NovoMix

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/1621	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	20/06/2023	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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IB/0115	C.I.7.a - Deletion of - a pharmaceutical form	22/05/2023		SmPC, Annex II, Labelling and PL	
PSUSA/1749/ 202209	Periodic Safety Update EU Single assessment - insulin aspart	14/04/2023	n/a		PRAC Recommendation - maintenance
WS/2351	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.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	09/02/2023	n/a		
WS/2302/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.4.e - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of an in-process test which may have a significant effect on the overall quality of the AS B.I.a.4.e - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of an in-process test which may have a significant effect on the overall quality of the AS	15/12/2022	n/a		
PSUSA/1749/ 202109	Periodic Safety Update EU Single assessment - insulin aspart	05/05/2022	n/a		PRAC Recommendation - maintenance

WS/2106	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.d.1.h - Change in the specification parameters and/or limits of the finished product - Update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur. for the finished product	02/09/2021	n/a		
IB/0110/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.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	16/07/2021	n/a		
WS/2056	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	10/06/2021	n/a		
PSUSA/1749/ 202009	Periodic Safety Update EU Single assessment - insulin aspart	06/05/2021	n/a		PRAC Recommendation - maintenance

II/0105	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	22/10/2020	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	19/10/2021	SmPC, Annex II, Labelling and PL	
PSUSA/1749/ 201909	Periodic Safety Update EU Single assessment - insulin aspart	17/04/2020	n/a		PRAC Recommendation - maintenance
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		
WS/1687	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.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	05/12/2019	n/a		
IG/1167	A.7 - Administrative change - Deletion of manufacturing sites	22/11/2019	n/a		

IAIN/0099	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	19/08/2019	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		
PSUSA/1749/ 201809	Periodic Safety Update EU Single assessment - insulin aspart	26/04/2019	01/07/2019		Based on the post-marketing data submitted within this PSUR, the PRAC concludes that anaphylactic reactions should be added to section 4.8 of the SmPC for Fiasp, in line with the SmPC for NovoRapid and NovoMix. Following 7 new reported cases of medically confirmed systemic allergic reactions for Fiasp and the already established evidence suggesting a causal relationship between insulin aspart and anaphylactic reactions, the updates to the section 4.8 of SmPC for Fiasp are justified.
WS/1564	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	04/04/2019	n/a		
II/0095	Update of sections 4.2 and 4.5 of the SmPC to include data on the use of NovoMix 30 in combination with GLP-1 receptor agonists. The PL is	31/01/2019	13/03/2019	SmPC and PL	NovoMix 30 can also be given in combination with GLP-1 receptor agonists. GLP-1 receptor agonists may reduce the patient's insulin requirements. In patients with type 2

	updated accordingly. The RMP is also updated (version 3.1). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				diabetes, a dose reduction of 20% is recommended for patients with an HbA1c less than 8% when a GLP-1 receptor agonist is added to NovoMix 30, to minimise the risk of hypoglycaemia. For patients with an HbA1c higher than 8% a dose reduction should be considered. Subsequently, dosage should be adjusted individually.
WS/1405	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	19/07/2018	n/a		
PSUSA/1749/ 201709	Periodic Safety Update EU Single assessment - insulin aspart	12/04/2018	n/a		PRAC Recommendation - maintenance
IB/0093	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/04/2018	13/03/2019	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 (excluding manufacturer for batch release)	19/03/2018	n/a		
IB/0090	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)	05/10/2017	n/a		

WS/1132	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.e.2 - Introduction of a post approval change management protocol related to the AS	05/05/2017	n/a		
PSUSA/1749/ 201609	Periodic Safety Update EU Single assessment - insulin aspart	05/05/2017	n/a		PRAC Recommendation - maintenance
II/0087	Update of section 4.4 of the SmPC to include a warning on the risk of accidental mix-ups/medication errors. The package leaflet has been updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/12/2016	18/12/2017	SmPC, Annex II and Labelling	Avoidance of accidental mix-ups/medication errors. Patients must be instructed to always check the insulin label before each injection to avoid accidental mix-ups between NovoMix and other insulin products.
PSUSA/1749/ 201509	Periodic Safety Update EU Single assessment - insulin aspart	14/04/2016	n/a		PRAC Recommendation - maintenance
N/0083	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/01/2016	12/12/2016	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	12/12/2016	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		
IB/0082	B.II.h.z - Adventitious Agents Safety - Other variation	04/09/2015	n/a		
PSUSA/1749/ 201409	Periodic Safety Update EU Single assessment - insulin aspart	07/05/2015	n/a		PRAC Recommendation - maintenance
II/0080/G	This was an application for a group of variations. Update of section 4.4 of the SmPC in order to update the safety information regarding neutralising antibodies upon request by PRAC following the assessment of the RMP for insulin aspart. In addition the MAH took the opportunity to implement minor editorial changes in the SmPC and Package Leaflet. In the type IA variation, the MAH proposed to update the ATC code in section 5.1 of the SmPC. A.6 - Administrative change - Change in ATC Code/ATC Vet Code C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	13/11/2014	SmPC and PL	
WS/0428	This was an application for a variation following a worksharing procedure according to Article 20 of	22/05/2014	n/a		

	Commission Regulation (EC) No 1234/2008. to introduce changes to the active substance manufacturing process B.I.a.z - Change in manufacture of the AS - Other variation				
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		
II/0077	Update of the product information to implement the QRD version 9 and to harmonise the product information with other insulins from the same MAH. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/11/2013	13/11/2014	SmPC, Annex II, Labelling and PL	The MAH has updated the product information to make the text compliant with the latest QRD template and to improve the linguistics. In addition, some text proposals are made to harmonise Novomix with other products in the Novo Nordisk product portfolio.
N/0075	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/07/2013	13/11/2014	PL	
IA/0076	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/0073/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	19/07/2012	19/07/2012		
N/0071	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/03/2012	13/11/2014	PL	
IAIN/0072	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	30/01/2012	n/a		
IG/0137	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	16/12/2011	n/a		
IA/0069	A.7 - Administrative change - Deletion of manufacturing sites	11/11/2011	n/a		

IB/0068/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 A.7 - Administrative change - Deletion of manufacturing sites	28/10/2011	n/a		
IA/0067	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	28/04/2011	n/a		
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.
IB/0066/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.3.e - Change in batch size (including batch size ranges) of AS or intermediate - The scale for a biological/immunological AS is increased/decreased without process change (e.g. duplication of line)	06/12/2010	n/a		
IB/0065	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	04/11/2010	n/a		
IB/0063/G	This was an application for a group of variations.	05/10/2010	05/10/2010	SmPC,	

	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 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 B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes			Labelling and PL	
II/0061	To introduce changes in the manufacturing site of the active substance. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product	23/09/2010	29/09/2010		
IA/0064	B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information	14/09/2010	n/a	PL	
IA/0062	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 -	01/08/2010	n/a	SmPC and PL	

	Device with CE marking				
R/0060	Renewal of the marketing authorisation.	22/04/2010	02/07/2010	SmPC, Annex II, Labelling and PL	
IA/0059	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	02/11/2009	n/a		
II/0058	Amendment of sections 4.4 and 4.5 of the SPC following the assessment of PSU 048, to introduce information on travelling and rewording the information on interactions. The PL is amended accordingly. Update of Summary of Product Characteristics and Package Leaflet	24/09/2009	13/10/2009	SmPC and PL	Following a CHMP request during the assessment of PSU 048 (01-Nov-2006 to 30-Sep-2008), the MAH introduced the following changes to the Summary of Product Characteristics: - Addition of a sentence in section 4.4 on the potential need to adjust the time of administration and meals while travelling between different time zones. - Rewording of the information on interactions (section 4.5) and inclusion of reference to the interaction with growth hormone. The Package Leaflet is updated accordingly.
II/0057	Addition of an alternative manufacturing site for the specified finished products. Update of or change(s) to the pharmaceutical documentation	24/09/2009	13/10/2009	PL	
IA/0056	IA_25_b_01_Change to comply with Ph. - compliance with EU Ph. update - active substance	01/07/2009	n/a		
IA/0055	IA_09_Deletion of manufacturing site	05/05/2009	n/a		
II/0054	To change the status of specified products	23/04/2009	28/04/2009		

	manufacturing sites from single product to multi product facilities. Change(s) to the manufacturing process for the finished product				
II/0053	Extension of the shelf-life of the drug substance. Quality changes	19/02/2009	26/02/2009		
II/0051	The Marketing Authorisation Holder applied for the addition of a new manufacturing site for the drug product. Change(s) to the manufacturing process for the finished product	20/11/2008	26/11/2008		
IA/0052	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	01/09/2008	n/a		
II/0047	Change(s) to the manufacturing process for the active substance	24/07/2008	29/07/2008		
II/0049	To update sections 4.2 and 5.1 of the SPC to include information regarding the transfer from biphasic human insulin to biphasic insulin aspart 30 Update of Summary of Product Characteristics and Package Leaflet	26/06/2008	28/07/2008	SmPC and PL	This variation concerns the update of sections 4.2 and 5.1 of the Summary of Product Characteristics (SPC) for NovoMix, to include information on transfer from biphasic human insulin 30 (BHI 30) to NovoMix 30 (BIAsp 30). These changes were supported by two clinical trials (038 and 1466) and an additional meta-analysis. Overall, In patients with type 2 diabetes a meta-analysis showed a reduced risk of overall nocturnal hypoglycaemic

					episodes (symptoms of low blood sugar) and major hypoglycaemia with NovoMix 30 compared to biphasic human insulin 30. The risk of overall daytime hypoglycaemic episodes was increased in patients treated with NovoMix 30.
II/0043	To update section 4.2 of the SPC following the assessment of the MAHs application to include a three times daily regimen for NovoMix 30 in the dosing guideline. In addition, minor changes to section 4.2 and 4.6 has been made. Update of Summary of Product Characteristics	24/04/2008	19/06/2008	SmPC	The CHMP reviewed the results from four clinical trials (1707, 1325, 1554 and 2174) that studied three times daily regimen with NovoMix 30. From an efficacy point of view, the CHMP did not consider that the data submitted supports the TID regimen in type 2 diabetes patients with advanced diabetes who have failed to achieve good metabolic control on oral antidiabetics. However, the TID regimen may have a potential to lower the frequency of hypoglycaemias in patients requiring high doses of insulin. The CHMP therefore considered that the wording"If twice daily dosing with NovoMix 30 results in recurrent daytime hypoglycaemic episodes, the morning dose can be split into morning and lunchtime doses (thrice daily dosing)." is supported by the data and therefore is acceptable.
II/0048	Change to the test procedure and/or specification of a raw material	30/05/2008	05/06/2008		
IA/0050	IA_09_Deletion of manufacturing site	07/05/2008	n/a		
II/0042	Change(s) to container	19/03/2008	18/04/2008	Labelling and PL	
N/0045	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/03/2008	n/a	Labelling	

N/0044	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/03/2008	n/a	PL	
II/0041	Change(s) to the manufacturing process for the finished product	24/01/2008	30/01/2008		
II/0040	Update of sections 4.2, 5.1 and 5.2 of the Summary of Product Characteristics (SPC) to include information about paediatric use. The Package Leaflet (PL) has been amended accordingly. Minor editorial changes were also made throughout all of the product information. Update of Summary of Product Characteristics, Labelling and Package Leaflet	15/11/2007	18/12/2007	SmPC, Labelling and PL	The Marketing Authorisation Holder (MAH) submitted in this variation three main clinical trials (studies 1240, 1073 and 1459) evaluating the efficacy and safety of NovoMix 30 in children and adolescents (6 to 17 years of age) with type 1 diabetes. The MAH also submitted a retrospective trial (study 1676) which provides data from children and adolescents treated with insulin aspart (IAsp) over a period of 30 months. Upon evaluation of the submitted data, the CHMP was of the view that the use of premixed insulin may be beneficial for some children as it reduces the number of injections. However, based on the results from the submitted studies, the efficacy of NovoMix 30 in the treatment of children younger than 10 years could not be considered as sufficiently established. There were no unexpected safety signals in the submitted studies, and there were indications that NovoMix 30 may be associated with less weight gain and less hypoglycaemia compared to human insulin. However, long-term safety data in children and adolescents are missing. Thus, the CHMP concluded that the product information for NovoMix could be updated with data on the use of children

					above 10 years, but that the benefit-risk balance for the use of NovoMix 30 in children younger than 10 years could not be considered as positive at the present time.
II/0039	Change(s) to the test method(s) and/or specifications for the active substance	15/11/2007	21/11/2007		
II/0038	Inclusion of the combination use of Novomix 30 with any oral antidiabetics (OAD) for which the combination with insulin is authorised. Update of Summary of Product Characteristics, Labelling and Package Leaflet	19/07/2007	27/08/2007	SmPC, Annex II, Labelling and PL	Novomix 30 is already authorized for use in combination with metformin for the treatment of type 2 diabetes. To extend the use of Novomix 30 in combination with any OAD for which the combination with insulin is authorised, the MAH submitted the results of studies investigating Novomix 30 in combination with either metformin + sulphonylurea, or pioglitazone, or metformin + pioglitazone. Overall, the addition of Novomix 30 to ongoing treatment with metformin, pioglitazone or a combination of these compounds resulted in clinically relevant reductions of HbA1c. Incidence of weight gain and oedema was higher with the regimen of NovoMix 30 and thiazolidinedione (TZD) together than with TZD, TZD-OAD combinations or NovoMix 30 alone. In the litterature the use of this combination has also been associated with an increased incidence of cardiac failure. Therefore, patients should be observed for signs and symptoms of heart failure, weight gain and oedema when NovoMix 30 is used in combination with pioglitazone.
II/0036	Change(s) to the manufacturing process for the active substance	24/05/2007	29/05/2007		
II/0035	Change(s) to the manufacturing process for the finished product	22/03/2007	24/04/2007	SmPC, Labelling and	

	Change in formulation Update of Summary of Product Characteristics, Labelling and Package Leaflet			PL	
IA/0037	IA_28_Change in any part of primary packaging material not in contact with finished product	14/03/2007	n/a		
II/0034	Change(s) to the manufacturing process for the finished product	16/11/2006	27/11/2006		
II/0033	Update of or change(s) to the pharmaceutical documentation	16/11/2006	27/11/2006		
IB/0032	IB_25_a_02_Change to comply with Ph. - compliance with EU Ph. - excipient	25/04/2006	n/a		
II/0031	The MAH applied with this variation for an update of the product information to include a dosing guidance for the product to assist practitioners in starting up and optimising the treatment based on a combination of clinical practice and results from relevant clinical experience available from the three trials included in this application. This implied revisions to section 4.2 and 5.1 of the SPC and relevant sections of the PL. In addition, minor amendments to harmonise the NovoMix30, NovoMix50 and NovoMix70 product information have been introduced together with additional details as how to store and discard the products. Update of Summary of Product Characteristics,	23/02/2006	29/03/2006	SmPC, Labelling and PL	The MAH submitted with this application clinical data from two controlled trials randomised, multi-centre, open-label parallel group trials designed to evaluate short-term efficacy and safety of BIAsp 30 initiation in people with type 2 diabetes who were insulin naïve and inadequately controlled on current OHA therapy. A third trial was included as a supportive trial. This was an open-label, multi-centre, consecutive, three-phase, observational trial with no comparator. The objective of this trial was to evaluate the applicability of a step-wise therapeutic approach to insulin therapy with NovoMix30 similar to standard clinical practice. The main trial triggering the update of the product information is a study with patients with type 2 diabetes,

	Labelling and Package Leaflet				insufficiently controlled on oral hypoglycaemic agents alone, were randomised to treatment with twice daily NovoMix 30 (117 patients) or once daily insulin glargine (116 patients). After 28 weeks treatment following the dosing guideline outlined in section 4.2 of the SPC, the mean reduction in HbA1c was 2.8% with NovoMix 30 (mean at baseline = 9.7%). With NovoMix 30, 66% and 42% of the patients reached HbA1c levels below 7% and 6.5%, respectively, and mean FPG was reduced by about 7 mmol/L (from 14,0 mmol/L at baseline to 7,1 mmol/L).
X/0019	The present line extension application refers to two new premixed dosage forms of rapid-acting IAsp and protamine co-crystallised IAsp, biphasic insulin aspart 70 (BIAsp 70) Annex I_2.(c) Change or addition of a new strength/potency	23/06/2005	05/10/2005	SmPC, Labelling and PL	The present line extension application refers to a new premixed dosage forms of rapid-acting IAsp and protamine co-crystallised IAsp, biphasic insulin aspart 70 (BIAsp 70). BIAsp 70 have been developed to supplement the already marketed BIAsp 30. This will increase flexibility in treatment options, allowing for treatments tailored to the individual needs of people with type 1 or type 2 diabetes. Except for the limited number of points, which can be addresed as part of the post authorisation commitments, the quality of this new premixed dosage form is considered to be acceptable when used in accordance with the conditions in the SPC. The pivotal study demonstrated that a BIAsp three times daily regimen is a treatment alternative that can provide acceptable glycaemic control and that postprandial blood glucose elevations can be reduced if such a regimen is compared with a BHI 30 twice daily regimen. The efficacy of these new compositions has been sufficiently well demonstrated and the pharmacodynamic action/time profiles are in agreement with what could be expected from the amounts and properties of the two components.

					The safety of BIAsp 70 has been sufficiently well characterised from a clinical point of view taking into account also the experience with pure soluble IAsp and BIAsp 30. The pattern of adverse events in the BIAsp treatment groups was similar to the pattern recorded in the BHI treated group in the pivotal study. The increased incidence of minor hypoglycaemic events among the BIAsp treated patients recorded in the pivotal study is most probably due to the higher total insulin doses and more frequent insulin administration as compared to the BHI treated patients. Please refer to Scientific Discussion:Novomix-H-308-X-19-SD
X/0018	The present line extension application refers to a new premixed dosage form of rapid-acting IAsp and protamine co-crystallised IAsp, biphasic insulin aspart 50 (BIAsp 50). Annex I_2.(c) Change or addition of a new strength/potency	23/06/2005	05/10/2005	SmPC, Labelling and PL	The present line extension application refers to a new premixed dosage form of rapid-acting IAsp and protamine co-crystallised IAsp, biphasic insulin aspart 50 (BIAsp 50). BIAsp 50 has been developed to supplement the already marketed BIAsp 30. This will increase flexibility in treatment options, allowing for treatments tailored to the individual needs of people with type 1 or type 2 diabetes. Except for the limited number of points, which can be addresed as part of the post authorisation commitments, the quality of this new premixed dosage form is considered to be acceptable when used in accordance with the conditions in the SPC. The pivotal study demonstrated that a BIAsp three times daily regimen is a treatment alternative that can provide acceptable glycaemic control and that postprandial blood glucose elevations can be reduced if such a regimen is compared with a BHI 30 twice daily regimen. The efficacy of these new compositions has been sufficiently well demonstrated and the pharmacodynamic action/time

					profiles are in agreement with what could be expected from the amounts and properties of the two components. The safety of BIAsp 50 has been sufficiently well characterised from a clinical point of view taking into account also the experience with pure soluble IAsp and BIAsp 30. The pattern of adverse events in the BIAsp treatment groups was similar to the pattern recorded in the BHI treated group in the pivotal study. The increased incidence of minor hypoglycaemic events among the BIAsp treated patients recorded in the pivotal study is most probably due to the higher total insulin doses and more frequent insulin administration as compared to the BHI treated patients. Please refer to Scientific Discussion:Novomix-H-308-X-18-SD
II/0021	Change(s) to the manufacturing process for the finished product	20/06/2005	10/08/2005		
II/0028	Change(s) to the test method(s) and/or specifications for the active substance	23/06/2005	08/07/2005		
II/0025	Change(s) to the manufacturing process for the finished product	21/04/2005	10/06/2005	Annex II and PL	
II/0026	Change(s) to the manufacturing process for the finished product	21/04/2005	12/05/2005		
IA/0029	IA_47_a_Deletion of a pharmaceutical form	23/03/2005	n/a	SmPC, Annex II, Labelling and PL	
II/0020	Change(s) to the manufacturing process for the	16/03/2005	21/03/2005		

	finished product				
N/0027	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	
IA/0024	IA_05_Change in the name and/or address of a manufacturer of the finished product	20/12/2004	n/a	Annex II and PL	
IA/0023	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	20/12/2004	n/a		
X/0011	X-1-iii_Qualitative change to the active substance(s)	03/06/2004	24/08/2004	Annex II	
II/0015	This variation concerns an update of section 4.2 and 5.1 of the Summary Product Characterstics and relevant section of the Package Leaflet (PL) to specify the use of NovoMix 30 in combination with metformin in patients with type 2 Diabetes mellitus that are insufficiently controlled on metformin alone. In addition, minor linguistic amendments are introduced in the PL. Update of Summary of Product Characteristics and Package Leaflet	22/04/2004	07/07/2004	SmPC and PL	

IB/0017	IA_37_a_Change in the specification of the finished product - tightening of specification limits	22/06/2004	n/a		
II/0016	Update of or change(s) to the pharmaceutical documentation	22/04/2004	27/04/2004		
II/0013	Update of Summary of Product Characteristics and Package Leaflet	26/02/2004	15/04/2004	SmPC and PL	
II/0012	The Marketing Authorisation Holder applied for a revision of the Summary of Product Characteristics and Package Leaflet (PL) to standardise the product information text for all Novo Nordisk A/S insulin products, and to reflect in the PL the results of the readability tests performed for Mixtard. Update of Summary of Product Characteristics and Package Leaflet	26/02/2004	15/04/2004	SmPC and PL	
II/0014	Update of or change(s) to the pharmaceutical documentation	24/03/2004	30/03/2004		
I/0009	20_Extension of shelf-life as foreseen at time of authorisation	08/08/2003	08/10/2003	SmPC	
I/0010	15_Minor changes in manufacture of the medicinal product	25/09/2003	02/10/2003		
I/0008	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	

II/0006	Change(s) to the test method(s) and/or specifications for the active substance	21/02/2002	28/02/2002		
I/0007	12_Minor change of manufacturing process of the active substance	21/02/2002	28/02/2002		
II/0005	Change(s) to the test method(s) and/or specifications for the active substance Quality changes	17/01/2002	28/01/2002		
I/0004	11_Change in or addition of manufacturer(s) of active substance	20/09/2001	08/10/2001		
II/0001	New presentation(s)	19/10/2000	22/01/2001	SmPC, Labelling and PL	
I/0003	20_Extension of shelf-life as foreseen at time of authorisation	30/10/2000	22/01/2001	SmPC	