Victoza

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
PSUSA/1892/ 202312	Periodic Safety Update EU Single assessment - liraglutide	19/09/2024	19/11/2024		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1892/202312.
IG/1796	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/10/2024		SmPC and PL	

[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).

IB/0068	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	28/07/2023	n/a		
II/0066	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/07/2023	08/07/2024	SmPC and PL	
IG/1621	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	20/06/2023	n/a		
WS/2353	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/2303/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	24/11/2022	n/a		

	of an in-process test which may have a significant effect on the overall quality of the AS				
IAIN/0062	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	10/12/2021	n/a		
IB/0061	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	03/09/2021	n/a		
IAIN/0060	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	09/06/2021	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		
PSUSA/1892/ 201912	Periodic Safety Update EU Single assessment - liraglutide	23/07/2020	24/09/2020	SmPC and PL	Please refer to (SAXENDA, VICTOZA) PSUSA-1892-201912 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
II/0057	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	03/09/2020	n/a		not applicable
IG/1172	A.7 - Administrative change - Deletion of manufacturing sites	16/01/2020	n/a		

IAIN/0054	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	11/10/2019	n/a		
PSUSA/1892/ 201812	Periodic Safety Update EU Single assessment - liraglutide	25/07/2019	09/10/2019	SmPC and PL	Please refer to PSUSA/00001892/201812 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
II/0050	Update of sections 4.2 and 5.1 of the SmPC, based on the phase 3b study NN2211-4315 (LIRA-ADD2SGLT2i), to include data on liraglutide vs placebo as add-on to SGLT-2 inhibitors (+/- metformin) in subjects with type 2 diabetes mellitus. The Package Leaflet has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	27/06/2019	09/08/2019	SmPC and PL	Study 4315 demonstrated superiority of liraglutide over placebo in improving glycaemic control in subjects with inadequately controlled type 2 diabetes mellitus when added to treatment with a sodium-glucose cotransporter 2 inhibitor (SGLT2i) ± metformin. The improvement in hbA1c was clinically relevant (approximately 0.7%). The decrease in body weight was not statistically significant and not clinically relevant (approximately 0.8 kg). No dose adjustments are required for Victoza when used in combination with an SGLT-2 inhibitor.
II/0049	Extension of Indication to include treatment of children and adolescents aged 10 years and above with type 2 diabetes mellitus based on Study NN2211-1800; a Phase 1 clinical pharmacology, multi-centre, randomised, double-blind placebo controlled trial, and Study NN2211-3659; a Phase 3a efficacy and safety, multi-centre, randomised, parallel group, placebo controlled trial with a 26-week double blind period followed by a 26-week open label period (main part). As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, and 5.2 of the SmPC are being updated and the Package Leaflet is	27/06/2019	09/08/2019	SmPC and PL	Please refer to Scientific Discussion 'Victoza-H-C-1026-II-49'

	updated accordingly. Additionally, in accordance with the excipients guideline from 2017, the MAH took the opportunity to include sodium in SmPC section 4.4 and the Package Leaflet. Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s). An updated RMP version 30.1 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				
IAIN/0053	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	05/04/2019	09/08/2019	SmPC and PL	
WS/1478	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	14/02/2019	n/a		
PSUSA/1892/201712	Periodic Safety Update EU Single assessment - liraglutide	12/07/2018	n/a		PRAC Recommendation - maintenance

IG/0872	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)	30/11/2017	n/a		
IA/0045	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	22/09/2017	27/08/2018	SmPC	
II/0042	Update of section 4.1 of the SmPC for Victoza based on the findings of the study LEADER (EX2211-3748), which constitutes the data set for the application; sections 4.2, 4.4, 4.7, 4.8, 5.1 and 6.5 of the SmPC are also updated to add warnings and update the safety information based on the findings of the LEADER (EX2211-3748) clinical study results. The Package Leaflet and Labelling (sections 17 and 18) are updated in accordance. Updates to the liraglutide RMP based on the LEADER study results are also proposed: RMP Version 27.3 was agreed. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	22/06/2017	25/07/2017	SmPC, Labelling and PL	Please refer to the published Assessment Report H-1026-II-42-AR.
PSUSA/1892/ 201612	Periodic Safety Update EU Single assessment - liraglutide	06/07/2017	n/a		PRAC Recommendation - maintenance
WS/0943	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final results from the Optum	21/04/2017	n/a		

	Database study (NN2211-3784, RMP category 3 study); this was a post-marketing safety surveillance study to observe the safety profile of liraglutide and to compare it with that of other antidiabetic medications when used in a real-life setting in the U.S. The study included a sub-study specifically addressing the safety concern of breast cancer. The updated RMP version 26 has been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
PSUSA/1892/ 201512	Periodic Safety Update EU Single assessment - liraglutide	21/07/2016	22/09/2016	SmPC, Labelling and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1892/201512.
II/0038	Extension of indication to include monotherapy with liraglutide when diet and exercise alone do not provide adequate glycaemic control in patients for whom use of metformin is considered inappropriate; additionally, the MAH updated information related to the hepatic and renal impairment. As a consequence, sections 4.1, 4.2, 5.1 and 5.2 of the SmPC have been updated with new efficacy and safety information. The Package Leaflet and RMP (v. 25.1) are updated in accordance. Furthermore, the Marketing authorisation holder (MAH) took the opportunity to align the PI with the QRD template version 9.1. C.I.6.a - Change(s) to therapeutic indication(s) -	28/04/2016	26/05/2016	SmPC and PL	Please refer to the Scientific Discussion Victoza-H-C-1026-II-38

	Addition of a new therapeutic indication or modification of an approved one				
WS/0892	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	25/02/2016	n/a		
II/0037	Update of section 5.1 of the SmPC to include data from clinical study LIRA-LIXI (NN2211-3867) which investigated efficacy and safety of liraglutide versus lixisenatide as add-on to metformin in subjects with type 2 diabetes. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 9.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/02/2016	26/05/2016	SmPC, Annex II and Labelling	
PSUSA/1892/ 201506	Periodic Safety Update EU Single assessment - liraglutide	14/01/2016	n/a		PRAC Recommendation - maintenance
WS/0778	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to	24/09/2015	26/05/2016	SmPC	

	new quality, preclinical, clinical or pharmacovigilance data				
WS/0784	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	24/09/2015	n/a		
II/0032	Submission of the final study report from the liraglutide 10-week juvenile toxicity study; consequently the RMP has been revised. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	24/09/2015	n/a		
IA/0033	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)	06/07/2015	n/a		
WS/0746	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	25/06/2015	n/a		

PSUV/0029	Periodic Safety Update	22/01/2015	19/03/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0029.
IB/0030	B.I.a.z - Change in manufacture of the AS - Other variation	17/02/2015	n/a		
II/0028	Update of SmPC sections 4.2, 4.8, 5.1 and 5.2 to reflect data from Study NN2211-3916 (efficacy and safety of liraglutide as add-on to existing diabetes medications in patients with type 2 diabetes and moderate renal impairment). The Package Leaflet has been updated accordingly as well as the RMP (revised edition 20 version 1 provided). In addition, the MAH took the opportunity to update the instructions for use in the Package Leaflet to comply with EN ISO14971:2012 (application of risk management to medical devices) and to reflect residual risk mitigations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/11/2014	19/12/2014	SmPC and PL	In a double-blind trial comparing the efficacy and safety of liraglutide 1.8 mg versus placebo as add-on to insulin and/or OAD in patients with type 2 diabetes and moderate renal impairment, liraglutide was superior to placebo treatment in reducing HbA1c after 26 weeks (–1.05% vs –0.38%). Significantly more patients achieved HbA1c below 7% with liraglutide compared with placebo (52.8% vs 19.5%). In both groups a decrease in body weight was seen: –2.4 kg with liraglutide vs –1.09 with placebo. There was a comparable risk of hypoglycaemic episodes between the two treatment groups. The safety profile of liraglutide was generally similar to that observed in other studies with liraglutide. Patients with type 2 diabetes and moderate renal impairment (CrCL 30-59 ml/min) had 26% lower liraglutide exposure when compared with a separate trial including patients with type 2 diabetes with normal renal function or mild renal impairment. Section 4.2 of the SmPC has been updated to reflect the fact that no dose adjustment is required for patients with mild or moderate renal impairment (creatinine clearance 60–-90 ml/min and 30–59 ml/min, respectively).
II/0027	Update of section 4.4 of the SmPC in order to implement the recommendations of an Art 5(3) procedure on GLP-1-based therapies and pancreatic safety. The Package Leaflet is updated accordingly.	25/09/2014	19/12/2014	SmPC and PL	Use of GLP-1 receptor agonists has been associated with a risk of developing acute pancreatitis. There have been few reported events of acute pancreatitis. Patients should be informed of the characteristic symptoms of acute

	Additionally, the MAH took the opportunity to introduce minor editorial changes to the PI. C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation				pancreatitis. If pancreatitis is suspected, Victoza should be discontinued; if acute pancreatitis is confirmed, Victoza should not be restarted. Caution should be exercised in patients with a history of pancreatitis.
II/0023	Update of sections 4.1, 4.2, 4.4, 4.7, 4.8 and 5.1 of the SmPC in order to include information on the use of liraglutide in combination with basal insulin. The Package Leaflet is updated accordingly. The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet. 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	28/04/2014	SmPC and PL	For further information please refer to the scientific conclusion: Victoza H-1026-II-23-AR.
R/0025	Renewal of the marketing authorisation.	20/02/2014	11/04/2014	SmPC, Annex II, Labelling and PL	Based on the efficacy and safety data retrieved during the 5 year renewal period since launch of Victoza (liraglutide), the knowledge on the efficacy and safety of liraglutide has been extended with information from both clinical trials and post-marketing data. No changes in the efficacy or safety warranting further action have been identified. Therefore, the risk-benefit balance for Victoza is considered positive and the CHMP recommends the renewal of the marketing authorisation with unlimited validity.
II/0024	Update to section 5.1 of the SmPC with results from a meta-analysis of major adverse cardiovascular	20/03/2014	28/04/2014	SmPC	The MACE (Major Adverse Cardiovascular Events) data included in this submission were already submitted and

	events (MACE). The requested variation proposed amendments to the Summary of Product Characteristics. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				reviewed as part of the original Marketing Authorisation Application, with the following conclusion: MACE were not more frequent in liraglutide compared to any of the comparators, however, overall events were low. Therefore, it was not either possible to confirm or dismiss a potential dose-relationship. As the applicant has agreed to conduct a CV outcome trial, the issue is considered resolved. During this procedure the submitted meta-analysis was reviewed in further detail in order to include its results in section 5.1 of the SmPC. The CHMP concluded that the post-hoc analysis showed no increase in cardiovascular risk versus all comparators. The limitations of the study design have been reflected in the SmPC, and the CHMP concludes that the benefit/risk balance for Victoza continues to be positive.
PSUV/0026	Periodic Safety Update	09/01/2014	n/a		PRAC Recommendation - maintenance
IB/0022	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	23/10/2013	n/a		
N/0020	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/09/2013	11/04/2014	PL	
IB/0021	B.I.b.z - Change in control of the AS - Other variation	21/08/2013	n/a		
IG/0280	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/04/2013	n/a		

II/0016	Update of section 4.8 of the SmPC after the assessment of PSURs 3 and 4 to include the adverse drug reactions (ADRs) of anaphylactic reactions, rash and pruritus. Update of section 4.9 of the SmPC to modify the existing information on overdose. The PL has been updated accordingly. The MAH has also modified the text in section 4.8 of the SmPC to reflect a change in the ADR frequency calculations; which has not resulted in a change of ADR frequencies. The MAH has taken the opportunity to make some minor editorial changes to the SmPC, Annex II and PL. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/09/2012	23/10/2012	SmPC, Annex II and PL	Following the assessment of PSUR 3 (covering the period from 1 July 2010 to 30 December 2010) and PSUR 4 (from 31 December 2010 to 30 June 2011), the MAH submitted responses with regards to several safety concerns including pruritus, pruritus generalized, rash pruritic, rash erythematous and drug rash with eosinophilia and systemic symptoms. The provided data by the MAH was suggestive of a causal association due to the positive de-challenges and the positive re-challenges. Consequently, the product information for Victoza has been updated in this variation to include anaphylactic reactions, rash and pruritus. Additionally, reports of overdose with higher doses from both spontaneous and clinical sources have been received. Therefore, the product information has been updated to reflect this information.
IA/0018	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	08/10/2012	n/a		
II/0015	Additional drug product manufacturing site. 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.	20/09/2012	20/09/2012		
IB/0017	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement	11/07/2012	n/a		

	or addition of a site where batch control/testing takes place				
II/0014	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 medicinal product and is not related to a protocol	21/06/2012	21/06/2012		
II/0013	Update of section 4.8 of the SmPC following the assessment of the 4th PSUR, to include the terms "pancreatitis" and "malaise". The Package Leaflet is updated in accordance. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	19/04/2012	25/05/2012	SmPC and PL	The variation concerns changes in the SmPC following the outcome of the CHMP assessment of the 4th PSUR (covering the period 31 December 2010 to 30 June 2011). During this reporting period medically confirmed cases of pancreatitis (82) and pancreatitis acute (41) were identified from spontaneous reports. In the previous PSUR period 83 and 35 cases respectively were identified. Considering the considerably high number of pancreatitis cases reported during post marketing, the CHMP concluded that section 4.8 of the SmPC should include that pancreatitis is also reported during post marketing. In the 4th PSUR reporting period a high number of spontaneous reports for 'malaise' (8 serious events and 71 non-serious events) was identified. De-challenges were reported in 45 of these reports and discontinuation of the treatment was reported in 47 reports. In view of these findings the CHMP concluded that the MAH should add 'malaise' to section 4.8 of the SmPC.
II/0011	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	15/03/2012	20/04/2012	SmPC, Annex II, Labelling and PL	
II/0010	C.I.4 - Variations related to significant modifications	19/01/2012	21/02/2012	SmPC	In support of this application, results from study 1797 were

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				presented. Both liraglutide and exenatide were associated with a decrease in HbA1c, but HbA1c decreased more with liraglutide 1.8 mg once daily (1.12 %) than with exenatide 10 µg twice daily (0.79 %). The estimated treatment difference was -0.33; 95 % CI: -0.47 to -0.18; p<0.0001 (superiority was confirmed). This finding is in line with previous studies. The change in HbA1c from baseline to the end of treatment with liraglutide+OAD(s) and exenatide+OAD(s) was comparable for all subjects regardless of previous OAD therapy. The results from the 14-week extension period demonstrated that further improvements in glycaemic control was obtained by switching from twice-daily exenatide 10 µg to once-daily liraglutide 1.8 mg. During the extension phase, mean HbA1c values decreased from 7.2 % to 6.9 % after the switch from exenatide to liraglutide and remained stable with continued liraglutide (7.0 % to 6.9 %). The group of subjects who switched from exenatide to liraglutide had a significant HbA1c reduction of 0.32 % from Week 26 to Week 40 (95 % CI: -0.408 to -0.239, p<0.0001, paired t-test), while HbA1c remained stable in the liraglutide treatment group during the extension (-0.06 % change; 95 % CI: -0.143 to 0.017, p=0.1222, paired t-test). After 26 weeks of treatment a significantly greater percentage of subjects reached the American Diabetes Association (ADA) target of <7 % for HbA1c with liraglutide 1.8 mg once-daily compared with exenatide 10 mg twice-daily (54.2 % versus 43.4 %, p=0.015). More subjects initially randomised to exenatide achieved ADA targets at Week 40 after switching to liraglutide at Week 26 (61.1 % vs. 57.9 %).

					The differences with respect to HbA1c goals and fasting plasma glucose are in line with the differences in HbA1c. In the main study, both GLP-1 analogues reduced weight to a similar extent. In addition, in the extension study, decreases in body weight were similar in the individuals that were previously treated with exenatide and liraglutide. In general liraglutide and exenatide were well tolerated, and the incidences of adverse events were not importantly different between treatment groups. Liraglutide was associated with an increase in heart rate compared to exenatide. As pulse rate is associated with future risk of cardiovascular disease, this elevation in pulse with liraglutide may influence later cardiovascular risk. The proportion of patients reporting nausea was lower with liraglutide than with exenatide, but it should be stressed that the difference was only small (25.5 vs. 28.0 %). Interestingly, this difference was of similar magnitude compared to the higher incidence of dyspepsia (8.9 vs. 4.7 %) and constipation (5.1 vs. 2.6) with liraglutide. Overall, there were more gastrointestinal side effects with liraglutide than with exenatide (45.5 vs. 42.7 %). The rate of serious adverse events (SAEs) with liraglutide was twice that with exenatide. During the 26 weeks, there were 12 serious events in 235 patients (5•1 %) using liraglutide, whereas there were 6 serious adverse events in 232 patients (2•6 %) using exenatide. This resulted in an odds ratio of 2•03 (95 % CI 0•75–5•51, p=0•16). This difference was not statistically significant, but is important in order to give a balanced overview of the study. Further support for a higher incidence of SAEs with liraglutide comes from the extension study. During the extension phase, all individuals were using liraglutide. During this

					relatively short period, the rate of serious adverse events with liraglutide (during 14 weeks 2.5 % and 2.1 % in patients previously treated with liraglutide and exenatide, respectively) also appeared to be higher than with exenatide treatment (2.6 % during 26 weeks). Minor hypoglycaemia was slightly less frequent with liraglutide than with exenatide. However, it should be pointed out that the study was not blinded. Hypoglycaemia is a subjective endpoint that may be subject to bias in unblinded studies. After review of the submitted data the CHMP agreed that the benefit/risk for treatment remains positive.
IAIN/0012	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	03/02/2012	n/a		
II/0007	Change to the active substance specification. B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP	15/12/2011	15/12/2011		
II/0006/G	This was an application for a group of variations. This was an application for a group of variations: Following the assessment of a PSUR the MAH updated section 4.8 of the SmPC to include injection site reactions as a new ADR and updated sections 4.4 and 4.8 regarding acute renal failure and renal	20/10/2011	22/11/2011	SmPC and PL	In order to be in line with the text in section 4.4 of the SmPC, section 4.8 was updated to include the term "dehydration". The term "renal function abnormal" was also replaced by the term "renal impairment". These terms were placed in the ADR table in section 4.8, both with a frequency of "unknown" and together with a footnote referring back to section 4.4.

	impairment. In addition urticaria was included as a new ADR in section 4.8 of the SmPC. Consequential changes were made in the package leaflet. The MAH also took the opportunity to make editorial changes throughout the PI. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				Section 4.8 of the SmPC was also updated to reflect that events of "injection site reactions" have lead to discontinuation of Victoza. The term was included in the ADR table with the following frequencies: * Liraglutide with metformin: common * Liraglutide with glimepiride: common * Liraglutide with metformin and glimepiride: uncommon * Liraglutide with metformin and rosiglitazone: common The above changes to section 4.8 of the SmPC were requested by the CHMP after the assessment of PSUR 3 (period covered 01.07.10 – 30.12.10). In addition to these changes, section 4.4 of the SmPC was also amended to harmonize the term "altered renal function" with the terms included in section 4.8. The MAH also updated the product information with spontaneous reports of "urticaria". The data to support this change was collected from the moment of marketing authorisation to 15 May 2011. In this period the MAH received 83 cases of urticaria, comprising of 85 events, in connection to treatment with Victoza. Out of these 83 cases, 56 cases were medically confirmed. Analysis of the non-medically confirmed cases did not generate any new information Events of urticaria were also reported in clinical trials with Victoza. The reporting rate (number of events/1,000 PYE) was 6.5 for liraglutide versus 4.1 for placebo as based on all trials with a clinical trial report finalised on or before 30 Dec 2010.

					The CHMP concluded that the data presented in the Clinical Overview support the inclusion of urticaria as an ADR reported from post-marketing experience. Therefore the MAH included "urticaria" in the appropriate SOC in the table that is currently part of section 4.8. The event was assigned a frequency of "unknown". Consequential changes were made to the package leaflet, together with editorial changes made throughout the product information.
II/0005/G	This was an application for a group of variations. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	22/09/2011	10/11/2011	SmPC, Annex II, Labelling and PL	For further information please refer to the scientific conclusion: Victoza H-1026-II-05-G-AR
IB/0008	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	10/11/2011	n/a		
IG/0048/G	This was an application for a group of variations. C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site	11/03/2011	n/a		

	undertaking pharmacovigilance activities C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
II/0004	Update of Summary of Product Characteristics and Package Leaflet regarding "pancreatitis" and "dehydration and renal function related to gastrointestinal reactions", "interaction with other medicinal products" and "thyroid adverse events". C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	18/11/2010	20/12/2010	SmPC and PL	This variation is consequential to the assessment of two PSURs and concerns an update of section 4.4 and 4.8 of the SmPC to update the wording regarding pancreatitis. Section 4.4 was also updated to better characterise the severity of the already listed gastrointestinal reactions by adding information on dehydration associated with vomiting and/or diarrhoea and altered renal function (in some cases associated with adverse reactions that could affect hydration status and in all patients on the background of concomitant medications known to affect renal function). Section 4.5 was amended to improve the readability of the description of the interaction of digoxin and lisinopril together with liraglutide. In the paragraph describing thyroid events (Section 4.8) the update concerns a typographical error and the addition of comparator data. The variation also included editorial changes to sections 4.2, 4.5 and 4.8. The Package Leaflet has been updated accordingly.
IA/0003	A.7 - Administrative change - Deletion of manufacturing sites	12/04/2010	n/a		
N/0002	The MAH took the opportunity to add the following adverse event as a bullet in the adverse event section in the patient leaflet section 4 Possible side	21/01/2010	n/a	PL	

	effect: Uncommon side effect: "thyroid events - like nodules, increased blood calcitonin and goitres". Furthermore, the MAH took the opportunity to replace some pictures in the user instruction of the pen to provide a better graphic design and correct a few spelling errors in the English version of patient leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)				
IB/0001	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	03/12/2009	n/a		