Package Leaflet was also updated with an additional telephone number for Italy.
IB/0061	IB_30_b_Change in supplier of packaging components - replacement/addition	25/09/2009	n/a		
IB/0060	IB_30_b_Change in supplier of packaging components - replacement/addition	25/09/2009	n/a		
II/0055	Update of Summary of Product Characteristics and Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	23/07/2009	17/09/2009	SmPC and PL	Update to section 6.6 of the SPC to clarify the instructions for use of the pre-filled pen Optiset and the pre-filled pen Solostar. The package leaflet was updated accordingly. The contact details of the local representative in Poland were also updated in the PL. Minor linguistic changes introduced in the SPC.
IB/0058	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	11/09/2009	n/a		
IA/0059	IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	04/09/2009	n/a	Annex II and PL	
II/0056	Changes in the batch size of the manufacturing process of the drug product for the 10 ml vials presentation Change(s) to the manufacturing process for the finished product	23/07/2009	30/07/2009		
N/0053	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/03/2009	n/a	Labelling	

IB/0054	IB_38_c_Change in test procedure of finished product - other changes	12/02/2009	n/a		
II/0051	To include an additional site for manufacture and batch release 01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	23/10/2008	28/11/2008	Annex II	
II/0052	Change in the holding time of a manufacturing intermediate for the manufacturing process of insulin glargine solution for injection 100 Units/ml in 3 ml cartridges. Change(s) to the manufacturing process for the finished product	20/11/2008	27/11/2008		
II/0050	To update section 5.1 of the SPC with additional information on the effects of Lantus (insulin glargine) on progression of diabetic retinopathy, based on results of study HOE901/4016. Update of Summary of Product Characteristics	24/07/2008	17/09/2008	SmPC	This variation concerns the update of section 5.1 (Pharmacodynamic properties) of the Summary of Product Characteristics for Lantus to include the results of study HOE901/4016, an open-label 5-year NPH-controlled study (NPH given bid) in 1024 type 2 diabetic patients in which progression of retinopathy by 3 or more steps on the Early Treatment Diabetic Retinopathy (ETDRS) scale was investigated by fundus photography. The results demonstrated that for all eye disease variables based on blinded evaluation of fundus photographs, there were no differences between treatments for 5 years with Lantus versus NPH insulin as basal insulin.
II/0045	Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/04/2008	25/06/2008	SmPC, Labelling and	Update of the Product Information (PI) to harmonise the Summary of Product Characteristics (SPC), Labelling and

	Update of Summary of Product Characteristics, Labelling and Package Leaflet			PL	Package Leaflet of the sanofi-aventis insulin containing products (insuline glargine, insulin glulisine and insulin human). Particularly for Lantus, the SPC has been revised and the package leaflet has been updated to reflect the outcome of the Readability User Testing performed to demonstrate the readability and usefulness of the PL to patients.
IB/0049	IB_38_c_Change in test procedure of finished product - other changes	20/02/2008	n/a		
IB/0048	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	01/02/2008	n/a		
IB/0047	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	01/02/2008	n/a		
II/0040	The Marketing Authorisation Holder applied for some minor optimizations to the manufacturing process of insulin glargine Quality changes	24/01/2008	30/01/2008		
IA/0046	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	09/01/2008	n/a		
II/0042	Quality changes of the drug product. Quality changes	13/12/2007	19/12/2007		
IB/0044	IB_27_b_Change to test proc. of immediate packaging - other changes (incl.	17/12/2007	n/a		

	replacement/addition)				
II/0041	Update of section 4.4 of the SPC to include a cross-reference to a warning on antibody formation already present in the section 4.8. The Package Leaflet was amended to update the list of local representatives in section 6 and to include some minor editorial corrections. Update of Summary of Product Characteristics and Package Leaflet	20/09/2007	14/11/2007	SmPC and PL	The MAH has updated section 4.4 'Special Warnings and precautions for use' of the SPC to include a cross-reference to antibody formation already present in section 4.8 'Undesirable effects', as previously requested by the CHMP. The Package Leaflet was amended to update the list of local representatives and to include some minor editorial corrections.
IB/0043	Addition of an alternative test procedure of the finished product used for release and stability testing IB_38_c_Change in test procedure of finished product - other changes	31/10/2007	n/a		
IA/0039	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	20/06/2007	n/a		
IA/0038	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	13/04/2007	n/a		
N/0035	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/04/2007	n/a	Labelling and PL	
IB/0037	IB_38_c_Change in test procedure of finished product - other changes	16/03/2007	n/a		
IA/0036	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	08/02/2007	n/a		

IB/0034	IB_25_a_02_Change to comply with Ph. - compliance with EU Ph. - excipient	06/12/2006	n/a		
II/0032	Update of section 4.8 of the SPC and relevant section of the PL to include safety information on patients </= 18 years of age. Update of Summary of Product Characteristics and Package Leaflet	21/09/2006	31/10/2006	SmPC and PL	Following the assessment of a clinical trial and post-marketing surveillance data in the paediatric population, the CHMP requested that section 4.8 of the SPC should be updated to reflect safety information on patients </= 18 years. Section 4.8 of the SPC has been updated with the following wording: In general, the safety profile for patients </= 18 years of age is similar to the safety profile for patients > 18 years. The adverse event reports received from Post Marketing Surveillance included relatively more frequent injection site reactions (injection site pain, injection site reaction) and skin reactions (rash, urticaria) in patients </= 18 years of age than in patients > 18 years. No clinical study safety data are available in patients below 6 years of age." The PL has been updated accordingly.
II/0031	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	31/10/2006	SmPC and PL	After the experience gained from the users through 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 Lantus. 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/0029	New presentation(s)	27/07/2006	01/09/2006	SmPC, Labelling and	

				PL	
IB/0033	IB_25_a_02_Change to comply with Ph. - compliance with EU Ph. - excipient	21/08/2006	n/a		
II/0030	This variation relates to an update of section 4.6 "Pregnancy and Lactation" of the Summary of Product Characteristics, following CHMP request further to the assessment of the FUM 025.1. Update of Summary of Product Characteristics	28/06/2006	07/08/2006	SmPC	Further to their conclusions of the assessment of cumulatively reported data of exposure during pregnancy, the CHMP requested a variation to change the section 4.6 of the SPC "Pregnancy and Lactation"to reflect the latest available information on exposed pregnancies.
II/0026	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/0027	Change(s) to the manufacturing process for the finished product	23/03/2006	30/03/2006		
IA/0028	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.)	03/03/2006	n/a	SmPC, Annex II, Labelling and PL	

	IA_05_Change in the name and/or address of a manufacturer of the finished product				
N/0025	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/09/2005	n/a	PL	
R/0024	Renewal of the marketing authorisation.	21/04/2005	08/07/2005	SmPC, Annex II, Labelling and PL	
II/0022	The Marketing Authorisation Holder applied for a change in the formulation of the finished product for Lantus 100 IU/ml solution for injection in a 10 ml vial. Change in formulation	16/03/2005	27/04/2005	SmPC, Labelling and PL	
II/0023	The Marketing Authorisation Holder applied for changes in specification limits and test procedures for the active substance. Change(s) to the test method(s) and/or specifications for the active substance	17/02/2005	25/02/2005		
II/0020	The Marketing Authorisation Holder applied for the use of an alternative rubber stopper for the 3 ml cartridge and for an extension of the shelf life of the finished product as packaged for sale, from 2 years to 3 years, for the current and proposed alternative container closure system of the 3 ml cartridge presentations.	18/11/2004	11/01/2005	SmPC	

	Change(s) to container				
IA/0021	IA_28_Change in any part of primary packaging material not in contact with finished product	19/10/2004	n/a	SmPC	
II/0018	The Marketing Authorisation Holder applied for the addition of a new manufacturing facility for the active substance, at a site where this active substance is currently manufactured. Change(s) to the manufacturing process for the active substance	16/09/2004	30/09/2004		
II/0019	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 Lantus OptiSet. Addition of a caution statement to the outer carton.. Update of Summary of Product Characteristics, Labelling and Package Leaflet	29/07/2004	20/09/2004	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 Lantus OptiSet has been completely revised. A caution statement has been added to the outer carton.
II/0017	Update of section 6.6 of the Summary ofProduct Characteristics to includeinstructions and warnings for handling theOptiPen in case of mechanical	23/06/2004	31/08/2004	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

	defects. Update of Summary of Product Characteristics, Labelling and Package Leaflet				meeting that the Product Information for Lantus solution for injection in a cartridge should be amended to include a warning in the 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 of Lantus solution for injection in a cartridge. This information was also added to the labelling of 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 Lantus 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/0015	The Marketing Authorisation Holder applied for a new cartridge, which consists of an already approved cartridge irreversibly integrated in the disposable module of an insulin pen delivery device (OptiClik). New presentation(s) Change(s) to container	23/06/2004	31/08/2004	SmPC, Labelling and PL	The Marketing Authorisation Holder applied for a new cartridge, which consists of an already approved cartridge irreversibly integrated in the disposable module of an insulin pen delivery device (OptiClik). This "cartridge for OptiClik" is to be used with the reusable part of the device (dialing module and pen cap), which is provided separately from the medicinal product.
II/0016	Update to include information regarding the effect of atypical antipsychotic products and protease inhibitors on hyperglycaemia in section 4.5 of the Summary of Product Characteristics (SPC). Section 2 of the Package Leaflet has been updated accordingly.	22/04/2004	13/07/2004	SmPC and PL	Based on publications submitted in this variation, it may be concluded that patients receiving atypical antipsychotics medicinal products or protease inhibitors are at risk of hyperglycemia, whether or not they have preexisting diabetes. This conclusion supports an update of section 4.5

	Update of Summary of Product Characteristics and Package Leaflet				of the SmPC and a consistent update is made to the package leaflet. The CHMP concluded that protease inhibitors and atypical antipsychotic medicinal product (e.g. clozapine and olanzapine) should be added to the list of substances, which may reduce the blood-glucose lowering effect listed in section 4.5 of the SPC.
II/0014	The Marketing Authorisation Holder applied for the use of non animal trypsin and for minor changes to 2 steps of the manufacturing process of the active substance. Change(s) to the manufacturing process for the active substance Change(s) to the test method(s) and/or specifications for the active substance	22/04/2004	26/04/2004		
II/0012	The Marketing Authorisation Holder applied for minor changes to 3 steps of the manufacturing process of the active substance. Change(s) to the manufacturing process for the active substance	25/09/2003	30/09/2003		
N/0013	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/08/2003	17/10/2003	Labelling	
I/0011	11b_Change in supplier of an intermediate compound used in manufacture of the active substance	19/06/2003	25/06/2003		
I/0010	16_Change in the batch size of finished product	25/04/2003	02/05/2003		1 Introduction

					The company has applied for an increase in the batch size of the bulk solution of the finished product (3 ml cartridges) from 200 - 400 liter (initially approved) up to 1600 liter. For the 10 ml filling this increase in batch size has already been submitted and approved (EMEA/H/C/284/II/06). In support of the variation the company has submitted validation data, a quality expert statement and an updated process narrative/flow chart. 2 Chemical, pharmaceutical and biological aspects The bulk solution of 1600 l is distributed into movable vessels of 400 l capacity each. As a result the filling process itself remains unaffected. The effect on the filling duration is appropriately validated with media fills. The (in-process and final product quality control) results of three batches were within established limits and met all specifications approved in the MAA. A comparison with three batches prepared on the 400 ml scale indicate no differences between batches produced on the 400 ml scale and the 1600 l scale. Therefore, the proposed variation to increase the batch size for the 3 ml cartridges from 400 l into 1600 l can be approved. This variation also fulfills follow-up measure 006.
I/0009	30_Change in pack size for a medicinal product	19/03/2003	22/04/2003	SmPC, Labelling and PL	
II/0007	Extension of Indication	21/11/2002	04/03/2003	SmPC and PL	

II/0008	Change in the dosing scheme for Lantus with the consequent change in section 4.2 of the Summary of Product Characteristics (SPC). The Package Leaflet has been updated accordingly. A warning concerning "hypoglycaemia" has been included in section 4.4 of the SPC and the Package Leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	19/09/2002	05/12/2002	SmPC and PL	
II/0006	Addition of a new volume vial of 10 ml. New presentation(s)	26/07/2001	28/01/2002	SmPC, Annex II, Labelling and PL	
II/0005	Change in the insulin glargine production process. Change(s) to the manufacturing process for the active substance	27/06/2001	02/08/2001		
II/0004	Demonstration of TSE compliance Update of or change(s) to the pharmaceutical documentation	26/04/2001	08/05/2001		
II/0003	Change(s) to the manufacturing process for the active substance	01/03/2001	01/04/2001		
II/0002	Additional presentations: Lantus OptiSet, solution for injection in 3 ml pre-filled pens. New presentation(s)	19/10/2000	06/02/2001	SmPC and PL	

II/0001	Change(s) to the manufacturing process for the active substance	19/10/2000	05/12/2000		