Ryzodeg

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
II/0054	TYPE II B.IV.1.c - Addition or replacement of a device which is an integrated part of the primary packaging: to add the 100 units/mL FlexPen solution for injection in pre filled pen presentation (EU/1/12/806/009)	15/02/2024		SmPC, Annex II, Labelling and PL	The SmPC sections 1, 2, 3, 4.2, 6.3, 6.4, 6.5, 6.6 has been updated to add the FlexPen pen-injector presentation (EU/1/12/806/009). The Labelling and PL have been updated accordingly.

[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).

	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				
IB/0053	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	05/07/2023	n/a		
IB/0052	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	15/03/2023	n/a		
WS/2357	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/2344	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	12/01/2023	n/a		
WS/2302/G	This was an application for a group of variations following a worksharing procedure according to	15/12/2022	n/a		

	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				
WS/2298/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. Please refer to the Recommendations section 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	17/11/2022	n/a		Not applicable
IB/0047/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a	15/07/2021	29/09/2021	Annex II and PL	Addition of a manufacturing site Novo Nordisk Production SAS 45, as a site responsible finished product Ryzodeg® FlexTouch® (EU/1/12/806/001 – 005) batch release.

	manufacturing site for the FP - Secondary packaging site B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing				Annex II and IIIB have been updated accordingly.
WS/2063	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/10036 /202009	Periodic Safety Update EU Single assessment - insulin degludec, insulin degludec / insulin aspart	10/06/2021	n/a		PRAC Recommendation - maintenance
IB/0045	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	30/03/2021	n/a		
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		
IAIN/0044	B.II.b.1.a - Replacement or addition of a	19/02/2021	n/a		

	manufacturing site for the FP - Secondary packaging site				
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	29/09/2021	SmPC, Annex II, Labelling and PL	
WS/1865	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	03/09/2020	n/a		Not applicable
WS/1841	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	02/07/2020	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.	05/12/2019	n/a		

	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				
IG/1167	A.7 - Administrative change - Deletion of manufacturing sites	22/11/2019	n/a		
WS/1669	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	07/11/2019	n/a		
IB/0036	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	04/09/2019	n/a		
WS/1635	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	25/07/2019	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		

WS/1615	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.z - Quality change - Active substance - Other variation	11/07/2019	n/a		
II/0030/G	This was an application for a group of variations. Update of sections 4.2 and section 5.1 of the SmPC in order to update the information on dosing and administration interval of Ryzodeg (insulin aspart/insulin degludec) based on data from 2 trials: • NN5401-4266, a 38 week trial comparing effect and safety of insulin degludec/insulin aspart vs. insulin glargine plus insulin aspart in subjects with type 2 diabetes treated with basal insulin with or without oral antidiabetic treatment in need of treatment intensification. • NN5401-3996, a 26-week trial comparing efficacy and safety of insulin degludec/insulin aspart BID and insulin degludec OD plus insulin aspart in subjects with type 2 Diabetes Mellitus treated with basal insulin in need of treatment intensification with mealtime insulin. In addition, the MAH took the opportunity to make editorial changes in the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/03/2019	03/05/2019	SmPC	Patients with type 2 diabetes mellitus: Ryzodeg can be administered once or twice daily with the main meal(s) alone, in combination with oral antidiabetic medicinal products, and in combination with bolus insulin. When using Ryzodeg once-daily, changing to twice daily should be considered when higher doses are needed, e.g. to avoid hypoglycaemia. Split the dose based on individual patient's needs and administer with main meals. Patients with type 1 diabetes mellitus: Ryzodeg can be administered once daily at mealtime in combination with short-/rapid-acting insulin at the remaining meals. Section 5.1 of the SmPC was updated to reflect the additional data provided (please refer to the product information for the detailed results).

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
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/0978	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)	07/09/2018	n/a		
II/0028	Update of section 5.1 of the SmPC based on new clinical data from a cardiovascular outcome trial EX1250-4080 (DEVOTE) conducted for insulin degludec. DEVOTE was a randomised, double-blind and event-driven clinical trial with a median duration of 2 years comparing the cardiovascular safety of insulin degludec versus insulin glargine (100 units/mL) in patients with type 2 diabetes mellitus at high risk of cardiovascular events. Based on the long-term exposure and safety data from DEVOTE which are also relevant for insulin	06/09/2018	03/05/2019	SmPC	The summary of product characteristics (section 5.1) was updated with new clinical data from a cardiovascular outcome study (DEVOTE) focusing on insulin degludec, the long-acting component of Ryzodeg. The data presented show that Ryzodeg did not alter the relative risk of cardiovascular disease and cardiovascular mortality when compared to insulin glargine in a population at high risk of cardiovascular events.

	degludec/insulin aspart, the Ryzodeg SmPC is updated with data from the trial in alignment with a recent update of the SmPC for insulin degludec. Section 6.5 of the SmPC is also being amended for an editorial improvement to more precisely describe the nature of the plunger stopper. The RMP version 7 has consequently been agreed. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
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/10036 /201709	Periodic Safety Update EU Single assessment - insulin degludec, insulin degludec / insulin aspart	12/04/2018	n/a		PRAC Recommendation - maintenance
WS/1222	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2, 4.4 and 6.6 of the SmPC and relevant sections of the labelling and PL to minimise	12/10/2017	20/09/2018	SmPC, Labelling and PL	The medicine must not be drawn from the cartridge of the pre-filled pen into a syringe. A new needle must always be attached before each use. Needles must not be re-used. The re-use of insulin pen needles increases the risk of blocked needles, which may cause under- or overdosing. In the event of blocked needles, patients must follow the

	the potential risk of medication error as requested by the PRAC in the course of a signal assessment (EPITT ref. No. 18893). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				instructions described in the instructions for use accompanying the package leaflet. The above warnings do not apply to the cartridge presentations of the medicine.
R/0024	Renewal of the marketing authorisation.	20/07/2017	21/09/2017	SmPC, Labelling and PL	
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/10036 /201609	Periodic Safety Update EU Single assessment - insulin degludec, insulin degludec / insulin aspart	05/05/2017	n/a		PRAC Recommendation - maintenance
IB/0019	B.I.a.z - Change in manufacture of the AS - Other variation	25/10/2016	n/a		
IA/0020	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)	19/10/2016	n/a		
II/0017	Extension of Indication to include treatment of diabetes mellitus in paediatric population from 2	23/06/2016	22/07/2016	SmPC, Annex II, Labelling	Please refer to the published Assessment Report Ryzodeg

	years of age for Ryzodeg; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Furthermore, the PI is brought in line with the QRD template version 10.0. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one			and PL	H-2499-II-17-AR.
PSUSA/10036 /201509	Periodic Safety Update EU Single assessment - insulin degludec, insulin degludec / insulin aspart	14/04/2016	n/a		PRAC Recommendation - maintenance
N/0015	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/07/2015	13/04/2016	PL	
IB/0016	B.II.h.z - Adventitious Agents Safety - Other variation	25/06/2015	n/a		
II/0012	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	23/04/2015	13/04/2016	SmPC, Labelling and PL	
PSUSA/10036 /201409	Periodic Safety Update EU Single assessment - insulin degludec, insulin degludec / insulin aspart	10/04/2015	n/a		PRAC Recommendation - maintenance
IB/0014	B.I.a.z - Change in manufacture of the AS - Other variation	16/02/2015	n/a		
PSUV/0011	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance

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		
PSUV/0007	Periodic Safety Update	08/05/2014	n/a		PRAC Recommendation - maintenance
IB/0009	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	25/02/2014	n/a		
IA/0008	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	03/02/2014	23/04/2014	SmPC	
IAIN/0006/G	This was an application for a group of variations. C.I.10 - Change in the frequency and/or date of submission of PSURs for human medicinal products C.I.12 - Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring	20/12/2013	23/04/2014	SmPC, Annex II and PL	
N/0005	Minor change in labelling or package leaflet not	20/11/2013	23/04/2014	PL	

	connected with the SPC (Art. 61.3 Notification)				
IAIN/0003	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	06/05/2013	23/04/2014	SmPC, Labelling and PL	
IAIN/0002	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	06/05/2013	23/04/2014	SmPC, Labelling and PL	
IG/0276	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	25/03/2013	n/a		