Trulicity

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/0065	Extension of indication to include treatment of type 2 diabetes mellitus (T2DM) in children and adolescents aged 10 to less than 18 years based on final results from study H9X-MC-GBGC; this is a phase 3, double-blind, randomised, multi-centre, placebo-controlled superiority trial to evaluate PK, PD, safety and efficacy of dulaglutide in children from 10 to less than 18 years of age, with an open label extension to evaluate safety. As a consequence, sections 4.1, 4.2, 4.8, 5.1, and 5.2 of the SmPC are updated. The	26/01/2023	06/03/2023	SmPC and PL	Please refer to Scientific Discussion 'Trulicity-H-C-2825-II-65'.

[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).

	Package Leaflet is updated in accordance. Version 7.2 of the RMP was agreed during the procedure. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IG/1565	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)	06/12/2022	n/a		
II/0064/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates	07/07/2022	n/a		

	to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product				
IB/0063	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)	13/04/2022	n/a		
PSUSA/10311 /202109	Periodic Safety Update EU Single assessment - dulaglutide	07/04/2022	n/a		PRAC Recommendation - maintenance
II/0062/G	This was an application for a group of variations. B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes	17/03/2022	n/a		
PSUSA/10311 /202009	Periodic Safety Update EU Single assessment - dulaglutide	22/04/2021	17/06/2021	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10311/202009.
IB/0060	C.I.7.a - Deletion of - a pharmaceutical form	05/05/2021	02/06/2022	SmPC, Labelling and PL	

IB/0059/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary 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	24/02/2021	17/06/2021	Annex II and PL	
II/0051	Update of section 4.8 of the SmPC to add 'delayed gastric emptying' as a new ADR with a frequency of rare, based on the final study report for the PASS category 3 dulaglutide drug utilisation study H9X-MC-B009: a multi-database collaborative research program of observational studies to monitor the utilisation and safety of dulaglutide in the EU (ref. PAM MEA 002-002.5), and taking into account the data from the pooled clinical trials, REWIND trial, post-marketing surveillance and Eudravigilance. The Package Leaflet has been updated accordingly. An updated RMP version 6.2 was agreed during the procedure. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	11/02/2021	17/06/2021	SmPC and PL	not applicable
N/0056	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/01/2021	17/06/2021	PL	
IB/0057	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a	15/12/2020	n/a		

	biological/immunological medicinal product				
II/0054	B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes	03/12/2020	n/a		n/a
X/0045	Extension of the marketing authorisation to add two new strengths; 3 mg and 4.5 mg (solution for injection in pre-filled pen) Annex I_2.(c) Change or addition of a new strength/potency	17/09/2020	18/11/2020	SmPC, Annex II, Labelling and PL	Please refer to Scientific Discussion 'Trulicity-H-C-2825-X-45'
II/0053/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method	22/10/2020	n/a		
IB/0052/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	11/08/2020	n/a		

	biological/immunological medicinal product				
II/0048	Submission of the final study report from Study B010, investigating the utilisation of dulaglutide in European countries: A cross-sectional, multi-country and multi-source drug utilisation study using electronic health record databases. Study B010 is listed as a category 3 study in the RMP (MEA 001). An updated RMP version 5.2 was agreed during the procedure. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	09/07/2020	n/a		N/A
IB/0050	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	29/04/2020	n/a		
PSUSA/10311 /201909	Periodic Safety Update EU Single assessment - dulaglutide	17/04/2020	n/a		PRAC Recommendation - maintenance
IB/0049	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	16/04/2020	n/a		
IB/0046	B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	06/03/2020	n/a		
II/0040	Update of sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 of the SmPC based on the data from Study H9X-MC-GBDJ (Researching Cardiovascular Events with a Weekly INcretin in Diabetes (REWIND)); a single pivotal Phase 3 long-term cardiovascular outcomes study, which assessed the efficacy	19/09/2019	21/10/2019	SmPC, Annex II and PL	Please refer to Scientific Discussion 'Trulicity-H-C-2825-II-40'

	and safety of treatment with once-weekly injection of dulaglutide 1.5 mg when added to glucose-lowering regimen of patients with type 2 diabetes (T2D), compared to the addition of a once weekly placebo injection. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to implement a minor correction in section 5.1 of the SmPC, to implement editorial changes and to align the annexes with the latest QRD template. An updated RMP version 3.3 was agreed during the procedure. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
R/0036	Renewal of the marketing authorisation.	27/06/2019	23/08/2019	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Trulicity in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IB/0044	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	02/08/2019	n/a		
IB/0043	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	28/06/2019	n/a		
IB/0042	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an	28/06/2019	n/a		

	approved test procedure				
IA/0041	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	31/05/2019	n/a		
N/0038	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/05/2019	23/08/2019	Labelling	
PSUSA/10311 /201809	Periodic Safety Update EU Single assessment - dulaglutide	11/04/2019	n/a		PRAC Recommendation - maintenance
II/0033	B.I.e.2 - Introduction of a post approval change management protocol related to the AS	04/04/2019	n/a		
IB/0039	B.II.g.4.b - Changes to an approved change management protocol - Minor changes that do not change the strategy defined in the protocol	03/04/2019	n/a		
IAIN/0037	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/03/2019	23/08/2019	SmPC and PL	
II/0032	Update of section 4.4 and 4.8 of the SmPC, following a cumulative review of Acute Kidney Injury events undertaken upon request by PRAC (EPITT No 19204), to add information regarding the potential for dulaglutide to possibly contribute to the volume depletion event, which could indirectly contribute to the occurrence of AKI. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the contact details of the local representatives in the package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new	31/01/2019	23/08/2019	SmPC and PL	Dehydration, sometimes leading to acute renal failure or worsening renal impairment, has been reported in patients treated with dulaglutide, especially at the initiation of treatment. Many of the reported adverse renal events occurred in patients who had experienced nausea, vomiting, diarrhoea, or dehydration. Patients treated with dulaglutide should be advised of the potential risk of dehydration, particularly in relation to gastrointestinal side-effects and take precautions to avoid fluid depletion.

	quality, preclinical, clinical or pharmacovigilance data				
IA/0035	B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	18/12/2018	n/a		
IB/0031	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	10/10/2018	n/a		
II/0030	B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method	19/07/2018	n/a		
PSUSA/10311 /201709	Periodic Safety Update EU Single assessment - dulaglutide	26/04/2018	02/07/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10311/201709.
II/0025	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/04/2018	02/07/2018	SmPC and PL	The product information of Trulicity is updated to include information from a new study which examined the efficacy and safety of Trulicity added in patients with type 2 diabetes mellitus who were already receiving therapy with a sodium-glucose co-transporter-2 inhibitors (SGLT2i, a recently approved class of drugs used to lower blood sugar) with or without concomitant metformin. The SmPC section 4.2 has been updated to explain

					that, when Trulicity is added to existing metformin and/or sodium-glucose co-transporter-2 inhibitor (SGLT2i) therapy, the dose of metformin and/or SGLT2i can be continued. Section 5.1 now contains a description of the results of the study. The PL was updated accordingly.
II/0026	B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method	19/04/2018	n/a		
IAIN/0029	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	27/03/2018	02/07/2018	SmPC and PL	
II/0027	Introduction of a new post-approval change management protocol to add an alternate batch size and a minor change in the manufacturing process related to the dulaglutide 1.5mg/0.5mL semi-finished syringes manufactured at the Vetter Pharma site (Vetter Pharma-Fertigung at Mooswiesen). This variation only concerns the high strength (1.5mg/0.5mL) presentations. B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	15/03/2018	n/a		
II/0022	Update of sections 4.2, 5.1 and 5.2 of the SmPC for Trulicity following completion of a Phase 3 study H9X-MCGBDX comparing the effect of once-weekly Trulicity with insulin glargine on glycaemic control over 52 weeks in patients with type 2 Diabetes Mellitus and moderate or severe chronic kidney disease. In addition, the MAH took to opportunity to	25/01/2018	22/02/2018	SmPC and PL	No dosage adjustment is required in patients with mild, moderate or severe renal impairment (eGFR <90 to ≥15 mL/min/1.73m2). There is very limited experience in patients with end stage renal disease (<15 ml/min/1.73m2), therefore Trulicity cannot be recommended in this population.

	update the ATC code and to correct the "Instructions for use" in Section 6.6 of the SmPC to make it consistent with instructions on "How to store Trulicity" in the Package Leaflet (PL), which was also updated in section 2 'Warnings and precautions' to reflect the information in the "renal impairment" section 4.2 of the SmPC. The RMP version 1.12 has also been agreed. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				In a 52 week study, Trulicity 1.5 mg and 0.75 mg were compared to titrated insulin glargine as add-on to prandial insulin lispro to evaluate the effect on glycaemic control and safety of patients with moderate to severe chronic kidney disease. Patients discontinued their prestudy insulin regimen at randomisation. The pharmacokinetic profile of Trulicity 0.75 mg and 1.5 mg once weekly was similar to that demonstrated in previous clinical studies. This clinical study did not include patients with end stage renal disease. At 26 weeks, both Trulicity 1.5 mg and 0.75 mg were non-inferior to insulin glargine in lowering of HbA1c and this effect was sustained at 52 weeks. A similar percentage of patients achieved HbA1c targets of < 8.0 % at 26 and 52 weeks with both dulaglutide doses as well as insulin glargine. The rates of documented symptomatic hypoglycaemia with Trulicity 1.5 mg and Trulicity 0.75 mg, and insulin glargine were 4.44, 4.34, and 9.62 episodes/patient/year, respectively. No patients reported cases of severe hypoglycaemia with Trulicity 1.5 mg, six with Trulicity 0.75 mg, and seventeen with insulin glargine. The safety profile of Trulicity in patients with renal impairment was similar to that observed in other studies with Trulicity.

					For more detailed information please refer to the Summary of Product Characteristics (SmPC).
IG/0898	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	12/02/2018	02/07/2018	Annex II	
II/0021	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	25/01/2018	n/a		
II/0023	B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes	18/01/2018	n/a		
PSUSA/10311 /201703	Periodic Safety Update EU Single assessment - dulaglutide	28/09/2017	n/a		PRAC Recommendation - maintenance
IB/0020	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	30/08/2017	n/a		
PSUSA/10311 /201609	Periodic Safety Update EU Single assessment - dulaglutide	21/04/2017	16/06/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10311/201609.
PSUSA/10311	Periodic Safety Update EU Single assessment - dulaglutide	13/10/2016	12/12/2016	PL	Refer to Scientific conclusions and grounds

/201603					recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10311/201603.
IA/0017/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	02/12/2016	n/a		
II/0013	Update of sections 4.2, 4.7, 4.8 and 5.1 of the Summary of Product Characteristics (SmPC) for Trulicity following completion of a phase 3b Study (Study H9X-MCGBDI (GBDI)) to reflect the study's findings concerning the use of dulaglutide in combination with basal insulin. The Package Leaflet is updated in accordance. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/10/2016	12/12/2016	SmPC and PL	With this variation the product information of Trulicity was updated to include information from a new study which examined the efficacy and safety of Trulicity in patients with type 2 diabetes mellitus who were already receiving therapy with basal insulin with or without metformin. The safety data from the new study were consistent with the findings of previous studies with Trulicity. In general, there were no significant new or unexpected findings and the new safety data from the study do not raise any major concerns. The key relevant safety information and warnings are already included in the SmPC but updates to Sections 4.2, 4.7, 4.8 and 5.1 were

					agreed to include the specific findings of the study about the concomitant use of dulaglutide with basal insulin.
II/0012	Update of sections 4.8 and 5.1 of the SmPC in order to update the safety information to reflect findings from a recently completed phase 3b study (Study H9X-MC-GBDG (GBDG)) concerning the use of dulaglutide in combination with sulphonylurea alone. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/10/2016	12/12/2016	SmPC and Labelling	With this variation the product information of Trulicity is updated to include information from a new study which examined the efficacy and safety of Trulicity in patients with type 2 diabetes mellitus who were already receiving therapy with a sulphonylurea, a common class of drugs used to lower blood sugar. The results of the study confirmed the efficacy of dulaglutide in type 2 diabetes mellitus patients, when taken as add-on to a sulphonylurea. New safety data from the study did not raise any new safety concerns. The relevant key safety information and warnings are already included in the SmPC but an update, as proposed by the MAH, was needed to include the specific findings of the study about the concomitant use of dulaglutide with a sulphonylurea alone. As a consequence, sections 4.8 and 5.1 of the Summary of Product Characteristics (SmPC) were updated.
IB/0016	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	04/07/2016	n/a		
IA/0014/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or	02/06/2016	n/a		

	address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) 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)				
PSUSA/10311 /201509	Periodic Safety Update EU Single assessment - dulaglutide	14/04/2016	n/a		PRAC Recommendation - maintenance
IB/0011	B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	03/03/2016	n/a		
IG/0662	A.1 - Administrative change - Change in the name and/or address of the MAH	23/02/2016	15/09/2016	SmPC, Labelling and PL	
IA/0009	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	04/12/2015	n/a		
PSUSA/10311 /201503	Periodic Safety Update EU Single assessment - dulaglutide	08/10/2015	n/a		PRAC Recommendation - maintenance
IAIN/0007	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	24/09/2015	n/a		
II/0006/G	This was an application for a group of variations. A.6 Update of the ATC code in section 5.1	24/09/2015	15/09/2016	SmPC, Annex II, Labelling and PL	The marketing authorisation holder conducted a study in rats in which it was determined that there were no detrimental effects at exposures well in excess of those achieved in patients taking the

	C.1.4 Update of section 5.3 of the SmPC to amend the safety information with results from the juvenile toxicity study. In addition the MAH is updating the PI in accordance with the QRD template (version 9.1) and correcting an error in section 5.2 of the SmPC with regards to the value provided for clearance of the dulaglutide 0.75mg dose. 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				product at the highest recommended dose. At the highest dose used, there were changes in that female sexual developmental landmarks were achieved slightly earlier in those given dulaglutide. The benefit-risk balance of Trulicity remains positive.
II/0005	B.I.e.2 - Introduction of a post approval change management protocol related to the AS	17/09/2015	n/a		
N/0004	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/08/2015	15/09/2016	Labelling and PL	
IAIN/0002/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	20/03/2015	n/a		
IB/0001	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	05/02/2015	n/a		