Bydureon

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
IB/0081	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/11/2024		SmPC and PL	
IB/0079	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/04/2024	24/07/2024	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).

IAIN/0078/G	This was an application for a group of variations. 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 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)	31/07/2023	24/07/2024	Annex II and PL	
IB/0077	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	03/05/2023	n/a		
IB/0076	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	31/10/2022	n/a		
II/0074	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 implement editorial changes in the SmPC.	14/07/2022	29/06/2023	SmPC and PL	n/a

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0073	Extension of indication to include the treatment of adolescents and children aged 10 years and above based on the results from Study BCB114 (D5551C00002); a phase 3, double-blind, placebo-controlled, randomized, multi-center study to assess the safety and efficacy of exenatide once weekly in adolescents with type 2 diabetes, which was initially submitted and assessed by the CHMP as part of the post-authorisation measure (PAM) P46 028. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated and the Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to update the contact details of the local representatives in the Package Leaflet. Version 35.1 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	22/04/2022	30/05/2022	SmPC and PL	Please refer to Scientific Discussion 'Bydureon-H-C-2020-II-73'
IA/0075/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.a - Change to importer, batch release arrangements and quality control testing of the FP -	03/05/2022	n/a		

	Replacement/addition of a site where batch control/testing takes place				
PSUSA/9147/ 202103	Periodic Safety Update EU Single assessment - exenatide	28/10/2021	n/a		PRAC Recommendation - maintenance
IA/0071/G	This was an application for a group of variations. 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 B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	22/04/2021	n/a		
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/0068	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	31/01/2020	n/a		
II/0067	B.II.d.z - Change in control of the Finished Product - Other variation	30/01/2020	n/a		
II/0066	Update of section 4.8 of the SmPC to include	30/01/2020	11/01/2021	SmPC,	Drug-induced thrombocytopenia (DITP) with exenatide-

	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			Labelling and PL	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.
II/0064	Update of sections 4.2 and 4.4 of the SmPC in order to remove the limitation of use in patients with moderate renal impairment (creatinine clearance [CrCl] 30 to 50 mL/min) based on pooled data from 8 EQW/EQWS studies undertaken in patients with mild renal impairment/chronic kidney disease stage 2 or moderate renal impairment/chronic kidney disease stage 3, and update of section 5.1 of the SmPC to include the results of a subgroup analysis from EXSCEL (Study D5551C00003/BCB109) in a subset of patients with moderate renal impairment. In addition, the MAH took the opportunity to introduce GFR as the main indicator of renal function rather than CrCl. The Package Leaflet has been updated accordingly and the MAH has taken the opportunity to implement some minor changes in the labelling. An updated RMP version 34 was provided with the application, which includes consequential changes as well as a proposal for the removal of Acute Renal Failure (ARF) as an Important Identified Risk based	12/12/2019	23/01/2020	SmPC, Labelling and PL	The SmPC has been updated to reflect that no dose adjustment is necessary for patients with mild or moderate renal impairment and that prolonged release exenatide is not recommended for use in patients with end stage renal disease or severe renal impairment (glomerular filtration rate [GFR] < 30 mL/min). In a pre-specified subgroup analysis in EXSCEL, the HR for MACE was 0.86 (95% CI: 0.77–0.97) in patients with baseline eGFR ≥ 60 mL/min/1.73 m2 and 1.01 (95% CI: 0.86–1.19) in patients with baseline eGFR < 60 mL/min/1.73 m2.

	on the GVP V Rev2 guidance. In addition, upon request following the assessment of II/54, a Pan EU epidemiological study to monitor events of pancreatic cancer has been included as an additional planned pharmacovigilance activity. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/9147/ 201903	Periodic Safety Update EU Single assessment - exenatide	31/10/2019	n/a		PRAC Recommendation - maintenance
IB/0065/G	This was an application for a group of variations. B.II.g.5.b - Implementation of changes foreseen in an approved change management protocol - Requires further supporting data B.II.g.5.b - Implementation of changes foreseen in an approved change management protocol - Requires further supporting data	19/09/2019	n/a		
II/0059	Submission of the final CSR for Study H80-MC-B016; a modified Prescription-Event Monitoring Program (Modified PEM) to be conducted in the UK, enrolling patients with Type 2 diabetes mellitus, to quantify the incidence of acute pancreatitis in the first 12 months after initiating treatment with prescription exenatide once weekly. An updated RMP version 33 was provided as part of the application. The provision of the final CSR addresses Post-authorisation Measure MEA 010.5.	11/07/2019	n/a		n/a

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IB/0062	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	02/07/2019	23/09/2019	SmPC, Labelling and PL	
II/0054	Submission of the final study report, upon request by PRAC following the assessment of MEA 11.5, from study H8O-MC-B015 extension/ D5550R00003; 'Incidence of Pancreatic Malignancy and Thyroid Neoplasm in Type 2 Diabetes Mellitus Patients who Initiate Exenatide Compared to Other Antihyperglycemic Drugs', as well as the feasibility study 'Incidence of pancreatic cancer and thyroid neoplasm among type 2 diabetes patients who initiated Bydureon (exenatide) as compared with those who initiated other glucose lowering drugs'. An updated RMP (version 32) 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	11/04/2019	n/a		n/a
IAIN/0061	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 -	08/04/2019	23/09/2019	Annex II and PL	

	Not including batch control/testing				
IAIN/0060	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	05/04/2019	23/09/2019	SmPC and PL	
II/0057	Update of sections 4.8 and 5.1 of the SmPC in order to implement minor changes in line with the revised study report for the DURATION 7 study (previously assessed as part of variation II/45). In addition, the MAH took the opportunity to implement editorial changes for increased clarity in the SmPC section 6.6 and the Package Leaflet of the pre-filled pen. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/02/2019	23/09/2019	SmPC and PL	The revision did not affect the results or conclusions of the study.
IA/0056/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.8 - Administrative change - Changes to date of the audit to verify GMP compliance of the manufacturer of AS B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	10/12/2018	n/a		
IAIN/0055	C.I.1.a - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a Union	27/11/2018	23/09/2019	PL	

	referral procedure - The product is not covered by the defined scope of the procedure				
PSUSA/9147/ 201803	Periodic Safety Update EU Single assessment - exenatide	31/10/2018	n/a		PRAC Recommendation - maintenance
II/0050	Update of sections 4.1, 4.2, 4.4 and 5.1 of the SmPC based on the final CSR of study EXSCEL (EXenatide Study of Cardiovascular Event Lowering; 'A randomized, placebo controlled clinical trial to evaluate cardiovascular outcomes after treatment with exenatide once weekly in patients with type 2 diabetes mellitus ') in fulfilment of LEG 009. In addition, RMP version 31 has been submitted as part of this application. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/09/2018	23/09/2019	SmPC	The SmPC section 5.1 has been updated as follows: EXSCEL was a pragmatic cardiovascular (CV) outcome study in patients with type 2 diabetes and any level of CV risk. A total of 14,752 patients were randomised 1:1 to either prolonged release exenatide 2 mg once weekly or placebo, added to the current usual care which could include SGLT2 inhibitors. Patients were followed as in routine clinical practice for a median of 38.7 months with a median treatment duration of 27.8 months. The primary safety (noninferiority) and efficacy (superiority) endpoint in EXSCEL was the time to first confirmed Major Adverse Cardiac Event (MACE): cardiovascular (CV) related death, nonfatal myocardial infarction (MI) or nonfatal stroke. All-cause mortality was the initial secondary endpoint assessed. Prolonged release exenatide did not increase the cardiovascular risk in patients with type 2 diabetes mellitus compared to placebo when added to current usual care (HR:0.91; 95% CI: 0.832, 1.004; P<0.001 for non-inferiority). The study, however, failed to show a statistically significant benefit with exenatide treatment with regards to CV events or CV-related death. The need for additional antihyperglycaemic medication was reduced by 33% with the prolonged-release exenatide group (exposure-adjusted incidence of 10.5 per 100 pt-year) compared to the placebo group (exposure-adjusted

					incidence of 15.7 per 100 pt-year). A reduction in HbA1c was observed over the course of the trial with an overall treatment difference of 0.53% (prolonged release exenatide vs. placebo). For more information, please refer to the Summary of Product Characteristics
IB/0053	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	30/08/2018	n/a		
X/0048/G	This was an application for a group of variations. Annex I_2.(d) Change or addition of a new pharmaceutical form C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/06/2018	27/08/2018	SmPC, Labelling and PL	
IB/0051	B.II.g.5.b - Implementation of changes foreseen in an approved change management protocol - Requires further supporting data	23/05/2018	n/a		
IB/0049	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	15/03/2018	n/a		
II/0045	Extension of Indication to include treatment in combination with basal insulin for Bydureon; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated based on the study D5553C00002 (Duration 7 study) which evaluated safety and efficacy of exenatide once weekly therapy	12/10/2017	10/11/2017	SmPC and PL	Please refer to Scientific Discussion Bydureon-H-C-2020-II-45

	added to titrated basal insulin in patients with type 2 diabetes who have inadequate glycemic control on basal insulin with or without metformin. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor corrections in sections 4.8 and 5.1 of the SmPC. Furthermore, the consolidated RMP version 29 has been agreed. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
PSUSA/9147/ 201703	Periodic Safety Update EU Single assessment - exenatide	26/10/2017	n/a		PRAC Recommendation - maintenance
II/0041	Extension of indication for Bydureon to include the add-on use of exenatide in combination with dapagliflozin to patients whose diabetes is not adequately controlled with metformin based on the study D5553C00003 (Duration 8 study); section 4.1 of the SmPC is updated in order to align the indication wording with more recently approved glucose-lowering agents. Section 5.1 of the SmPC is also updated with the results of study D5553C00003 (Duration 8 study). The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial changes in the SmPC and Package Leaflet and to update the Irish local representative information in the Package Leaflet. Furthermore, the consolidated RMP version 27 has been agreed.	20/07/2017	24/08/2017	SmPC and PL	Please refer to the scientific discussion Bydureon EMEA/H/C/002020/II/41

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IG/0821	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	28/07/2017	10/11/2017	SmPC	
IA/0044/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.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	05/05/2017	n/a		
II/0042	Submission of the updated RMP version 25 following closure and final summary of Exenatide Pregnancy Registry (a prospective, observational study conducted in the United States that actively collected information on exposure to antidiabetic medication during pregnancy and the associated pregnancy outcomes in patients with Type 2 diabetes mellitus). Moreover, the MAH included additional minor updates to the RMP. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	21/04/2017	n/a		

IA/0043/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) B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	03/03/2017	n/a		
IB/0040/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 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	16/12/2016	n/a		
II/0038	Update of section 5.1 of the SmPC in order to include data from study 2993LAR-105: a randomized open-label, multicenter, comparator-controlled study to examine the effects of exenatide long-acting release on glucose control (HbA1c) and safety in subjects with type 2 diabetes mellitus managed with diet modification and exercise and/or oral anti-diabetic	10/11/2016	24/08/2017	SmPC and Labelling	In the uncontrolled study extension of a clinical study in which prolonged-release exenatide 2 mg once weekly has been compared to immediate release exenatide 5 mcg given twice daily for 4 weeks followed by immediate release exenatide 10 mcg given twice daily, evaluable patients who switched from immediate release to prolonged-release exenatide at week 30 (n=121), achieved the same

	medications (long-term extension). In addition, the MAH took the opportunity to bring the Labelling in line with the latest QRD template version 10. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				improvement in HbA1c of 2.0% at week 52 compared to baseline as patients treated with prolonged-release exenatide. For all patients completing the uncontrolled study extension of 7 years (n=122 of 243 patients included in the extension phase), HbA1c gradually increased over time from week 52 onwards, but was still reduced compared to baseline after 7 years (-1.1%). Weight loss was sustained over 7 years in these patients.
PSUSA/9147/ 201603	Periodic Safety Update EU Single assessment - exenatide	27/10/2016	n/a		PRAC Recommendation - maintenance
IA/0039/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 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	03/08/2016	n/a		
II/0035	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	03/03/2016	n/a		
IB/0036	B.II.z - Quality change - Finished product - Other variation	23/02/2016	n/a		
R/0031	Renewal of the marketing authorisation.	17/12/2015	18/02/2016	SmPC, Annex II, Labelling	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of

				and PL	Bydureon in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IB/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 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.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 B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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 B.I.c.1.z - Change in immediate packaging of the AS - Other variation 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	18/12/2015	n/a		
PSUSA/9147/	Periodic Safety Update EU Single assessment -	22/10/2015	16/12/2015	SmPC	Refer to Scientific conclusions and grounds recommending

201503	exenatide				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		
IB/0032	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	04/12/2015	n/a		
IB/0030	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	22/06/2015	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		
PSUV/0024	Periodic Safety Update	20/11/2014	19/01/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0024.
IAIN/0027/G	This was an application for a group of variations. 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 B.II.b.2.c.1 - Change to importer, batch release	19/12/2014	16/12/2015	Annex II and PL	

	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				
T/0026	Transfer of Marketing Authorisation from Bristol-Myers Squibb/AstraZeneca EEIG to AstraZeneca AB Transfer of Marketing Authorisation	12/09/2014	01/10/2014	SmPC, Labelling and PL	
PSUV/0018	Periodic Safety Update	22/05/2014	31/07/2014	SmPC and PL	Please refer to Bydureon PSUV-18 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
IA/0025/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.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.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 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	30/07/2014	n/a		

	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				
II/0017/G	This was an application for a group of variations. Addition of a new excipient to the new presentation: sodium hydroxide. Addition of a new site responsible for the packaging of the drug product and new single container closure system (pre-filled pen presentation). Addition of an alternative manufacturing processspecific for the diluent in the new presentation in dual-chamber cartridge. Addition of an alternative pen injector device that contains the exenatide powder for injection and solvent for injection in a dual chamber cartridge, exclusive to the pre-filled pen presentation. To introduce an additional test for the excipient – carboxymethylcellulose sodium. Addition of an alternative specification on the finished cartridge of the pre-filled pen. Addition of a new immediate packaging of the finished product: single container closure system	24/07/2014	01/10/2014	SmPC, Labelling and PL	

	(pre-filled pen presentation). Amendment to the current Risk Management Plan (version 20) to include details of the new Bydureon prefilled pen presentation (version 21). B.II.a.3.b.2 - Changes in the composition (excipients) of the finished product - Other excipients - Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the product B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products B.II.b.3.b - Change in the manufacturing process of the finished or intermediate product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product B.IV.1.c - Change of a measuring or administration device - Addition or replacement of a device which is an integrated part of the primary packaging B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a				

	new specification parameter to the specification with its corresponding test method B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products 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				
IB/0023	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	08/07/2014	n/a		
IB/0022/G	This was an application for a group of variations. B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation 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	04/06/2014	n/a		

	material/intermediate 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				
II/0019	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/04/2014	31/07/2014	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 Bydureon remains unchanged.
IB/0020	B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF	27/02/2014	n/a		
PSUV/0014	Periodic Safety Update	24/10/2013	08/01/2014	SmPC and PL	For further information please refer to: Bydureon-H-2020-Grounds-PSU-14-en.
II/0013	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 Bydureon remains unchanged. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/12/2013	31/07/2014	SmPC, Annex II 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 Bydureon remains unchanged.

IA/0016/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.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	13/12/2013	n/a		
IAIN/0015/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.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 B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	08/11/2013	31/07/2014	Annex II and PL	
IA/0012	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	06/09/2013	n/a		

IG/0301	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	01/07/2013	n/a		
IB/0009/G	This was an application for a group of variations. B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF 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 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	28/06/2013	n/a		
II/0008/G	This was an application for a group of variations. 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 C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	30/05/2013	08/01/2014	SmPC, Labelling and PL	

II/0004/G	This was an application for a group of variations. Update of sections 4.8 and 5.1 in order to include post-marketing experience of 'anaphylactic reactions, rash, pruritus, urticaria and angioedema', as a result of the assessment of PSUR 13, to update the SmPC with regard to pancreatitis reporting and to address a number of other minor editorial changes in these sections. In addition, the MAH took the opportunity to update annex II in line with the latest QRD template version 8.3. The Package Leaflet is updated accordingly. 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 C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/03/2013	26/07/2013	SmPC, Annex II and PL	The scope of these type II variations was to update section 4.8 of the SmPC regarding Bydureon post-marketing experience of 'anaphylactic reactions, rash, pruritus, urticaria and angioedema', which was requested as a result of the assessment of PSUR 13. Furthermore, the scope was to make the Bydureon SmPC consistent with the Byetta SmPC with respect to pancreatitis reporting and consequent revision of the frequency category in section 4.8 (table 2) of the SmPC for Bydureon. Additionally, a number of other minor editorial changes were proposed in section 4.8 (table 1) and 5.1 (table 4 and table 5). The MAH implemented frequency categories or the additional category 'not known' for 'anaphylactic reactions' , 'rash', 'pruritus', 'urticaria' and 'angioedema' and moved the information from table 2 (reflecting experience from Byetta) to table 1 (reflecting experience from Bydureon) in section 4.8 of the SmPC and changed the lay-out of table 1 and table 2 according to the lay-out of table 1 of Byetta. In order to assign consistency between Byetta and Bydureon, the MAH proposed to change the frequency category for 'acute pancreatitis' in table 2 for Bydureon (reflecting experience from Byetta) in section 4.8 from 'uncommon' to 'rare' to be consistent with Byetta, on which the experience with acute pancreatitis with exenatide is based on, which was accepted by the CHMP. Further minor editorial changes proposed by the MAH in section 4.8 and 5.1 of the SmPC were endorsed by the CHMP. The benefit-risk for Bydureon remains favourable.
T/0007	Transfer of Market Authorisation from Eli Lilly	18/02/2013	13/03/2013	SmPC,	Transfer of the Marketing Authorisation to Bristol-Myers

	Nederland B.V. to Bristol-Myers Squibb/AstraZeneca EEIG. Transfer of Marketing Authorisation			Labelling and PL	Squibb/AstraZeneca EEIG.
IB/0006	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)	12/12/2012	13/03/2013	SmPC	
IB/0005	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	14/11/2012	n/a		
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/0001	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)	24/08/2011	n/a		
IA/0002/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	11/08/2011	n/a		

	the pharmacovigilance system				