BYETTA

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
IA/0082	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	05/11/2024		SmPC and PL	
IAIN/0080/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name	06/07/2023	27/06/2024	Annex II 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).

	and/or 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) A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release A.7 - Administrative change - Deletion of manufacturing sites				
IB/0079	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	15/05/2023	n/a		
II/0078	Update of section 4.8 of the SmPC in order to add cholelithiasis and cholecystitis to the list of adverse drug reactions (ADRs) with frequency (uncommon) based on the cumulative review of pre-clinical and clinical study data, post-marketing data, medical/scientific literature and signal searches in internal and external databases on 'Gallbladder-related disorders' and exenatide. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/07/2022	17/07/2023	SmPC and PL	n/a

PSUSA/9147/202103	Periodic Safety Update EU Single assessment - exenatide	28/10/2021	n/a		PRAC Recommendation - maintenance
IA/0077/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	03/09/2021	17/07/2023	Annex II and PL	
II/0075	Update of sections 4.2 and 5.1 of the SmPC based on the results of Study H8O-MC-GWBQ (assessed by CHMP as part of PAM P46 048); a 28-week, randomised, double-blind, placebo-controlled study to evaluate the safety and efficacy of exenatide twice daily in 120 patients aged 10 to 17 years, and Study 2993-124; a randomised, single-blind, placebo-controlled, dose-rising study to evaluate the PK, PD and tolerability of exenatide in adolescent patients). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/06/2021	17/07/2023	SmPC	The efficacy and safety of immediate release exenatide was evaluated in a 28-week randomized, double-blind, placebo controlled study conducted in 120 patients aged 10 to 17 years with type 2 diabetes who had HbA1c 6.5% to 10.5% and who were either naive to anti-diabetes agents or were treated with metformin alone, a sulfonylurea alone, or metformin in combination with a sulfonylurea. Patients received twice daily treatment with immediate release exenatide 5 µg, immediate release exenatide 10 µg or equivalent dose of placebo for 28 weeks. The primary efficacy endpoint was the change in HbA1c from baseline to 28 weeks of treatment; the treatment difference (pooled doses) from placebo was not statistically significant [0.28% (95% CI: 1.01, 0.45)]. No new safety findings were identified in this paediatric study.
PSUSA/9147/202003	Periodic Safety Update EU Single assessment - exenatide	12/11/2020	11/01/2021	SmPC and PL	Please refer to exenatide PSUSA-9147-202003 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation

IG/1321	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	08/12/2020	n/a		
IA/0072	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	18/02/2020	n/a		
II/0071	Update of section 4.8 of the SmPC to include information about 'drug-induced thrombocytopenia (DITP)' based on spontaneous reports post-marketing and to include it as a new ADR with unknown frequency. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to implement minor editorial changes in line with the latest QRD template. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	30/01/2020	11/01/2021	SmPC, Labelling and PL	Drug-induced thrombocytopenia (DITP) with exenatide-dependent anti-platelet antibodies has been reported in the post-marketing setting. DITP is an immune-mediated reaction that is caused by drug-dependent platelet-reactive antibodies. These antibodies cause destruction of platelets in the presence of the sensitizing drug.
PSUSA/9147/ 201903	Periodic Safety Update EU Single assessment - exenatide	31/10/2019	n/a		PRAC Recommendation - maintenance
II/0069	Submission of a justification for extrapolating exenatide once weekly clinical data (previously assessed for Bydureon) to exenatide twice daily (Byetta) in order to include the latest agreed RMP versions for Bydureon (v30, v31s2 and v32s2) also in the dossier for Byetta. As a consequence, the removal of the important potential risk 'Cardiac	11/07/2019	n/a		n/a

	Events' is proposed also for Byetta. 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				
IAIN/0067/G	This was an application for a group of variations. 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 B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	12/04/2019	06/06/2019	Annex II and PL	
IAIN/0068	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/04/2019	06/06/2019	SmPC and PL	
IA/0065/G	This was an application for a group of variations. 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) A.7 - Administrative change - Deletion of manufacturing sites	10/12/2018	n/a		

	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
PSUSA/9147/ 201803	Periodic Safety Update EU Single assessment - exenatide	31/10/2018	n/a		PRAC Recommendation - maintenance
IB/0062	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/06/2018	06/06/2019	PL	
II/0061/G	This was an application for a group of variations. B.I.a.1.b - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a manufacturer of the AS supported by an ASMF 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	17/05/2018	n/a		
IAIN/0060	C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	21/12/2017	n/a		
PSUSA/9147/ 201703	Periodic Safety Update EU Single assessment - exenatide	26/10/2017	n/a		PRAC Recommendation - maintenance
IG/0821	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	28/07/2017	11/07/2018	SmPC	

IAIN/0057	C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	09/06/2017	n/a		
IA/0056/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 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) B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	05/04/2017	n/a		
PSUSA/9147/ 201603	Periodic Safety Update EU Single assessment - exenatide	27/10/2016	n/a		PRAC Recommendation - maintenance
R/0053	Renewal of the marketing authorisation.	26/05/2016	22/07/2016	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Byetta in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IA/0055/G	This was an application for a group of variations.	04/07/2016	n/a		

	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) 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) A.7 - Administrative change - Deletion of manufacturing sites 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				
PSUSA/9147/ 201503	Periodic Safety Update EU Single assessment - exenatide	22/10/2015	16/12/2015	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/9147/201503.
IG/0633	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	09/12/2015	n/a		
IG/0522	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	12/03/2015	n/a		
IAIN/0049	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer	17/02/2015	16/12/2015	Annex II and PL	

	responsible for importation and/or batch release - Not including batch control/testing				
PSUV/0045	Periodic Safety Update	20/11/2014	15/01/2015	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0045.
II/0046	This variation concerned the update of sections 4.8 and 5.1 of the SmPC to include new safety and efficacy information from Study H-80-EW-GWDM. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/10/2014	15/01/2015	SmPC	Study H-80-EW-GWDM was a 30-week, open-label, active comparator-controlled, non-inferiority study, which evaluated the safety and efficacy of BYETTA (n=315) versus titrated insulin lispro three times daily (n=312) on a background of optimized basal insulin glargine and metformin in patients with type 2 diabetes. Following a basal insulin optimization (BIO) phase, patients with HbA1c above 7.0% were randomized to add either BYETTA or insulin lispro to their existing regimen of insulin glargine and metformin. In both treatment groups, subjects continued to titrate their insulin glargine doses using an algorithm reflecting current clinical practice. All patients assigned to BYETTA initially received 5 mcg BID for four weeks. After four weeks, their dose was increased to 10 mcg BID. Patients in the BYETTA-treated group with an HbA1c of less than or equal to 8.0% at the end of the BIO phase decreased their insulin glargine dose by at least 10%. BYETTA lowered HbA1c by 1.1% from a baseline of 8.3% and insulin lispro lowered HbA1c by 1.1% from a baseline of 8.2% and non-inferiority of BYETTA to titrated lispro was demonstrated. The proportion of patients achieving HbA1c < 7% was 47.9% with BYETTA and 42.8% with insulin lispro. Weight loss of 2.6 kg from a baseline of 89.9 kg was observed with BYETTA whereas a weight gain of 1.9 kg

					from a baseline of 89.3 kg was observed with insulin lispro. The safety data from the study are in line with the known safety profile of exenatide and has not given rise to any new safety concerns. Only minor changes to section 4.8 of the SmPC were considered necessary. No changes to the identified or potential safety concerns in the RMP or the activities related to these issues are warranted. The variation application does not have any impact on the overall benefit / risk balance for BYETTA which remains unchanged for the authorised indication(s).
IAIN/0048	C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	14/10/2014	n/a		
IA/0047/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.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	17/09/2014	n/a		

T/0044	Transfer of the Marketing Authorisation EMEA/H/C/000698/T/0044 - BYETTA from Bristol-Myers Squibb/AstraZeneca EEIG to AstraZeneca EEIG. Transfer of Marketing Authorisation	04/07/2014	28/07/2014	SmPC, Labelling and PL	
PSUV/0042	Periodic Safety Update	08/05/2014	n/a		PRAC Recommendation - maintenance
II/0043	Update of section 4.4 of the SmPC in order to update the safety information on acute pancreatitis. The Package Leaflet is updated accordingly. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/04/2014	28/07/2014	SmPC and PL	The scope of this variation was to update section 4.4 of the SmPC to update the safety information on acute pancreatitis following recommendations of an Art 5(3) procedure on GLP-1-based therapies and pancreatic safety. The Package Leaflet is updated accordingly. The benefit/risk balance of Byetta remains unchanged.
II/0039	Update of section 4.8 of the SmPC to include 'intestinal obstruction' and its frequency in the list of adverse reactions. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 9.0 and minor editorial corrections are implemented. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/12/2013	28/07/2014	SmPC, Annex II, Labelling and PL	The scope of this variation was to update section 4.8 of the SmPC to include 'intestinal obstruction' and its frequency in the list of adverse reactions and to update the Package Leaflet accordingly. This variation was subsequent to the assessment of a signal for intestinal stenosis and a cumulative review of gastrointestinal stenosis and obstruction with the use of exenatide. The benefit/risk balance of Byetta remains unchanged.
IA/0041	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	06/12/2013	n/a		

PSUV/0040	Periodic Safety Update	10/10/2013	n/a		PRAC Recommendation - maintenance
IAIN/0038/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.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 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 B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	26/09/2013	28/07/2014	Annex II and PL	
IA/0037/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	03/09/2013	n/a		

	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				
IA/0036/G	This was an application for a group of variations. 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) 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)	03/09/2013	n/a		
IA/0034/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 supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS	23/07/2013	n/a		
IG/0301	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	01/07/2013	n/a		
T/0032	Transfer of Market Authorisation from Eli Lilly Nederland B.V. to Bristol-Myers Squibb/AstraZeneca	18/02/2013	06/03/2013	SmPC, Labelling and	Transfer of the Marketing Authorisation to Bristol-Myers

	EEIG. Transfer of Marketing Authorisation			PL	Squibb/AstraZeneca EEIG.
IG/0189	A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS	22/06/2012	n/a		
IB/0030	B.IV.z - Quality change - Change in Medical Devices - Other variation	22/06/2012	29/10/2012	SmPC and PL	
II/0029	Extension of indication to include Byetta as adjunctive therapy to basal insulin with or without metformin and/or pioglitazone in adults who have not achieved adequate glycaemic control with these agents.. As a consequence, update of sections 4.1, 4.2, 4.4., 4.6, 4.7, 4.8 and 5.1 of the SmPC. The Package Leaflet is updated in accordance. Furthermore, the MAH took this opportunity to introduce minor editorial updates throughout the PI. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	16/02/2012	19/03/2012	SmPC and PL	For further information please refer to the scientific conclusion: Byetta H-698-II-29-AR.
R/0028	Renewal of the marketing authorisation.	21/07/2011	19/09/2011	SmPC, Annex II, Labelling and PL	Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Byetta (exenatide) remains positive, but considers that its safety profile is to be closely monitored for the following reasons:

					A number of safety issues have been identified for Byetta, in particular the potential association between exenatide and pancreatic cancer and thyroid neoplasms. The latter will be further investigated in a new epidemiological study. Also the possible drug interaction between exenatide and tacrolimus and exenatide and lamotrigine needs further evaluation. In addition, the CHMP agreed on a common PSUR for Byetta and Bydureon (exenatide prolonged release formulation) following the timelines for PSUR frequency of Bydureon as required per Regulation 726/2004. Therefore, based upon the safety profile of Byetta, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.
IA/0027/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD 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	04/03/2011	n/a	Annex II	
IA/0026/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name	30/11/2010	n/a		

	and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier				
II/0025/G	This was an application for a group of variations. Addition of two new alternate primary container/closure components for BYETTA (exenatide solution for injection). A new bilayer combi-seal for both the 1.5 mL and 2.7 mL cartridge sizes and a slightly smaller (10.0 mm) diameter plunger for the 2.7 mL cartridge have been qualified. The product contact materials are identical to those currently approved. B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products	23/09/2010	01/10/2010		

II/0021	Extension of indication for the treatment of exenatide as add-on to thiazolidinediones (TZDs) (with or without metformin). Also Annex II has been updated to reflect the new version number of the Risk Management Plan (RMP). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	24/06/2010	06/08/2010	SmPC, Annex II and PL	Refer to the Scientific Discussion: Byetta-H-698-II-21-AR.
IB/0024	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	29/04/2010	n/a		
IB/0023	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	26/03/2010	n/a		
II/0018	Update of section 5.2 of the Summary of Product Characteristics to incorporate the PK data from study H80-EW-GWCC as requested by the CHMP on 29 May 2009 following the review of FUM 009. Update of Summary of Product Characteristics	21/01/2010	15/03/2010	SmPC	Long-term controlled data from in very elderly subjects are limited. In pharmacokinetic study H80-EW-GWCC in patients with type 2 diabetes, administration of exenatide (10µg) resulted in a mean increase of exenatide AUC by 36% in 15 elderly subjects aged 75 to 85 years compared to 15 subjects aged 45 to 65 years likely related to reduced renal function in the older age group. There was also a slight difference in weight between groups. Hence, the difference in renal function and weight might explain the difference in exposure between the groups. A combined analysis of PK data from 7 studies suggested that the relationship between exenatide clearance and creatinine clearance is similar for elderly and non-elderly subjects,

					indicating that there is no additional age-related decreased in clearance apart from that caused by reduced renal function in the elderly. Following assessment of these results the MAH submitted a type II variation to update the SPC. Subsequently section 5.2 was updated with pharmacokinetic data in patients >75 years.
II/0011	To include information on weight loss, alopecia and anti-exenatide antibodies as a result of a Company Core Data Sheet update (sections 4.4 and 4.8 of the SPC). The PL has been amended accordingly. In addition, the term 'incretin mimetic' in section 5.1 of the SPC is changed to 'glucagon-like peptide-1 (GLP-1) receptor antagonist'. Update of Summary of Product Characteristics and Package Leaflet	21/01/2010	15/03/2010	SmPC and PL	Company Core Data Sheet has been revised as new information became available from clinical trials and post marketing experience. New data is related to safety information, particularly weight loss, alopecia and anti-exenatide antibodies. Weight loss is well known effect associated with exenatide treatment. However, new data support that rapid weight loss may be harmful for some patients. MAH proposed to include relevant information in sections 4.4 and 4.8 of the SPC. Further revision of CCDS suggested association between exenatide treatment and alopecia as well as development of anti-exenatide antibodies. As a result of these findings appropriate changes in section 4.8 of the SPC were proposed by MAH and accepted by CHMP. PL was also updates accordingly to reflect changes in SPC. In addition, the MAH took the opportunity of this variation to make an administrative change, amending the term 'incretin mimetic' to 'glucagon-like peptide-1 (GLP-1) receptor agonist for consistency purpose. MAH also discussed CHMP's request to include text around the increase of heart rate in the SPC. It was agreed by CHMP that observed increase in heart rate most likely is not of clinical relevance and therefore this information does not need to be added to SPC.

IB/0022	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	05/03/2010	n/a	SmPC	
IB/0020	IB_37_a_Change in the specification of the finished product - tightening of specification limits	20/01/2010	n/a		
IA/0017	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	17/11/2009	n/a		
IA/0016	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	17/11/2009	n/a		
IA/0015	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	17/11/2009	n/a		
IA/0014	IA_05_Change in the name and/or address of a manufacturer of the finished product	17/11/2009	n/a		
IA/0013	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	17/11/2009	n/a		
IA/0012	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	17/11/2009	n/a		
II/0007	Update of sections 4.4 and 4.8 of the Summary of Product Characteristics (SPC) and section 4 of the Package Leaflet (PL) with information regarding pancreatitis in patients taking exenatide, following the submission of a cumulative report on cases of pancreatitis requested by the CHMP.	22/01/2009	06/03/2009	SmPC and PL	Following a cumulative analysis of pancreatitis cases performed by the MAH at request of the CHMP after assessment of PSUR 03, the MAH submitted a type II variation to update the SPC and the Package Leaflet. Section 4.4 was updated to emphasise the fact that serious, including fatal, cases of pancreatitis have been

	Update of Summary of Product Characteristics and Package Leaflet				reported, as well as to clearly advise against resuming treatment in patients after pancreatitis has been diagnosed. Section 4.8 has also been updated to include pancreatitis in the table of adverse reactions reported in long term phase III controlled studies with the appropriate frequency. The Package Leaflet has been updated accordingly.
IB/0008	IB_33_Minor change in the manufacture of the finished product	14/01/2009	n/a		
II/0006	Update of sections 4.2 and 5.2 of the SPC with information regarding pharmacokinetic data in adolescents, in line with the CHMP conclusions of FUM 008, where the results from study 2993-124 (PK/PD in adolescents) were presented. Also two minor errors are corrected in sections 4.4 and 5.1 of the SPC. Update of Summary of Product Characteristics	20/11/2008	07/01/2009	SmPC	The Product information was updated following the assessment of study 2993-124 ('A randomized, single-blind, dose-rising, placebo-controlled, crossover study to evaluate the pharmacokinetics, pharmacodynamics, and tolerability of exenatide in adolescent subjects with type 2 diabetes mellitus'). In 13 patients with type 2 diabetes and between the ages of 12 and 16 years, administration of exenatide (5 g) resulted in slightly lower mean AUC (16% lower) and Cmax (25% lower) compared to those observed in adults. The PK, PD and tolerability parameters determined in Study 2993-124 were comparable to those previously observed in adults and likely attributable to similar body size of adolescents and adults with type 2 diabetes. From this study, it was concluded that no further PK and/or PD-based adjustments for age, weight, or other demographic factors are necessary.

N/0005	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	11/09/2008	n/a	PL	
II/0003	Update of sections 4.4 and 4.8 of the SPC to include altered renal function and acute pancreatitis following the review of 1st PSUR. The Package Leaflet has been updated accordingly. In addition, the contact details of the Icelandic local representative in the Package Leaflet have been updated. Update of Summary of Product Characteristics and Package Leaflet	13/12/2007	28/01/2008	SmPC and PL	Following the review of the 1st PSUR the MAH was requested to submit a type II variation regarding the renal safety of BYETTA. Sections 4.4 of the SPC have been updated to reflect that there have been rare, spontaneously reported events of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure and acute renal failure, sometimes requiring hemodialysis. Section 4.8 of the SPC has also been updated to reflect this undesirable effect. The SPC, sections 4.4 and 4.8 have also been updated to reflect acute pancreatitis. Section 4.4 of the SPC have been updated to include that there have been rare, spontaneously reported events of acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed with supportive treatment. If pancreatitis is suspected, BYETTA and other potentially suspect medicinal products should be discontinued. Section 4.8 have been updated to include acute pancreatitis. The Package Leaflet has been updated accordingly.
II/0002	Update of section 4.5 of the SPC to delete the restriction of intake of BYETTA when taking oral contraceptives and to reflect the results of an interaction study between exenatide and oral contraceptives (follow-up measure). The Package	20/09/2007	31/10/2007	SmPC and PL	The MAH performed an interaction study between BYETTA and a combined oral contraceptive. This was an open label, three-period, three-sequence, randomised crossover study. The administration of a combination oral contraceptive (30 µg ethinyl estradiol plus 150 µg levonorgestrel) one hour

	Leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet				before BYETTA (10 µg BID) did not alter the AUC, Cmax or Cmin of either ethinyl estradiol or levonorgestrel. Administration of the oral contraceptive 30 minutes after BYETTA did not affect AUC but resulted in a reduction of the Cmax of ethinyl estradiol by 45%, and Cmax of levonorgestrel by 27-41%, and a delay in tmax by 2-4 h due to delayed gastric emptying. The reduction in Cmax is of limited clinical relevance and no adjustment of dosing of oral contraceptives is required. Based on these data the CHMP was also of the opinion that no specific recommendations with regards to the dose-timing of oral contraceptives are required when taking BYETTA.
II/0001	Quality changes	19/07/2007	30/08/2007	SmPC, Labelling and PL	