Mixtard

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
IG/0859	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)	01/12/2017	n/a		
WS/1197	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	26/10/2017	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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	Submission of an updated RMP version 2.2 according to GVP Module V, in order to remove three important potential risks (immunogenicity, allergic reactions and lack of efficacy) related to the new NN729 manufacturing process from the RMP, remove hypoglycaemia and anaphylactic reactions, remove peripheral neuropathy, refraction disorders, lipodystrophy, urticaria, rash, oedema and diabetic retinopathy and remove missing information concerning special populations. No changes are proposed to the product information. 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				
IG/0796	A.7 - Administrative change - Deletion of manufacturing sites	28/06/2017	n/a		
IB/0071	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/03/2017	01/03/2018	SmPC, Annex II, Labelling and 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	10/12/2015	n/a		

	finished product, including quality control sites (excluding manufacturer for batch release)				
IG/0627	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	10/11/2015	n/a		
WS/0802	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.h.z - Adventitious Agents Safety - Other variation	29/10/2015	n/a		
IG/0594	A.7 - Administrative change - Deletion of manufacturing sites	04/09/2015	n/a		
IB/0065	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/1753/ 201410	Periodic Safety Update EU Single assessment - insulin human, insulin human / insulin isophane (subcutaneous and intravenous routes of administration)	11/06/2015	n/a		PRAC Recommendation - maintenance
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/0062/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.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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)	26/03/2015	n/a		
WS/0454	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of the SmPC, Annex II, labelling and Package Leaflet in line with the QRD template version 9.0, revision 1, together with a harmonisation of the product information across Novo Nordisk A/S insulin products. Further, “international units” has been implemented throughout the annexes instead of the abbreviation “IU”.	26/06/2014	19/02/2015	SmPC, Labelling and PL	N/A

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IG/0407	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	21/03/2014	19/02/2015	SmPC	
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		
IA/0058	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		
II/0055/G	This was an application for a group of variations. To approve an additional site for: - formulation and filling of Mixtard® 50, 3 ml cartridge, 100 IU/ml, - secondary packaging of Mixtard® 50 Penfill® 3 ml, 100 IU/ml. B.II.b.1.c - Replacement or addition of a	21/02/2013	n/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. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site				
IG/0251	B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	11/01/2013	20/12/2013	SmPC, Annex II, Labelling and PL	
WS/0273/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. Update of section 4.5 of the SmPC with modified wording regarding effect of alcohol on hypoglycemia following the assessment of the latest PSUR. Update of sections 4.2 and 4.8 of the SmPC to modify the wording on lipodystrophy to make it more legible; update to section 4.4 of the SmPC to add new information about "concomitant illness" to harmonise with the product information of other insulins; and additionally hypoglycaemia to be moved from section 4.3 to section 4.4. The PL has been updated accordingly. Furthermore, the PI is being brought in line with the latest QRD template version 8.0 rev. 1 and with the SmPC Guideline. Minor changes to the labelling have been made in	18/10/2012	19/11/2012	SmPC, Annex II, Labelling and PL	The information about the risk of developing lipodystrophy including information on how to reduce this risk has been clarified throughout the product information. This has been done to make the information more legible for both healthcare professionals and patients, and specifically to highlight that rotating the injection site does not necessarily prevent development of lipodystrophy but may help to reduce the risk for such development. In addition, the MAH has provided calculations showing that the human insulin products involved in this procedure can be considered “sodium-free”. Furthermore, changes to all annexes have been introduced in order to comply with latest version of the QRD template (v. 8.0, rev. 1). The variation also includes changes to sections 4.6 and 4.8 of the SmPC which are based on the recommendations in the SmPC Guideline. The SmPC has also been modified in order to align it with the updates already implemented for other insulin products from the same MAH.

	relation to the implementation of the new design on Novo Nordisk A/S cartons and labels. Lastly, the information relating to counterfeit needles has been deleted and the sentence in section 4.5 of the SmPC with regards to “Octreotide/lanreotide” has been linguistically improved. 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 C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
II/0054/G	This was an application for a group of variations. Additional manufacturing site for Mixtard 30.3 ml cartridge Addition of secondary packaging site for Mixtard 30 Penfill 3 ml 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. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	15/11/2012	n/a		addition of formulation and filing site for Mixtard 30, 3ml cartridge addition of secondary packaging for Mixtard 30 Penfill 3ml, 100 IU/ml

II/0052/G	This was an application for a group of variations. To introduce an additional manufacturing site for 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. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.b.3 - Change to batch release arrangements and quality control testing of the FP - Including batch control/testing for a biol/immunol product and one of the test methods is a biol/immunol/immunochemical method 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)	24/05/2012	27/06/2012	Annex II and 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 test procedure (including replacement or addition) for the AS or a starting	16/02/2012	16/02/2012		

	material/intermediate				
IB/0047	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		
IA/0050	A.7 - Administrative change - Deletion of manufacturing sites	21/11/2011	n/a		
IA/0046	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	12/04/2011	n/a	SmPC, Labelling and PL	
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 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	17/02/2011	17/03/2011	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 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

	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				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		
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	
IB/0044	Deletion of - a strength. De-registration of Mixtard® 10 & 20.	30/03/2010	n/a	SmPC, Annex II, Labelling	

	C.I.7.b - Deletion of - a strength			and PL	
II/0043	To introduce some changes to a manufacturing site for the production of the finished product. Change(s) to the manufacturing process for the finished product	18/02/2010	11/03/2010		
IA/0042	Addition of a manufacturing site for part of the manufacturing process of the finished product. This variation only affects Mixtard 30 FlexPen: Presentations (EU/1/02/231/033-035) IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	18/12/2009	n/a		
N/0041	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/11/2009	n/a	Labelling	
X/0009	Annex I_1.(c) Replacement of a biological AS with one of a slightly different molecular structure	25/06/2009	01/10/2009		The present line extension application refers to the implementation of a new manufacturing process for the drug substance insulin human. A comparative characterisation of the insulin human drug substance produced by the new manufacturing process and insulin human from the current production was performed. No adverse effects on safety or efficacy of the insulin human drug product have been reported. Pharmacovigilance and Risk Management 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/0040	IA_25_b_01_Change to comply with Ph. - compliance with EU Ph. update - active substance	30/06/2009	n/a		
IA/0039	IA_09_Deletion of manufacturing site	05/05/2009	n/a		
II/0038	To change the status of specified products manufacturing sites from single product to multi product facilities. Change(s) to the manufacturing process for the finished product	23/04/2009	27/04/2009		
II/0037	The Marketing Authorisation Holder applied for a new needle platform. The current needle platform (i.e. NovoFine) uses a classic thread, while the new needle platform (i.e. NovoTwist) is attached to FlexPen by a bayonet coupling. The modified FlexPen will be able to fit both the NovoFine and the NovoTwist needle. Labelling and package leaflet are consequently updated to reflect the change and to obtain a more user friendly language in the package leaflet. In addition, in order to lower the dose force, three components of the FlexPen will have minor modifications. Change(s) to container	20/11/2008	12/12/2008	SmPC, Labelling and PL	

IA/0036	IA_09_Deletion of manufacturing site	31/07/2008	n/a		
IA/0035	IA_09_Deletion of manufacturing site	07/07/2008	n/a		
II/0034	Change to the test procedure and/or specification of a raw material	30/05/2008	05/06/2008		
N/0032	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/0031	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/03/2008	n/a	PL	
II/0030	Quality changes	15/11/2007	21/11/2007		
II/0029	Quality changes	18/10/2007	24/10/2007		
R/0026	Renewal of the marketing authorisation.	19/07/2007	18/09/2007	SmPC, Annex II, Labelling and PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile continues to be favourable. The CHMP was also of the opinion that the renewal can be granted with unlimited validity.
IA/0028	IA_09_Deletion of manufacturing site	03/07/2007	n/a		
II/0024	Change(s) to the manufacturing process for the active substance	26/04/2007	03/05/2007		
IA/0027	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	10/04/2007	n/a		

IB/0025	IB_25_a_02_Change to comply with Ph. - compliance with EU Ph. - excipient	19/03/2007	n/a		
II/0022	Change(s) to the manufacturing process for the active substance	22/02/2007	27/02/2007		
IA/0023	IA_05_Change in the name and/or address of a manufacturer of the finished product	22/01/2007	n/a		
II/0020	Update of or change(s) to the pharmaceutical documentation	16/11/2006	22/11/2006		
II/0017	Change(s) to the manufacturing process for the finished product	01/06/2006	07/06/2006		
N/0019	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/05/2006	n/a		
II/0016	Change(s) to the manufacturing process for the active substance	27/04/2006	10/05/2006		
IB/0018	IB_25_a_02_Change to comply with Ph. - compliance with EU Ph. - excipient	24/04/2006	n/a		
N/0015	The Marketing Authorisation Holder (MAH) applied for minor changes to the 10 ml insulin vial outer cartons and labels (changing the labels from being attached with glue to being self-adhesive, and changing the background colour of the area where the production date, expiry date and batch number are printed on the outer carton).	19/08/2005	n/a	Labelling	

	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)				
II/0012	Change(s) to the manufacturing process for the active substance	26/05/2005	06/06/2005		
IA/0014	IA_09_Deletion of manufacturing site	23/05/2005	n/a		
N/0013	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/04/2005	n/a	Labelling	
N/0010	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	Labelling and PL	
IA/0011	IA_05_Change in the name and/or address of a manufacturer of the finished product	03/03/2005	n/a	Annex II and PL	
II/0008	Update of or change(s) to the pharmaceutical documentation	29/07/2004	03/08/2004		
II/0007	Update of section 4.8 of the SPC and corresponding section of the Package Leaflet. Introduction of changes to reflect the CHMP Note for Guidance on Declaration of Storage Conditions and an update to	23/06/2004	02/08/2004	SmPC, Labelling and PL	Update of section 4.8 of the SPC in order to better reflect the adverse drug reactions reported in clinical trials, to list undesirable effects using the MedDRA terminology, and to list them according to frequencies.

	bring the SPC, labelling and Package Leaflet in accordance with the latest QRD template and to harmonise with the MAH's other insulin products. Update of Summary of Product Characteristics, Labelling and Package Leaflet				The introduction to section 4.8 of the SPCs has also been updated to state that hypoglycaemia is the most frequent undesirable effect, but no exact frequency is included, as the frequency of hypoglycaemia is highly variable among various patient populations and dose regimens. This update of section 4.8 also includes the removal of hyperglycaemia. All information on hyperglycaemia (including symptoms) has been located in section 4.4, including the warning of the risk of fatal outcome of untreated hyperglycaemic events. The terms `diabetic retinopathy' and `painful neuropathy' have been added to section 4.8. The adverse event "Fainting/loss of consciousness" is also added to the list in section 4.8. These changes have been reflected in the section 5 of the Package Leaflet. In addition changes have been made to the Product Information to reflect the CHMP Note for Guidance on Declaration of Storage Conditions, linguistic amendments in accordance to the latest QRD template (version 6, 1/2004) and to harmonise with other insulin products from NovoNordisk.
I/0006	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	22/10/2003	27/10/2003		
II/0003	Change(s) to the manufacturing process for the active substance Change(s) to the test method(s) and/or specifications for the active substance	25/09/2003	01/10/2003		

	Change(s) to shelf-life or storage conditions				
I/0005	15_Minor changes in manufacture of the medicinal product	25/09/2003	01/10/2003		
I/0004	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	16/07/2003	22/08/2003	Annex II and PL	
I/0002	30_Change in pack size for a medicinal product	09/07/2003	13/08/2003	SmPC, Labelling and PL	
II/0001	Change(s) to container	23/01/2003	28/01/2003		