Levemir

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
IB/0103	B.II.c.3.a.2 - Change in source of an excipient or reagent with TSE risk - From TSE risk material to vegetable or synthetic origin - For excipients or reagents USED in the manufacture of a biol/immunol AS or in a biol/immunol medicinal product	19/04/2021	n/a		

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

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II/0101	Update of sections 4.6 and 5.1 of the SmPC in order to update information on pregnancy, based on final results from the non-interventional Post-Authorisation Safety Study, NN304-4016, listed as a category 3 study in the RMP. This is a diabetes pregnancy registry study conducted to assess the long-term safety of insulin use in pregnant women. The RMP version 21.0 has also been submitted. The requested variation proposed amendments to the Summary of Product Characteristics and to the Risk Management Plan (RMP). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/04/2021		SmPC	The use of Levemir in pregnant women with diabetes has been investigated in a clinical trial and in a prospective non-interventional post-authorisation safety study. Post-marketing data in pregnant women using Levemir, with more than 4,500 pregnancy outcomes do not indicate any increased risk of malformative or feto/neonatal toxicity.
WS/1997	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	11/03/2021	n/a		
WS/1901	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/09/2020		SmPC, Annex II, Labelling and PL	
WS/1865	This was an application for a variation following a	03/09/2020	n/a		Not applicable

	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				
IG/1184	A.7 - Administrative change - Deletion of manufacturing sites	07/02/2020	n/a		
IG/1172	A.7 - Administrative change - Deletion of manufacturing sites	16/01/2020	n/a		
IG/1167	A.7 - Administrative change - Deletion of manufacturing sites	22/11/2019	n/a		
IG/1149	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	04/10/2019	n/a		
IG/1092	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	12/07/2019	n/a		
WS/1615	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	11/07/2019	n/a		

	B.I.z - Quality change - Active substance - Other variation				
PSUSA/1750/ 201810	Periodic Safety Update EU Single assessment - insulin detemir	16/05/2019	n/a		PRAC Recommendation - maintenance
IG/1066	A.7 - Administrative change - Deletion of manufacturing sites	29/03/2019	n/a		
IA/0091	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)	04/03/2019	n/a		
II/0089	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	08/11/2018	n/a		
PSUSA/1750/ 201710	Periodic Safety Update EU Single assessment - insulin detemir	14/06/2018	n/a		PRAC Recommendation - maintenance
IB/0088	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	09/04/2018	25/03/2019	SmPC and PL	
IG/0897	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites	19/03/2018	n/a		

	(excluding manufacturer for batch release)				
II/0084	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	22/06/2017	n/a		
PSUSA/1750/ 201610	Periodic Safety Update EU Single assessment - insulin detemir	09/06/2017	n/a		PRAC Recommendation - maintenance
II/0083	B.II.f.1.c - Stability of FP - Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol	26/01/2017	16/11/2017	SmPC, Labelling and PL	Levemir FlexPen/Levemir FlexTouch During use or when carried as a spare: Store below 30°C. Can be stored in a refrigerator (2°C–8°C). Do not freeze. Keep the pen cap on the pen in order to protect it from light.
II/0082	Update of sections 4.4 of the SmPC with additional information regarding avoidance of accidental mix-ups and medication errors. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 9.1 and 10.0 and to correct a mistake in the recommendation for use of the first of the two titration algorithms in section 4.2 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/12/2016	16/11/2017	SmPC, Annex II and Labelling	In order to minimise the accidental mix-ups/medication errors section 4.4 of SmPC has been updated with the following text: "Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups". A mistake on section 4.2 of PL on recommendation for use of the first titration algorithm has also been corrected.
PSUSA/1750/ 201510	Periodic Safety Update EU Single assessment - insulin detemir	13/05/2016	n/a		PRAC Recommendation - maintenance

N/0081	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/04/2016	16/12/2016	PL	
IG/0642	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	21/12/2015	16/12/2016	Annex II and PL	
IG/0644	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)	10/12/2015	n/a		
WS/0784	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	24/09/2015	n/a		
IG/0594	A.7 - Administrative change - Deletion of manufacturing sites	04/09/2015	n/a		
II/0070	Extension of Indication for Levemir to include new population, i.e. children between 1 and less than 2 years of age; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add the PK, efficacy and safety information. The Package Leaflet is updated accordingly. C.I.6.a - Change(s) to therapeutic indication(s) -	25/06/2015	28/07/2015	SmPC and PL	Please refer to the Scientific Discussion Levemir-H-C-528-II-70

	Addition of a new therapeutic indication or modification of an approved one				
IB/0075	B.II.h.z - Adventitious Agents Safety - Other variation	03/07/2015	n/a		
IB/0074	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	23/06/2015	n/a		
PSUSA/1750/ 201410	Periodic Safety Update EU Single assessment - insulin detemir	11/06/2015	n/a		PRAC Recommendation - maintenance
II/0071	Extension of indication to use levemir in combination with GLP-1 receptor agonists for the treatment of type 2 diabetes mellitus. Consequently, the MAH proposed the update of sections 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC. The Package Leaflet is updated in accordance. The variation proposed amendments to the Summary of Product Characteristics and Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	23/04/2015	27/05/2015	SmPC and PL	Please refer to the scientific discussion Levemir EMEA/H/C/000528/II/0071 for further information.
WS/0692	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.z - Change in manufacture of the AS - Other	23/04/2015	n/a		

	variation				
II/0066	Update of section 4.2 of the SmPC in order to add information on an alternative titration algorithm, referred to as the 3-0-3 titration algorithm. In addition the MAH took the opportunity to amend the product information in order to harmonise with other insulins from the same MAH. Furthermore, the PI is being brought in line with the latest QRD template version 9. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/12/2013	29/01/2014	SmPC, Annex II, Labelling and PL	With the present application the MAH proposed the following changes to the product's posology: Switching from NPH insulin to Levemir The first proposed change concerns addition of information with regards to dose reduction when switching from twice daily NPH insulin to once daily Levemir. A level of 20-30% reduction was proposed by the MAH in accordance with clinical practice. In support of this variation the MAH submitted 4 clinical trials in which a subset of subjects switched from twice daily NPH insulin to once daily Levemir and had their daily dose reduced by 20−30% according to protocol. The data presented revealed no increased risk of no reduction in the Levemir dose when switching, and therefore the relevance of the proposed changes are questioned. More important is, however, that none of the four trials presented were designed to answer the question whether a dose reduction of Levemir (and to which extent), is appropriate when switching from twice daily NPH insulin to once daily Levemir. Thus the subjects were not randomized to different levels of dose-reduction of Levemir, but on levels of reduction chosen at the discretion of the investigators. Furthermore the studies were not powered to demonstrate differences between the groups of dose reduction. In fact the groups compared were small and in several cases there were so few events that comparison between the groups was difficult or inappropriate. Therefore the CHMP concluded that the changes related to the switching from NPH insulin to Levemir were not

					approvable. The MAH agreed with the CHMP and did not introduce the proposed changes to the product information. 3-0-3 titration algorithm The MAH further proposed to include a self-managed 3-0-3 algorithm allowing patients to titrate their Levemir dose in steps of ±3 units every third day. In support of this change data from 3 randomised controlled clinical trials including 6454 subjects with type 2 diabetes have been submitted. The data submitted demonstrates that a similar level of glycaemic control can be obtained with the use of the self-managed 3-0-3 titration algorithm compared to standard care titration. The use of the 3-0-3 regime is however associated with an increased risk of hypoglycaemia, although not major hypoglycemia, especially when using the more aggressive titration. Therefore a warning of hypoglycaemia has been included in section 4.2 of the SmPC. Due to the benefits for the patients in terms of optimised self-care with this algorithm, the benefit risk ratio is however considered positive.
WS/0437	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 material/intermediate	23/01/2014	n/a		
IB/0068	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	15/01/2014	n/a		

N/0064	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/07/2013	29/01/2014	PL	
IA/0065	A.7 - Administrative change - Deletion of manufacturing sites	26/07/2013	n/a		
IG/0280	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/04/2013	n/a		
IB/0062	B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product	08/03/2013	n/a		
IB/0061	B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product	16/11/2012	n/a		
N/0059	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/03/2012	29/01/2014	PL	
WS/0209	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	16/02/2012	16/02/2012		

	test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IAIN/0060	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	30/01/2012	n/a		
II/0052	Update of sections 4.2, 4.6, 4.8 and 5.1 of the SmPC in order to include the results from a clinical study comparing the efficacy and safety of Levemir versus NPH insulin in the treatment of pregnant women with type I diabetes and to make the information regarding lipodystrophy clearer. The Package Leaflet was proposed to be updated in accordance. In addition, the MAH deleted the version number of the RMP in Annex II in order to align the text to the current 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	17/11/2011	19/12/2011	SmPC, Annex II and PL	Overall, Levemir was as efficacious as NPH insulin when administered as basal insulin in combination with IAsp as mealtime bolus insulin. Non-inferiority of IDet to NPH measured by HbA1c at Gestational Week (GW) 36 was shown. The upper limit of the 95% CI for the estimated mean treatment difference in HbA1c was below the pre-specified non-inferiority criterion of 0.4% for both the Full Analysis Set (FAS)Pregnant analysis set (IDet-NPH [95% CI]; 0.06 [-0.21;0.08]) and the Per Protocol (PP)Pregnant analysis set (IDet-NPH [95% CI]; -0.15 [-0.34;0.04]). IDet was not superior to NPH. With Estimated HbA1c values at GW 36 follows: FASPregnant analysis set, IDet 6.27%, NPH 6.33% PPPregnant analysis set, IDet 6.22%, NPH 6.37%. Secondary outcome measures showed a trend toward superior glycaemic control with Levemir compared to NPH as basal insulin treatment. Some adverse outcomes including early foetal deaths and stillbirths, in combination with more serious adverse events in mothers such as pre-eclampsia and minor and major malformations in newborn children were numerically (but not statistically) more frequent in the Levemir group compared to the in the NPH group. It was concluded that a trial of this size cannot demonstrate minor, nevertheless clinically relevant, differences in the

					safety outcomes investigated. Randomised clinical drug trials in pregnant women are rare, and the inherent difficulties in interpreting these studies from a safety perspective are well illustrated by this case. A number of uncertainties regarding the safety of Levemir in pregnant women still exist – mainly related to the low power for detecting differences between IDet and NPH insulin. Even if it cannot be excluded that the observed excess of a number of untoward events on Levemir may represent a signal for a true difference, the observed differences could also very well be chance findings. Consequently, it is concluded that treatment with Levemir can be considered during pregnancy, but that any potential benefit must be weighed against a possibly increased risk of an adverse pregnancy outcome.
IB/0054	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	30/11/2011	n/a		
II/0053/G	This was an application for a group of variations. To add a manufacturing site for part of the manufacturing process of the finished product and to change the batch size range of the finished product. 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, batch control, and secondary packaging, for biological/immunological medicinal products.	20/10/2011	22/11/2011	PL	

	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) B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				
IA/0057	A.7 - Administrative change - Deletion of manufacturing sites	21/11/2011	n/a		
II/0051	Extension of indication for the use of Levemir in children aged 2-5 years. Also Annex II has been updated to reflect new version number of the Risk Management Plan. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	22/09/2011	24/10/2011	SmPC, Annex II and PL	The Scientific discussion of the CHMP Assessment Report will be published.
II/0048	Extension of indication for the use of Levemir as add-on therapy to liraglutide treatment affecting sections 4.2, 5.1 and 5.2 of SmPC. Package Leaflet has been updated accordingly. In addition minor changes have been made throughout the Product Information. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	22/09/2011	24/10/2011	SmPC and PL	The Scientific discussion of the CHMP Assessment Report will be published.

II/0049	To introduce a post approval change management protocol related to the finished product. B.II.g.2 - Design Space - Introduction of a post approval change management protocol related to the finished product	18/08/2011	18/08/2011		
II/0047/G	This was an application for a group of variations. Addition of a device which is an integrated part of the primary packaging of the finished product. B.IV.1.c - Change of a measuring or administration device - Addition or replacement of a device which is an integrated part of the primary packaging B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	14/04/2011	27/05/2011	SmPC, Labelling and PL	

IA/0050	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	07/04/2011	n/a	SmPC, Labelling and PL	
II/0046/G	This was an application for a group of variations. To introduce changes in the specification parameters and test procedures for the active substance. B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP 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	17/03/2011	29/03/2011		
WS/0091	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Further to a CHMP request based on the recommendations from PhVWP, the Product Information (Summary of Product Characteristics section 4.4 and Package Leaflet section 2) is updated by adding a warning on an increased incidence of heart failure when pioglitazone is used in combination with	17/02/2011	28/03/2011	SmPC, Annex II and PL	The PhVWP was requested to consider whether the increased risk of fluid retention and exacerbation of heart failure with the concomitant use of pioglitazone and insulin should apply to all centrally authorised insulin products. After the review of the available evidence, during its October 2010 meeting the PhVWP has concluded this review with a recommendation to the CHMP on the need to harmonise the SmPC and PL for all insulin products by including appropriate warning. The CHMP endorsed this recommendation, and in this context the Committee agreed that all centrally authorised insulin

	insulin, especially in patients with predisposing factors. In addition to the above the MAH took the opportunity to update annex IIB "Other conditions" with the latest wording as per October 2010 CHMP announcment regarding the Pharmacovigilance system. This application was submitted for a group of variations consisting of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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				containing products should include warning on increased cardiac failure when pioglitazone is used in combination with insulin, especially in patients with predisposing factors in the in the section 4.4 of the SmPC and section 2 of the PL. Annex IIB "Other conditions" was also updated with the latest wording as per October 2010 CHMP announcment regarding the Pharmacovigilance system.
IG/0048/G	This was an application for a group of variations. C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	11/03/2011	n/a		
X/0044	Replacement of a biological substance or product of	22/07/2010	23/09/2010	SmPC, Annex	The present line extension application refers to the

	biotechnology with one of a slightly different molecular structure. Modification of the vector used to produce the source material. Annex I_1.(d) Modification of the vector used to produce the antigen or the source material, including a new master cell bank from a different source			II, Labelling and PL	implementation of a new manufacturing process for the drug substance insulin detemir. A comparative characterisation of the insulin detemir drug substance produced by the new manufacturing process and insulin detemir from the current production was performed. No adverse effects on safety or efficacy of the insulin detemir drug product have been reported. Pharmacovigilance and Risk Managment Plan have been updated to monitor potential changes in frequency or severity of adverse reaction or lack of effect compared to the cumulative experience with the current process.
IA/0045	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	01/08/2010	n/a	SmPC and PL	
IA/0043	IA_43_a_01_ Add./replacement/del. of measuring or administration device - addition or replacement	02/12/2009	02/12/2009	SmPC, Labelling and PL	
IA/0042	IA_43_a_01_ Add./replacement/del. of measuring or administration device - addition or replacement	02/12/2009	02/12/2009	SmPC, Labelling and PL	
II/0041	Exceptionally reprocessing of specified batches. Change(s) to the test method(s) and/or specifications for the active substance	19/11/2009	25/11/2009		
II/0039	To implement new testing methods and specification limits in the purification process of the drug substance. Change(s) to the test method(s) and/or specifications	29/05/2009	04/06/2009		

	for the active substance				
IA/0040	IA_09_Deletion of manufacturing site	05/05/2009	n/a		
II/0038	To introduce some changes to the manufacturing process for the finished products. Change(s) to the manufacturing process for the finished product	23/04/2009	27/04/2009		
R/0037	Renewal of the marketing authorisation.	19/02/2009	16/04/2009	SmPC, Annex II, 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 Levemir continues to be favourable.
IA/0036	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	02/09/2008	n/a		
IB/0035	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	15/07/2008	n/a		
II/0032	Change to the test procedure and/or specification of a raw material	30/05/2008	06/06/2008		
IB/0034	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	28/05/2008	n/a	SmPC	
IA/0033	IA_09_Deletion of manufacturing site	07/05/2008	n/a		

II/0030	Change(s) to container	19/03/2008	18/04/2008	Labelling and PL	
N/0028	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/03/2008	n/a	Labelling and PL	
N/0027	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/03/2008	n/a	PL	
II/0026	Change(s) to the manufacturing process for the finished product	21/02/2008	28/02/2008		
N/0025	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/01/2008	n/a	PL	
IA/0029	IA_28_Change in any part of primary packaging material not in contact with finished product	15/01/2008	n/a		
II/0024	Quality changes	15/11/2007	21/11/2007		
II/0023	Change(s) to the manufacturing process for the finished product	20/09/2007	15/10/2007	Annex II and PL	
II/0022	Change(s) to the manufacturing process for the active substance	20/09/2007	25/09/2007		
II/0020	Change in formulation	24/05/2007	21/06/2007	SmPC, Labelling and PL	
II/0021	Change(s) to the manufacturing process for the finished product	26/04/2007	08/06/2007	Annex II and PL	

II/0019	Change(s) to the manufacturing process for the active substance	22/02/2007	27/02/2007		
II/0016	Update of Section 4.2 of the Summary of Product Characteristics (SPC) to include information on the combination with oral antidiabetic drugs (OAD). Consequential changes to sections 4.8 and 5.1 of the SPC were made and were also reflected in Package Leaflet. The Product Information has been also updated in accordance with the QRD template version 7.1 Update of Summary of Product Characteristics, Labelling and Package Leaflet	24/01/2007	27/02/2007	SmPC, Annex II, Labelling and PL	Data from three confirmatory and one supportive trial performed in subjects with type 2 diabetes provided adequate evidence that detemir as add-on to OADs is non-inferior to NPH insulin and insulin glargine in terms of glycaemic control. It also seems that insulin detemir as add-on to OADs might be associated with a smaller weight gain than the comparator insulins. Furthermore insulin detemir as add on to OAD was in general well tolerated. Especially the safety-profile in terms of hypoglycaemic events seems to be favourable. As demonstrated in previous trials application site disorders, lipodystrophy and potential allergic adverse events were reported with higher frequency for insulin detemir than for NHP insulin and also a rise in specific and cross-reacting antibody formation associated with insulin detemir treatment was observed in the insulin detemir groups whereas this was not the case to the same extent in the NPH group. However, these safety issues are known and not related to the concomitant use of OAD. Sections 4.2, 4.8 and 5.1 of the SPC have been changed as well as the relevant section in the PL.
II/0017	Change(s) to the manufacturing process for the active substance	24/01/2007	29/01/2007		
II/0015	Update of or change(s) to the pharmaceutical documentation	16/11/2006	22/11/2006	SmPC, Annex II, Labelling	

				and PL	
II/0014	Change(s) to the manufacturing process for the finished product	21/09/2006	25/09/2006		
II/0012	Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SPC) and corresponding sections of the Package Leaflet (PL) with more precise information regarding injection site reactions. Additionally, update of the whole product information to be in accordance with the latest QRD template and minor changes to the PL. Update of Summary of Product Characteristics, Labelling and Package Leaflet	01/06/2006	06/07/2006	SmPC, Annex II, Labelling and PL	Based on recent information on adverse events from clinical trials as well as on spontaneous reports of adverse drug reactions from general practitioners and healthcare providers using the marketed product, the MAH considered that the product information for Levemir should be updated with new relevant information regarding the frequency of application site disorders, how this compares to NPH insulin and the rare need for discontinuation of Levemir after such reactions. Consequently, section 4.4 of the SPC was updated with a warning including more precise information regarding injection site reactions and the recommendation to rotate the injection site in order to prevent these reactions, as well as the necessity to discontinue the treatment on the rare occasion that this reactions are not resolved in a few days to a few weeks. Additionally, the sentence related to the frequency of injection site reactions in section 4.8 of the SPC was updated to reflect that these reactions are seen more frequently during the treatment with Levemir than with human insulin.
IB/0013	IB_25_a_02_Change to comply with Ph. - compliance with EU Ph. - excipient	31/05/2006	n/a		
II/0011	Change(s) to the manufacturing process for the active substance	23/03/2006	27/03/2006		
II/0010	Change(s) to shelf-life or storage conditions	15/12/2005	20/12/2005		

II/0009	Change(s) to the manufacturing process for the active substance	17/11/2005	22/11/2005		
II/0008	Change(s) to the test method(s) and/or specifications for the active substance	13/10/2005	18/10/2005		
II/0006	This variation concerns the revision of the warning section of the Package Leaflet (PL) regarding what to do when the patient feels a hypoglycaemia coming on. Additionally, an altered wording regarding the action profile in section 5.1 of the Summary of Product Characteristics (SPC) was proposed. A correction was also made to the list of excipients. The MAH also took the opportunity to include editorial and typographical changes to the SPC, labelling and PL. Update of Summary of Product Characteristics, Labelling and Package Leaflet	26/05/2005	04/07/2005	SmPC, Labelling and PL	This variation concerned the revision of the warning section in the Package Leaflet (PL) regarding what to do when the patient feels a hypoglycaemia coming on. The most common reasons of appearance of hypoglycaemia were added to the PL, as well as instructions on how to proceed in this situation. Additionally, an altered wording of a sentence regarding the predictable action of insulin levemir in section 5.1 of the Summary of Product Characteristics (SPC) was introduced. A correction was also made to the list of excipients. The MAH also took the opportunity to include editorial and typographical changes to the SPC, labelling and PL.
IA/0007	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	27/06/2005	n/a		
II/0001	This variation relates to an update of sections 4.2 (Posology and method of administration) and 5.1 (Pharmacodynamic properties) of the Summary of Product Characteristics (SPC) to include paediatric posology (from 6-17 years of age). Update of Summary of Product Characteristics and Package Leaflet	17/02/2005	29/03/2005	SmPC and PL	This variation relates to an update of sections 4.2 (Posology and method of administration) and 5.1 (Pharmacodynamic properties) of the Summary of Product Characteristics (SPC) to include treatment of children and adolescents 6 to 17 years of age, as result of a study in children and adolescents that was performed as part of the clinical post authorisation commitments. The Package Leaflet has been updated accordingly. Additionally, the MAH took the opportunity to

					include editorial changes to the SPC and Package Leaflet (PL) and to include the new ATC code for Levemir in the SPC.
IA/0005	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	18/03/2005	n/a		
N/0004	Changes to include the increase in the dimensions of the Package Leaflet, and the outer packing material, as well as the introduction of an optimised blister packing material (introduction of air cushions to protect the cartridges) in accordance with article 61 (3) of Directive 2001/83/EC. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/03/2005	n/a	PL	
II/0003	Change(s) to the manufacturing process for the active substance	18/11/2004	29/11/2004		