EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

NovoRapid

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
N/0146	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/03/2023		PL	
WS/2351	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	09/02/2023	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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	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				
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		
IB/0143	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	10/11/2022	n/a		
PSUSA/1749/ 202109	Periodic Safety Update EU Single assessment - insulin aspart	05/05/2022	n/a		PRAC Recommendation - maintenance
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	10/06/2021	n/a		

	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				
PSUSA/1749/202009	Periodic Safety Update EU Single assessment - insulin aspart	06/05/2021	n/a		PRAC Recommendation - maintenance
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		
IB/0137/G	This was an application for a group of variations. B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	04/11/2020	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	22/09/2021	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		
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		
II/0128	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	18/07/2019	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.
IAIN/0127	C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	10/05/2019	n/a		
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		
IG/1066	A.7 - Administrative change - Deletion of manufacturing sites	29/03/2019	n/a		
N/0123	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/12/2018	28/03/2019	Labelling	

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		
II/0121	Update of section 4.2 of the SmPC to include a passive discouragement of withdrawing insulin with a syringe from cartridges and pre-filled pens; update of section 6.6 of the SmPC not to allow the withdrawal of insulin with a syringe from cartridges and pre-filled pens in emergency situations. This variation was submitted to fulfil a recommendation by the PRAC in November 2017, subsequent to the evaluation of the signal on potential increased risk of medication error associated with withdrawing insulin from pre-filled pens and cartridges, leading to dysglycaemia. The PL is updated accordingly. In addition, the MAH took the opportunity to reinsert and clarify information in the SmPC regarding mixing of NovoRapid with NPH insulin (sections 4.2 and 6.2), which has previously been deleted from the SmPC by mistake. Other editorial changes are also proposed within this variation. Moreover, Annex A is updated to reflect that only the vial is to be used intravenously. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/04/2018	28/03/2019	SmPC, Labelling and PL	NovoRapid (from a reusable pen) is only suitable for subcutaneous injections. If administration by syringe or intravenous injection is necessary, a vial should be used. If administration by infusion pump is necessary, a vial or NovoRapid PumpCart should be used. NovoRapid can only be mixed with NPH (Neutral Protamine Hagedorn) insulin in a syringe for subcutaneous use. When NovoRapid is mixed with NPH insulin, NovoRapid should be drawn into the syringe first, and the mixture should be injected immediately after mixing. Insulin mixtures should not be administered intravenously or used with a subcutaneous insulin infusion pump.

PSUSA/1749/201709	Periodic Safety Update EU Single assessment - insulin aspart	12/04/2018	n/a		PRAC Recommendation - maintenance
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		
II/0118	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	22/06/2017	18/09/2017	SmPC, Labelling and PL	During use or when carried as a spare, NovoRapid FlexPen/NovoRapid FlexTouch should be stored below 30°C. Alternatively, they can be stored in a refrigerator (2°C - 8°C). Do not freeze. Keep the pen cap on the pen in order to protect from light.
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/0115	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	26/01/2017	n/a		
II/0112	Extension of Indication to include the use of NovoRapid in children from 1 to 2 years of age for the treatment of diabetes mellitus; as a	15/09/2016	21/10/2016	SmPC, Labelling and	Please refer to the published Assessment Report Novorapid H/C/000258/II/0112

	consequence, sections 4.1, 4.2, 4.4 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Furthermore, the PI is brought in line with the latest QRD template version 10. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one			PL	
II/0114	Update of sections 4.4 and 4.8 of the SmPC with additional information regarding avoidance of accidental mix-ups and medication errors. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/10/2016	18/09/2017	SmPC	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 NovoRapid and other insulin products.
N/0113	Update of Annex IIIA for Novorapid Pumpcart packsize 25 (5x5) cartridges (multipack) following a change in the package design of the multipack. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/08/2016	21/10/2016	Labelling	
II/0111	Update of sections 4.2 and 4.4 of the SmPC to add the use of the YpsoPump insulin pump for the NovoRapid PumpCart presentation. The Package Leaflet and Labelling are updated accordingly. The RMP was updated (Edition 2, version 1) to reflect the use of the YpsoPump insulin pump. In addition, the Marketing authorisation holder	23/06/2016	21/10/2016	SmPC, Annex II, Labelling and PL	The product information for NovoRapid has been updated to allow for use of the NovoRapid Pumpcart presentation with the YpsoPump system, a pump system suitable for insulin infusion.

	(MAH) took the opportunity to bring the product information in line with the QRD template version 9.1 and to implement minor corrections throughout. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/1749/ 201509	Periodic Safety Update EU Single assessment - insulin aspart	14/04/2016	n/a		PRAC Recommendation - maintenance
II/0107	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	28/01/2016	n/a		
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	25/01/2016	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		
IG/0594	A.7 - Administrative change - Deletion of manufacturing sites	04/09/2015	n/a		
IB/0105	B.II.h.z - Adventitious Agents Safety - Other variation	04/09/2015	n/a		
IB/0104	B.II.b.2.a - Change to importer, batch release	23/06/2015	n/a		

	arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place				
PSUSA/1749/201409	Periodic Safety Update EU Single assessment - insulin aspart	07/05/2015	n/a		PRAC Recommendation - maintenance
IB/0102	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	16/01/2015	25/01/2016	SmPC, Labelling and PL	
WS/0428	This was an application for a variation following a worksharing procedure according to Article 20 of 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	22/05/2014	n/a		
IA/0101	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	14/04/2014	n/a		
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	23/01/2014	n/a		

	starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
II/0092	B.II.e.1.b.2 - Change in immediate packaging of the finished product - Type of container - Sterile medicinal products and biological/immunological medicinal products	21/11/2013	10/01/2014	SmPC, Labelling and PL	
N/0096	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/07/2013	10/01/2014	PL	
IA/0098	A.7 - Administrative change - Deletion of manufacturing sites	26/07/2013	n/a		
II/0097/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, 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	25/07/2013	n/a		
IG/0280	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/04/2013	n/a		
IAIN/0094	B.II.b.1.a - Replacement or addition of a	18/01/2013	n/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	10/01/2014	SmPC, Annex II, Labelling and PL	
II/0091	Update of sections 4.2 and 4.8 of the SmPC in order modify the wording regarding lipodystrophy; and update of sections 4.6 and 4.8 of the SmPC to reflect the SmPC guideline. The Package Leaflet is updated accordingly. Furthermore, the PI is being brought in line with the latest QRD template version 8.0 rev. 1. The MAH has also taken the opportunity to implement the results from the readability test bridging report The MAH has also made editorial changes throughout the text to allign it with the PI of Levemir and NovoMix. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/06/2012	31/07/2012	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. 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 NovoMix and Levemir in relation to the renewal EMEAH/C/308/R/60 and extension EMEA/H/C/528/X/44 applications respectively. No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to NovoMix and Levemir. The bridging report submitted by the applicant has been found acceptable.
IAIN/0090	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging	30/01/2012	n/a		

	site				
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/0088	A.7 - Administrative change - Deletion of manufacturing sites	11/11/2011	n/a		
IB/0087/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		
II/0085/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	14/04/2011	11/07/2011	SmPC, Labelling and PL	

	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				
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 system. This application was submitted for a group of	17/02/2011	08/04/2011	SmPC 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 latest wording as per October 2010 CHMP announcment regarding the Pharmacovigilance system.

	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				
IA/0086	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	08/04/2011	n/a	SmPC, Labelling and PL	
IB/0084/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/0082	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	04/11/2010	n/a		

	quality of the AS				
IA/0083/G	This was an application for a group of variations. 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	03/11/2010	03/11/2010	SmPC, Labelling and PL	
II/0080	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	28/09/2010		
IA/0081	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	
N/0079	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/12/2009	n/a	Labelling and PL	
II/0077	Update of the SPC section 4.4 "Special warnings and	25/06/2009	27/07/2009	SmPC	The NovoRapid EU recent renewal application (R/72)

	precautions for use" with warning about travelling and section 4.6 "Pregnancy and lactation" with the number of exposed pregnancies to align it with the Company Core Data Sheet (CCDS). Update of Summary of Product Characteristics				obtained positive CHMP opinion on 20 February 2009. During the renewal review it was noted that the Company Core Data Sheet (CCDS) for NovoRapid had been updated with clinical trial data concerning the use during pregnancy and hypoglycaemia precautions. The CHMP has recommended to the MAH to update the SPC accordingly. Section 4.4 was updated with warning about the use during travelling and section 4.6 with the number of exposed pregnancies.
IA/0078	IA_25_b_01_Change to comply with Ph. - compliance with EU Ph. update - active substance	30/06/2009	n/a		
II/0075	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	12/05/2009		
IA/0076	IA_09_Deletion of manufacturing site	05/05/2009	n/a		
R/0072	Renewal of the marketing authorisation.	19/02/2009	30/04/2009	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 NovoRapid continues to be favourable. The CHMP was also of the opinion that the renewal can be

					granted with unlimited validity
II/0073	Extension of the shelf-life of the drug substance. Quality changes	19/02/2009	03/03/2009		
IA/0074	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	08/01/2009	n/a		
IA/0071	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	01/09/2008	n/a		
II/0068	Change(s) to the manufacturing process for the active substance	24/07/2008	29/07/2008		
II/0069	Change to the test procedure and/or specification of a raw material	30/05/2008	11/06/2008		
IA/0070	IA_09_Deletion of manufacturing site	07/05/2008	n/a		
II/0065	Change(s) to container	19/03/2008	23/04/2008	Labelling and PL	
N/0063	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/03/2008	n/a	Labelling	
N/0062	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/03/2008	n/a	PL	
IA/0066	IA_41_a_01_Change in pack size - change in no. of units within range of appr. pack size	25/02/2008	25/02/2008	SmPC, Labelling and PL	

IA/0064	IA_28_Change in any part of primary packaging material not in contact with finished product	18/01/2008	n/a		
II/0060	Change(s) to the test method(s) and/or specifications for the active substance	15/11/2007	23/11/2007		
IA/0061	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	10/10/2007	n/a		
II/0059	Quality changes	20/09/2007	25/09/2007		
II/0058	Inclusion of information about the use of Novorapid in elderly and patients with renal and hepatic impairment. Update of Summary of Product Characteristics and Package Leaflet	19/07/2007	30/08/2007	SmPC and PL	Three studies were submitted in support of the variation: - A randomised controlled, double-blind, study in subjects with type 2 diabetes aged ? 65 years - Two open-label, single dose PK studies in non-diabetic subjects with varying degrees of hepatic impairment and in subjects with type 1 diabetes complicated by varying degrees of renal impairment, respectively. Differences in pharmacokinetic properties between insulin aspart and soluble human insulin in elderly subjects with type 2 diabetes were similar to those observed in healthy subjects and in younger subjects with diabetes. A decreased absorption rate was observed in elderly subjects with type 2 diabetes compared to younger type 2 diabetes patients and to younger type 1 diabetes patients. In subjects with hepatic impairment the absorption rate was decreased and more variable. Data were limited in subjects with moderate and severe renal impairment, but did not suggest any major influence of renal impairment on pharmacokinetic properties between insulin aspart.

II/0057	Change(s) to the manufacturing process for the active substance	24/05/2007	30/05/2007		
II/0056	Update of or change(s) to the pharmaceutical documentation	16/11/2006	21/11/2006		
II/0055	Update of or change(s) to the pharmaceutical documentation	16/11/2006	21/11/2006		
II/0052	This variation relates to the inclusion of information about usage of NovoRapid during pregnancy in the Summary of Product Characteristics sections 4.6 and 5.1, and the package leaflet. Further minor changes were made to the product information in line with the latest QRD templates (version 7) and for harmonisation of texts across the presentations. Finally the MAH took this opportunity to include recommendations for changes of the injection site in the package leaflet. Update of Summary of Product Characteristics, Labelling and Package Leaflet	01/06/2006	20/07/2006	SmPC, Annex II, Labelling and PL	The MAH submitted the result of two studies: - ANA-1474 was a randomised, controlled, open label, parallel-group trial comparing insulin aspart (IAsp) with human insulin (HI) in subjects with type 1 diabetes. Subjects enrolled were either already pregnant at the screening visit or were planning to become pregnant in the immediate future. - ANA-2067 was a randomised, controlled, open label, trial comparing IAsp and HI in subjects diagnosed with gestational diabetes, enrolled between gestational age 18 to 28 weeks. Results from study ANA-1474 (322 exposed pregnancies: 157 to IAsp and 165 to HI) support the use of IAsp during pregnancy. The effect of IAsp, as measured by change in HbA1c, was similar to that of HI. The use of IAsp during pregnancy also seems logical considering the wide spread use in non pregnant women with type 1 diabetes and is further supported by the result of the Quality of Life assessment. There was a lower risk of major hypoglycaemia (diurnal and nocturnal) episodes with IAsp compared to HI in ANA-1474 even though the differences

					were not statistically significant. There were no clinically significant differences in pregnancy outcomes between the treatments. No definite conclusions can be drawn from the analyses of maternal and foetus antibodies since the samples were small. However, the results do not indicate any important difference between insulin aspart and human insulin. No other unexpected adverse advents have been identified in the study. Study ANA-2067 (27 exposed pregnancies: 14 to IAsp and 13 to HI) can only be seen as exploratory due to the limited number of subjects enrolled and concerns over the methodology concerning HbA1c measurements.
N/0054	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/05/2006	n/a		
II/0051	Quality changes	27/04/2006	02/05/2006		
IB/0053	IB_25_a_02_Change to comply with Ph. - compliance with EU Ph. - excipient	25/04/2006	n/a		
N/0050	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/12/2005	n/a	Labelling	
II/0048	Change(s) to the manufacturing process for the finished product	17/11/2005	25/11/2005		
IA/0049	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	25/10/2005	n/a		

IA/0047	IA_09_Deletion of manufacturing site	12/09/2005	n/a	Annex II and PL	
II/0040	Change(s) to the manufacturing process for the finished product	27/07/2005	03/08/2005		
IA/0046	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	12/07/2005	n/a		
II/0041	Change(s) to the manufacturing process for the finished product	26/05/2005	08/07/2005	Annex II and PL	
II/0043	Change(s) to the test method(s) and/or specifications for the active substance	23/06/2005	30/06/2005		
IA/0045	IA_09_Deletion of manufacturing site	23/05/2005	n/a		
N/0044	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/04/2005	n/a	Labelling	
II/0034	Change(s) to the test method(s) and/or specifications for the active substance Update of Summary of Product Characteristics, Labelling and Package Leaflet	17/02/2005	30/03/2005	SmPC, Labelling and PL	This variation concerns an update of sections 4.2, 5.1 and 5.2 of the SPC and relevant sections of the PL to include information on the use of NovoRapid in children within the age group 2-6 years. Minor amendments have also been included in the labelling.
N/0042	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.	11/03/2005	n/a	PL	

	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)				
II/0036	Change(s) to the manufacturing process for the finished product	20/01/2005	27/01/2005		
II/0035	Change(s) to the manufacturing process for the finished product	20/01/2005	27/01/2005		
IA/0038	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/0037	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	20/12/2004	n/a		
R/0032	Renewal of the marketing authorisation.	29/07/2004	18/10/2004	SmPC, Annex II, Labelling and PL	Based on the review of the available information, the CHMP was of the opinion that the quality, the safety and the efficacy of NovoRapid continues to be adequately and sufficiently demonstrated and that the benefit/risk profile of NovoRapid continues to be favourable in the treatment of patients with diabetes mellitus.
II/0033	Update of or change(s) to the pharmaceutical documentation	16/09/2004	18/10/2004	SmPC, Labelling and PL	The Marketing Authorisation Holder applied to extend the shelf life for Novorapid from 24 months to 30 months.
X/0027	X-1-iii_Qualitative change to the active substance(s)	03/06/2004	24/08/2004	Annex II	
II/0031	Update of or change(s) to the pharmaceutical documentation	22/04/2004	28/04/2004		

II/0029	The Marketing Authorisation Holder applied for an update of section 4.8 of the Summary of Product Characteristics (SPC) and correspondent section in the Package Leaflet. In addition a class warning regarding early warning symptoms of hypoglycaemia included in Section 4.4 of the SPC has been modified. Update of Summary of Product Characteristics and Package Leaflet	26/02/2004	07/04/2004	SmPC and PL	
II/0028	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 Actrapid. Annex II has also been included with a complete list of presentations related to each manufacturer responsible for batch release. Update of Summary of Product Characteristics and Package Leaflet	26/02/2004	07/04/2004	SmPC, Annex II and PL	
II/0030	Update of or change(s) to the pharmaceutical documentation	24/03/2004	31/03/2004		
I/0026	15_Minor changes in manufacture of the medicinal product	25/09/2003	29/09/2003		
I/0025	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/0024	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	20/06/2003	18/07/2003	Annex II and PL	
II/0022	Update of Summary of Product Characteristics and Package Leaflet	23/01/2003	06/06/2003	SmPC, Labelling and PL	
X/0019	X-3-v_Addition of a new route of administration	19/12/2002	04/06/2003	SmPC, Labelling and PL	
X/0016	X-3-v_Addition of a new route of administration	19/12/2002	04/06/2003	SmPC, Labelling and PL	
II/0021	New presentation(s)	18/12/2002	04/06/2003	SmPC, Labelling and PL	
II/0013	Update of Summary of Product Characteristics and Package Leaflet	21/03/2002	15/07/2002	SmPC, Labelling and PL	
I/0018	15_Minor changes in manufacture of the medicinal product	27/06/2002	10/07/2002		
I/0017	16_Change in the batch size of finished product	30/05/2002	10/06/2002		
I/0015	30_Change in pack size for a medicinal product	16/01/2002	02/04/2002	SmPC, Labelling and PL	
II/0012	Change(s) to the test method(s) and/or	21/02/2002	26/02/2002		

	specifications for the active substance				
I/0014	12_Minor change of manufacturing process of the active substance	21/02/2002	26/02/2002		
I/0011	16_Change in the batch size of finished product	13/12/2001	07/01/2002		
II/0010	Quality changes	20/09/2001	22/10/2001		
II/0008	Quality changes	26/04/2001	26/07/2001	SmPC and PL	
II/0007	Update of Summary of Product Characteristics and Package Leaflet	14/12/2000	23/04/2001	SmPC and PL	
I/0009	24_Change in test procedure of active substance 25_Change in test procedures of the medicinal product	01/03/2001	02/04/2001		
II/0006	Update of Summary of Product Characteristics and Package Leaflet	28/08/2000	15/01/2001	SmPC, Labelling and PL	
II/0005	Update of Summary of Product Characteristics and Package Leaflet	18/11/1999	13/04/2000	SmPC, Labelling and PL	
II/0004	New presentation(s)	21/10/1999	08/02/2000	SmPC, Labelling and PL	
II/0003	New presentation(s)	21/10/1999	08/02/2000	SmPC, Labelling and	

				PL	
II/0002	New presentation(s)	21/10/1999	08/02/2000	SmPC, Labelling and PL	
I/0001	12_Minor change of manufacturing process of the active substance	18/11/1999	15/12/1999		