Tresiba

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/0060	B.IV.1.c (Type II): 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 pen-injector presentation (EU/1/12/807/017).	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/1/12/807/xxx). 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/0059	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	24/07/2023	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/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	17/11/2022	n/a		Not applicable

	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				
IAIN/0055	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	17/02/2022	n/a		
II/0054	Update of sections 4.6 and 5.1 of the Summary of product characteristics in order to include new clinical data from the pregnancy trial EXPECT conducted for Tresiba. This was a multi-centre, randomised, active controlled trial comparing the efficacy and safety of Tresiba once daily with insulin detemir once or twice daily both in combination with insulin aspart 2-4 times daily with meals in pregnant women or women who intended to become pregnant, all with type 1 diabetes. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to introduce minor administrative changes. The RMP version 9.0 is also submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/01/2022	16/12/2022	SmPC and PL	Results from this study support the use of the medicinal product during pregnancy. The metabolic control achieved with Tresiba during pregnancy was non-inferior to that of the comparator. The safety profile with regards to hypoglycaemia was in line with previous data for Tresiba. There were differences noted regarding maternal safety, as reflected in SmPC section 5.1. No new safety concerns arose with regards to maternal or foetal/infant health. For more information, please refer to the Summary of Product Characteristics.

IB/0053/G	This was an application for a group of variations. B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	03/08/2021	29/09/2021	Annex II and PL	Annex II and IIIB have been update to reflect addition of a manufacturing site Novo Nordisk Production SAS, Chartres, France as a site responsible finished product Tresiba® 100 U/ml FlexTouch® (EU/1/12/806/001 – 005) quality control and batch release.
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
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/0051	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging	19/02/2021	n/a		

	site				
II/0047	Update of section 5.1 of the SmPC in order to update the description of day-to-day variability in glucose-lowering effect further to assessment of post-authorisation measure LEG013. In addition, the MAH took the opportunity to make editorial corrections in section 5.2 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	06/11/2020	29/09/2021	SmPC	The presentation of the data on day-to-day variability has been updated. For more information, please refer to the Summary of Product Characteristics.
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	02/07/2020	n/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				
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		
IAIN/0043	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	14/10/2019	n/a		
IB/0041	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	26/08/2019	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		
IG/1066	A.7 - Administrative change - Deletion of manufacturing sites	29/03/2019	n/a		
IG/1038	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	14/01/2019	n/a		
IB/0035	B.II.z - Quality change - Finished product - Other variation	12/11/2018	04/11/2019	SmPC	
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		
IAIN/0033	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g.	10/07/2018	20/09/2018	SmPC, Labelling and	

	tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes			PL	
IB/0032	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	20/06/2018	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
N/0031	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/02/2018	20/09/2018	Labelling and PL	
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 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	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 instructions described in the instructions for use accompanying the package leaflet. The above warnings do not apply to the cartridge presentations of the medicine.
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 Tresiba. DEVOTE was a randomised, double-blind and event-	28/09/2017	20/09/2018	SmPC	

	driven clinical trial with a median duration of 2 years comparing the cardiovascular safety of Tresiba versus insulin glargine (100 units/mL) in patients with type 2 diabetes mellitus at high risk of cardiovascular events. The RMP version 8.1 has consequently been agreed. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
R/0027	Renewal of the marketing authorisation.	20/07/2017	21/09/2017	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Tresiba in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10036 /201609	Periodic Safety Update EU Single assessment - insulin degludec, insulin degludec / insulin aspart	05/05/2017	n/a		PRAC Recommendation - maintenance
II/0024/G	This was an application for a group of variations. Grouping of two variations to update sections 4.2 and 5.1 of the SmPC in order to include updated information on the use of Tresiba in terms of transfer from other basal insulin regimens and the effects of Tresiba on hypoglycaemia. The Package Leaflet and Labelling are proposed to be updated accordingly. An updated RMP (version 7.0) was submitted with this procedure.	23/03/2017	28/04/2017	SmPC, Annex II, Labelling and PL	Data from the following two studies were submitted conducted for insulin degludec: NN1250-3995 (SWITCH 1) and NN1250-3998 (SWITCH 2). The trials were identically designed to compare the safety and efficacy of insulin degludec and insulin glargine U-100. The main objective of the trials was to document the hypoglycaemia profile in type 1 diabetes and type 2 diabetes, respectively. The prescribing information for Tresiba was updated with new information on the use of insulin degludec in terms of transfer from other basal insulin regimens and the hypoglycaemia benefit of Tresiba.

	The proposed changes reflect the findings from two studies submitted: NN1250-3995 (SWITCH 1) and NN1250-3998 (SWITCH 2), comparing the safety and efficacy of Tresiba and insulin glargine U-100, mainly to document the hypoglycaemia profile in type 1 diabetes and type 2 diabetes, respectively. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.0 and implement minor changes to the SmPC section 4.2 and the corresponding section of the Package Leaflet to clarify the correct use of Tresiba. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				The findings from the two trials were included in section 4.2 (Transfer from other insulin medicinal products) and section 5.1 (Clinical efficacy and safety) of the SmPC. Minor changes were also made to the SmPC section 4.2 and the corresponding section of the PL to clarify the correct use of insulin degludec.
IB/0023	B.I.a.z - Change in manufacture of the AS - Other variation	25/10/2016	n/a		
II/0022	To update the Risk Management Plan. 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	15/09/2016	n/a		

IB/0021	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	27/05/2016	n/a		
PSUSA/10036 /201509	Periodic Safety Update EU Single assessment - insulin degludec, insulin degludec / insulin aspart	14/04/2016	n/a		PRAC Recommendation - maintenance
IB/0020	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	31/03/2016	n/a		
IB/0018	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	27/11/2015	n/a		
N/0016	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	21/07/2015	14/04/2016	PL	
IB/0017	B.II.h.z - Adventitious Agents Safety - Other variation	25/06/2015	n/a		
II/0013	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	14/04/2016	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/0015	B.I.a.z - Change in manufacture of the AS - Other	17/02/2015	n/a		

	variation				
II/0011	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	18/12/2014	30/01/2015	SmPC and PL	
II/0012	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	18/12/2014	n/a		
PSUV/0010	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance
PSUV/0007	Periodic Safety Update	08/05/2014	n/a		PRAC Recommendation - maintenance
II/0006	Update of sections 4.2 and 5.1 of the SmPC in order to include guidance for prescribers on the use of Tresiba in combination with GLP-1 receptor agonists. The Package Leaflet is updated accordingly. Furthermore, the PI is being brought in line with the latest QRD template version 9 and to include some editorial changes. This variation application contains an updated RMP. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	20/03/2014	07/05/2014	SmPC, Annex II, Labelling and PL	For further information please refer to the scientific conclusion: Tresiba H-2498-II-23-AR.
IB/0008	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	24/02/2014	n/a		

IB/0005	B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product	08/07/2013	n/a		
IAIN/0004/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 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	07/05/2014	SmPC, Labelling and PL	
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	03/05/2013	07/05/2014	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		