Yervoy

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/0102/G	This was an application for a group of variations. B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process	23/11/2022	n/a		

[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).

	of the AS B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material				
WS/2187	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.8 of the SmPC in alignment with the recommendations made by the CHMP to revise the pooling approach used to describe irARs and tabulated summaries of ADRs following II/0096. Individual study data included within this application has been previously reviewed by the CHMP. The updated Opdivo RMP version 29.0 and Yervoy RMP version 37.0 have also been submitted. The MAH took the opportunity to introduce editorial changes. The Package Leaflet was updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	27/10/2022		SmPC and PL	Not applicable Please refer to the Summary of Product Characteristics.
WS/2289	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To update sections 4.8 and 5.1 of the SmPC to	01/09/2022		SmPC	A statistically significant improvement in OS was observed with nivolumab monotherapy (HR 0.63 [95% CI: 0.52, 0.77]) and the combination of nivolumab + ipilimumab (HR 0.53 [95% CI: 0.44, 0.65]) over ipilimumab. Median OS for all randomized subjects was 72.08 months (95% CI: 38.18,

	include 7.5 years of minimum follow-up for all subjects based on addendum 04 Clinical Study Report for Study CA209067; this is a phase 3 randomized, double-blind study of nivolumab monotherapy or nivolumab in combination with ipilimumab versus ipilimumab monotherapy in subjects with previously untreated, unresectable melanoma. MAH has taken the opportunity to introduce minor editorial revisions in the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				N.A.) in the nivolumab + ipilimumab group whereas it was 36.93 months (95% CI: 28.25, 58.71) for nivolumab monotherapy group as compared to 19.94 months (95%CI: 16.85, 24.61) in the ipilimumab group. OS rates (95% CI) at 90 months were 42% (36%, 47%), 48% (42%, 53%), and 22% (18%, 27%) in the nivolumab, nivolumab + ipilimumab, and ipilimumab groups, respectively. For the exploratory analysis of OS for nivolumab + ipilimumab in comparison with nivolumab, HR was 0.84 (95% CI: 0.68, 1.04). For the other dual primary endpoint, PFS, an HR of 0.42 (95% CI: 0.35, 0.51) was estimated for the comparison between nivolumab + ipilimumab and ipilimumab, with a median PFS of 11.50 (95% CI: 8.90, 20.04) months for the nivolumab + ipilimumab arm and 2.86 (95% CI: 2.79, 3.09) for the ipilimumab arm. For more information, please refer to the Summary of Product Characteristics.
IA/0101/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.7 - Administrative change - Deletion of manufacturing sites 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	30/08/2022	n/a		

IB/0097	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	22/04/2022		Annex II	Update Annex II of the PI with revised due date related to a PAES study.
WS/2153	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2 and 6.6 of the SmPC to change the infusion time for ipilimumab at a dose of 3 mg/kg from 90 minutes to 30 minutes when used as monotherapy or in combination with nivolumab in the melanoma indications. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/02/2022	01/04/2022	SmPC, Annex II and PL	Change the infusion time for ipilimumab at a dose of 3 mg/kg from 90 minutes to 30 minutes when used as monotherapy or in combination with nivolumab in the melanoma indications. For more information, please refer to the Summary of Product Characteristics.
WS/2113	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Extension of indication to include treatment of first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) with tumour cell PD-L1 expression ≥ 1% for Opdivo in combination with Yervoy; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version	24/02/2022	01/04/2022	SmPC and PL	OPDIVO/Yervoy-H-C-3985/2213/WS/2113’

	26.2 of the Opdivo RMP and version 35.0 of the Yervoy RMP have also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IAIN/0096/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.6 - Administrative change - Change in ATC Code/ATC Vet Code	17/02/2022	01/04/2022	SmPC, Annex II and PL	
WS/2170	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.8 and 5.1 of the SmPC in order to update efficacy information based on 5 years follow-up OS data from study CA209214; this is a phase 3, randomised, open-label study in previously untreated, intermediate/poor risk advanced RCC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/01/2022	01/04/2022	SmPC	SmPC new text: With a minimum of 60 months follow-up from study CA209214 in RCC, no new safety signals were identified. OS results at an additional descriptive analysis undertaken at a minimum follow up of 60 months show outcomes consistent with the original primary analysis. For more information, please refer to the Summary of Product Characteristics.
PSUSA/9200/ 202103	Periodic Safety Update EU Single assessment - ipilimumab	11/11/2021	07/01/2022	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for

					PSUSA/9200/202103.
IA/0095	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	10/12/2021	n/a		
WS/2134	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2, 4.8, and 5.1 of the SmPC following based on final results from study CA209908; this is a Phase Ib/II clinical trial of nivolumab monotherapy and nivolumab in combination with ipilimumab in paediatric subjects with high grade primary CNS malignancies; The RMP version 22.4 for Opdivo has also been submitted. C.I.3.b - 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 - Change(s) with new additional data submitted by the MAH	28/10/2021	07/01/2022	SmPC	SmPC new text: Currently available data of nivolumab monotherapy or nivolumab in combination with ipilimumab in paediatric subjects are described in sections 4.8 and 5.1 of the SmPC but no recommendation on a posology can be made. Only limited safety data of nivolumab as monotherapy or in combination with ipilimumab in children below 18 years of age are available. No new safety signals were observed in clinical study CA209908 of 151 paediatric patients with high grade primary central nervous system (CNS) malignancies, relative to data available in adult studies across indications. Results for OS, PFS, and ORR observed in study CA209908 do not suggest clinically meaningful improvement over what is expected in these patient populations. For more information, please refer to the Summary of Product Characteristics.
IAIN/0092	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/08/2021	07/01/2022	SmPC and PL	
WS/1840	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Extension of indication to include the combination of	20/05/2021	24/06/2021	SmPC and PL	Please refer to Scientific Discussion 'Opdivo, Yervoy-H-C-3985 & 2213-WS-1840'

	nivolumab with ipilimumab in the treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability_high (MSI-H) metastatic colorectal cancer (CRC) after prior fluoropyrimidine based combination chemotherapy; as a consequence, sections 4.1, 4.2 ,4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 20.2 for Opdivo and version 30.2 for Yervoy of the RMP have also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
WS/2043	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	10/06/2021	07/01/2022	Annex II	
WS/1881	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Extension of indication to include first-line treatment of adult patients with unresectable malignant pleural mesothelioma (MPM) for combination treatment of Opdivo and Yervoy; as a consequence, sections 4.1,	22/04/2021	01/06/2021	SmPC and PL	Please refer to Scientific Discussion Opdivo-H-C- 3985-WS-1881 and Yervoy-H-C-2213-WS-1881

	4.2, 4.4, 4.8, 5.1 (for both products) and 6.6 (for Opdivo) of the SmPC are updated. The Package Leaflet is updated in accordance. Version 20.1 for Opdivo and version 30.1 for Yervoy of the RMP has also been adopted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IA/0088	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	15/04/2021	n/a		
PSUSA/9200/ 202003	Periodic Safety Update EU Single assessment - ipilimumab	12/11/2020	07/01/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/9200/202003.
II/0086	B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS	10/12/2020	n/a		
WS/1783	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Extension of indication to include first-line treatment	17/09/2020	05/11/2020	SmPC and PL	Please refer to Scientific Discussion 'OPDIVO-H-C-3985 & Yervoy-H-C-2213-WS-1783.

	of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation for combination of OPDIVO/Yervoy and chemotherapy; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 17.1 of the RMP for OPDIVO and version 28.1 for Yervoy have also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0083/G	This was an application for a group of variations. B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line) B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	15/10/2020	n/a		Not applicable
WS/1790	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.8 and 5.1 of the SmPC in order	23/07/2020	05/11/2020	SmPC	SmPC new text After 60 months of follow-up, median durations of response for patients with tumour PD L1 expression level ≥5% were not reached (range: 18.07 N.A.) in the combination arm, not reached (range: 26.71 N.A.) in the nivolumab

	to include at least 5 years (60 months) of follow-up for all subjects from study CA209067. Updated efficacy data provided in this submission include overall survival (OS), progression-free survival (PFS) and objective response rate (ORR). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				monotherapy arm and 31.28 months (range: 6.08 N.A.) in the ipilimumab arm. At tumour PD-L1 expression <5%, median durations of response were not reached (range: 40.08 N.A.) in the combination arm, were not reached (range: 50.43 N.A.) in the nivolumab monotherapy arm and 12.75 months (range: 5.32 53.65) in the ipilimumab monotherapy arm. After 60 months of follow-up, BRAF[V600] mutation positive and BRAF wild type patients randomised to nivolumab in combination with ipilimumab had a median PFS of 16.76 months (95% CI: 8.28, 32.0) and 11.7 months (95% CI: 7.0, 18.14), while those in the nivolumab monotherapy arm had a median PFS of 5.6 months (95% CI: 2.79, 9.46) and 8.18 months (95% CI: 5.13, 19.55), respectively. BRAF[V600] mutation positive and BRAF wild type patients randomised to ipilimumab monotherapy had a median PFS of 3.38 months (95% CI: 2.79, 5.19) and 2.83 months (95% CI: 2.76, 3.06), respectively. After 60 months of follow up, BRAF[V600] mutation positive and BRAF wild type patients randomised to nivolumab in combination with ipilimumab had an ORR of 67.0% (95% CI: 57.0, 75.9; n = 103) and 54.0% (95% CI: 47.1, 60.9; n = 211), while those in the nivolumab monotherapy arm had an ORR of 37.87% (95% CI: 28.2, 48.1; n = 98) and 47.7% (95% CI: 40.9, 54.6; n = 218), respectively. BRAF[V600] mutation positive and BRAF wild type patients randomised to ipilimumab monotherapy had an ORR of 23.0% (95% CI: 15.2, 32.5; n = 100) and 17.2% (95% CI: 12.4, 22.9; n = 215). After 60 months of follow up, in BRAF [V600] mutation positive patients median OS was not reached in the combination arm and 45.5 months in the nivolumab

					monotherapy arm. Median OS for BRAF [V600] mutation positive patients in the ipilimumab monotherapy arm was 24.6 months. In BRAF wild type patients median OS was 39.06 months in the combination arm, 34.37 months in the nivolumab monotherapy arm and 18.5 months in the ipilimumab monotherapy arm. The OS HRs for nivolumab in combination with ipilimumab vs. nivolumab monotherapy were 0.70 (95% CI: 0.46, 1.05) for BRAF[V600] mutation positive patients and 0.89 (95% CI: 0.69, 1.15) for BRAF wild type patients. For more information, please refer to the Summary of Product Characteristics.
II/0080	Submission of an updated RMP version 28.0 in order to propose the discontinuation of the Healthcare Professional Adverse Reaction Management Guide as an additional risk minimization measure described in the RMP Annex 6 and in the Product Information Annex II.D. The RMP and the annex II.D are updated accordingly. The MAH also took the occasion to align the PI to the latest QRD version 10.1 and to include standard text on sodium excipient information. 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	09/07/2020	05/11/2020	SmPC, Annex II, Labelling and PL	Not applicable.

IB/0081	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	22/06/2020	n/a		
IAIN/0079	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	11/05/2020	05/11/2020	Annex II and PL	
IB/0076	B.I.b.1.i - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Where there is no monograph in the European/National Ph. for the AS, a change in specification from in-house to a non-official/third country Ph.	03/02/2020	n/a		
WS/1714	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2 and 4.4 of the SmPC in order to update the safety information on myocarditis management for nivolumab monotherapy or for nivolumab in combination with ipilimumab therapy. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/12/2019	20/01/2020	SmPC	The diagnosis of myocarditis requires a high index of suspicion. Patients with cardiac or cardio-pulmonary symptoms should be assessed for potential myocarditis. If myocarditis is suspected, prompt initiation of a high dose of steroids (prednisone 1 to 2 mg/kg/day or methylprednisolone 1 to 2 mg/kg/day) and prompt cardiology consultation with diagnostic workup according to current clinical guidelines should be initiated. Once a diagnosis of myocarditis is established, nivolumab or nivolumab in combination with ipilimumab should be withheld (grade 2 myocarditis) until symptoms resolve and management with corticosteroids is complete or permanently discontinued (grade 3 myocarditis).

PSUSA/9200/ 201903	Periodic Safety Update EU Single assessment - ipilimumab	17/10/2019	17/12/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/9200/201903.
IB/0075	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	04/11/2019	n/a		
IA/0074/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits	30/10/2019	n/a		
II/0064	Update of sections 4.4 and 4.8 of the SmPC to add stomatitis to the list of ADRs with a frequency uncommon, to further explain the components of the existing ADR musculoskeletal pain in a footnote and to update safety information based on final results from study CA184143 (A Multi-National, Prospective, Observational Study in Patients with Unresectable or	03/10/2019	17/12/2019	SmPC, Annex II and PL	The safety data for patients with unresectable or metastatic melanoma, treated with ipilimumab (3 mg/kg, with a minimum of 3 year follow up) and enrolled in multi national, prospective, observational study CA184143 (N= 1151) were similar to what has been reported in ipilimumab clinical trials for advanced melanoma. Musculoskeletal pain as an adverse drug reaction of

	Metastatic Melanoma) listed as a category 3 study in the RMP (MEA017.11); the Package Leaflet and the RMP have been updated accordingly (version 26.2). In addition, minor changes to improve clarity were introduced in section 5.1 of the SmPC and to the Annex II of the Product Information and minor changes were also made in relation to the Dutch Melanoma Treatment Registry (DMTR) in the RMP, partly as recommended in conclusion to MEA 036.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				ipilimumab treatment is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain.
IB/0072	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	29/08/2019	n/a		
N/0071	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	31/07/2019	17/12/2019	PL	
IAIN/0070	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	05/07/2019	n/a		
IB/0066/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.2.a - Change in test procedure for AS or	13/06/2019	n/a		

	starting material/reagent/intermediate - Minor changes to an approved test procedure 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.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.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				
IB/0068/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	30/04/2019	n/a		
IA/0067	B.II.c.3.z - Change in source of an excipient or reagent with TSE risk - Other variation	03/04/2019	n/a		

IG/1059	A.1 - Administrative change - Change in the name and/or address of the MAH	15/02/2019	02/04/2019	SmPC, Labelling and PL	
WS/1278	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Extension of indication to include the combination treatment with nivolumab and ipilimumab of adult patients with intermediate/poor-risk advanced renal cell carcinoma. As a consequence sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the Opdivo and Yervoy SmPCs were proposed to be updated. The Package Leaflet and the Risk Management Plan (version 19.0 for Yervoy and version 13.0 for Opdivo) were proposed to be updated in accordance. In addition, the Worksharing applicant (WSA) would take the opportunity to correct some typos throughout the Yervoy and Opdivo product information. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	15/11/2018	11/01/2019	SmPC and PL	Please refer to the published assessment report Opdivo-Yervoy H-C-WS-1278: EPAR – Assessment Report - Variation
IAIN/0062	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/11/2018	02/04/2019	SmPC	
IB/0061	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	19/11/2018	n/a		

PSUSA/9200/201803	Periodic Safety Update EU Single assessment - ipilimumab	04/10/2018	n/a		PRAC Recommendation - maintenance
II/0058/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.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method B.II.b.2.c.3 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing for a biol/immunol product and any of the test methods is a biol/immunol/immunochemical method B.II.d.2.c - Change in test procedure for the finished product - Substantial change to or replacement of a biol/immunol/immunochemical test method or a method using a biol. reagent or replacement of a biol. reference preparation not covered by an approved protocol	13/09/2018	11/01/2019	Annex II and PL	The Annex II has been updated to include Swords Laboratories T/A Bristol-Myers Squibb Cruiserath Biologics, Cruiserath Road Mulhudarft, Dublin 15 Ireland as an alternative batch release site. The PL has also been updated to include the site as alternative manufacturing site.
IB/0060	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	30/08/2018	n/a		

II/0054	Update of section 5.1 of the SmPC to update the overall survival data of ipilimumab 3mg/kg monotherapy pooled across studies based on the final results of studies CA184332 and CA184338 listed as category 3 studies in the RMP, in order to fulfil MEA 035 and MEA 030.1 respectively. Study CA184332 is a multi-site retrospective observational study of US patients with unresectable or metastatic melanoma receiving ipilimumab as first line therapy in a community practice setting and study CA184438 is a multi-site retrospective observational study of US patients with unresectable or metastatic melanoma receiving ipilimumab as first line therapy. The RMP version 22.0 (according to revision 2 of the template) has also been submitted. In addition the MAH has taken the opportunity to correct some typographical errors throughout the SmPC and to update the contact details of the Bulgarian, Estonian, Icelandic, Latvian, Lithuanian, Hungarian and Romanian 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	14/06/2018	11/01/2019	SmPC and PL	The overall survival data of ipilimumab 3mg/kg monotherapy, pooled across studies based on the final results of studies CA184332 and CA184338, was updated. Patients with brain metastases in study CA184332 had a median OS of 7 months (95% CI: 5.06 12.81) and patients without brain metastases had a median OS of 14.1 months (95% CI: 9.96 Not estimated). Patients with brain metastases in study CA184338 had a median OS of 6.3 months (95% CI: 3.2 12.0) and patients without brain metastases had a median OS of 17.7 months (95% CI: 13.6 – 12.1).
II/0055	Extension of indication to include the treatment of advanced (unresectable or metastatic) melanoma in adults in combination with nivolumab for Yervoy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and	26/04/2018	31/05/2018	SmPC and PL	Please refer to Scientific Discussion Yervoy-H-C-2213-II-0055

	5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 20.1) are updated in accordance. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to update the contact details of the Irish local representative in the Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IB/0056	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	04/05/2018	n/a		
II/0044	Extension of indication to include the treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older for Yervoy. As a consequence sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 15) are updated in accordance. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	14/12/2017	18/01/2018	SmPC and PL	Please refer to Scientific Discussion: Yervoy EMEA/H/C/002213/II/0044
PSUSA/9200/ 201703	Periodic Safety Update EU Single assessment - ipilimumab	09/11/2017	08/01/2018	SmPC and PL	Please refer to Yervoy-EMEA/H/C/PSUSA/00009200/201703 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation

II/0042	Update of sections 4.4, 4.8 and 5.1 of the SmPC to reflect the final results of study CA184-169, a randomized double-blind phase III study of ipilimumab administered at 3 mg/kg versus at 10 mg/kg in subjects previously treated or untreated with unresectable or metastatic melanoma, in order to fulfil ANX 014.1. The MAH also provided with this variation application efficacy and safety data from study CA184-169 in two subgroups: female ≥ 50 years of age and with brain metastases in order to fulfil MEA 015.1. Annex II.D and the RMP (version 14.1) are updated accordingly. In addition the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet, to include some editorial changes and correct some typos throughout the product information, and to bring the product information in line with the latest QRD template version 10. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/11/2017	08/01/2018	SmPC, Annex II, Labelling and PL	Results from study CA184 169 showed that overall survival compared between ipilimumab 10 mg/kg and 3 mg/kg groups showed HR = 0.84 (95% CI: 0.70, 0.99; P-value = 0.04). No statistically significant difference in progression free survival (PFS) was observed between the 10 mg/kg and the 3 mg/kg groups. (HR 0.89 with a 95% CI of 0.76, 1.04 and log-rank test P-value = 0.1548). Best overall response rate was similar in the 10 mg/kg and 3 mg/kg groups. Best overall response rate in the 10 mg/kg group was 15.3% (95% CI: 11.8, 19.5) and in the 3 mg/kg group was 12.2% (95% CI: 9.0, 16.0). Ipilimumab 10 mg/kg was associated with higher rates of adverse events compared with the 3 mg/kg dose. The frequencies of serious adverse reactions in the 10 mg/kg and 3 mg/kg groups were 37% and 18%, with the 3 most common serious adverse reactions being diarrhea (10.7% vs 5.5%), colitis (8.0% vs 3.0%), and hypophysitis (4.4% versus 1.9%). Adverse events leading to discontinuation in the 10 mg/kg and 3 mg/kg groups occurred in 31% and 19% of patients, with adverse events (AEs) leading to death in 4 and 2 patients, respectively. At the recommended dose of 3 mg/kg median OS was similar in the subgroup of females ≥ 50 years of age compared to the overall population: (11.40 vs 11.53 months). Median OS in the subgroup with brain metastases at baseline was 5.67 months at the recommended dose of 3 mg/kg. In addition, patients with ocular melanoma were not included in the CA184-169 clinical trial. However, patients with brain metastases were included in this study, if they were free of neurologic symptoms related to metastatic brain lesions and if they did not require or receive systemic corticosteroid therapy in the 10 days prior to beginning ipilimumab therapy. The overall safety profile

					of ipilimumab 3 mg/kg in clinical trial CA184-169 (N=362) was consistent with that established for ipilimumb in patients treated for advanced melanoma.
IB/0052	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	05/09/2017	n/a		
II/0049	Submission of an updated RMP (version 17.1) in order to amend the study objectives and milestones for two studies: - study CA184332, a multi-site retrospective observational study of US patients with unresectable or metastatic melanoma receiving ipilimumab (Yervoy) as first line therapy in a community setting, a category 3 study in the RMP (MEA 029): to submit the final study report with 2-years of follow-up - study CA184338, a multi-site retrospective observational study of US patients with unresectable or metastatic melanoma receiving ipilimumab (Yervoy) as first line therapy, a category 3 study in the RMP (MEA 030): to submit the final study report with 4-years of follow-up. 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	01/09/2017	n/a		
II/0047/G	This was an application for a group of variations.	01/09/2017	08/01/2018	SmPC	Following a request from the PRAC as part of Yervoy (ipilimumab) PSUSA/00009200/201603, the MAH

	Update of section 4.4 to revise the current warning on concurrent administration with vemurafenib to enhance awareness on the potential of hypersensitivity reactions when ipilimumab is used sequentially with vemurafenib as requested by the PRAC following the assessment of PSUSA/00009200/201603. Update of sections 4.8 of the SmPC to amend the frequency of the adverse drug reaction 'Vogt-Konyanagi-Haranda syndrome' from 'not known' to 'rare'. The Package Leaflet and RMP (version 16.1) have been updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement some editorial changes to sections 4.2 and 4.4 of the SmPC to update the dose modification information for hepatotoxicity management guidelines in line with National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) recommendations (version 4). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.3.b - 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 - Change(s) with new additional data submitted by the MAH				conducted a review of clinical trials data, post-marketing data and the literature on the risk of sequential administration of Yervoy with vemurafenib. In a Phase 2 trial, the sequential treatment with vemurafenib followed by 10 mg/kg ipilimumab in patients with BRAF-mutated metastatic melanoma showed a higher incidence of Grade 3+ skin adverse reactions than with ipilimumab alone. Caution should be used when ipilimumab is administered following prior vemurafenib. In addition, based on a review of the MAH's safety database, the frequency of the adverse drug reaction 'Vogt-Konyanagi-Haranda syndrome' is updated from 'not known' to 'rare'. Finally regarding the grading criteria and numerical threshold criteria for withholding and discontinuation of ipilimumab, sections 4.2 and 4.4 of the ipilimumab SmPC are aligned with the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0, a standard procedure for drug management.
II/0048/G	This was an application for a group of variations.	06/07/2017	n/a		

	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS				
IB/0050	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	07/06/2017	n/a		
IB/0043/G	This was an application for a group of variations. 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.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	19/05/2017	n/a		
IB/0045	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	04/04/2017	n/a		

IA/0046	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	31/03/2017	31/05/2017	Annex II	
IAIN/0041	C.I.12 - Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring	30/11/2016	31/05/2017	SmPC and PL	
PSUSA/9200/ 201603	Periodic Safety Update EU Single assessment - ipilimumab	27/10/2016	n/a		PRAC Recommendation - maintenance
II/0038	Submission of a Final Study Report for Study CA184242 - YERVOY Risk minimization tool effectiveness evaluation survey. An updated Risk Management Plan (Version 13.1), containing all the relevant updates is being submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	15/09/2016	n/a		
II/0036/G	This was an application for a group of variations. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting	23/06/2016	31/05/2017	Annex II	

	material [-] used in the manufacture of a biological/immunological product B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line) 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 B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material				

N/0039	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/05/2016	31/05/2017	PL	
R/0035	Renewal of the marketing authorisation.	25/02/2016	21/04/2016	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Yervoy in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity. Based on a pooled analysis of long term OS data from clinical trials in patients with previously treated and treatment naïve advanced melanoma presented by the MAH, sections 5.1 of the SmPC was proposed to be updated.
PSUSA/9200/ 201503	Periodic Safety Update EU Single assessment - ipilimumab	22/10/2015	14/12/2015	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/9200/201503.
II/0005/G	This was an application for a group of variations. To replace a test method for the control of ipilimumab active substance and drug product, to update the SOP to qualify new reference materials and to update the specifications of the active substance B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS	20/09/2012	14/12/2015		

	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits				
N/0037	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/11/2015	21/04/2016	PL	
IB/0034	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	19/10/2015	n/a		
IB/0033	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	08/10/2015	n/a		
IB/0031	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	16/07/2015	n/a		
PSUSA/9200/ 201409	Periodic Safety Update EU Single assessment - ipilimumab	23/04/2015	19/06/2015	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/9200/201409.
II/0028/G	This was an application for a group of variations. 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	23/04/2015	14/12/2015	Annex II	

	which may have a significant impact on the medicinal product and is not related to a protocol B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product 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.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.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS 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.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line) B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.f.1.a.1 - Stability of FP - Reduction of the shelf life of the finished product - As packaged for sale				
II/0029	Update of section 5.1 of the SmPC in order to revise the description of mechanism of action in the Yervoy (ipilimumab). The requested variation leads to 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	26/03/2015	19/06/2015	SmPC	

PSUV/0025	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance
II/0027	C.I.3.b - 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 - Change(s) with new additional data submitted by the MAH	25/09/2014	19/06/2015	SmPC and PL	
II/0026/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	25/09/2014	19/06/2015	SmPC	
IB/0024	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	06/06/2014	n/a		
PSUV/0023	Periodic Safety Update	10/04/2014	n/a		PRAC Recommendation - maintenance
PSUV/0020	Periodic Safety Update	24/10/2013	18/12/2013	SmPC and PL	Update of section 4.8 of the SmPC to add the adverse reaction anaphylactic reactions with a frequency very rare. The Package leaflet is updated accordingly. Please refer to Yervoy-H-C-2213-PSUV-0020 - Scientific conclusions and grounds recommending the variation to the

					terms of the marketing authorisation.
IB/0018/G	This was an application for a group of variations. B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	18/12/2013	n/a		
IA/0022	B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	12/12/2013	n/a		
IB/0021	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	09/12/2013	n/a		
II/0008	Extension of indication of Yervoy for the treatment of previously untreated adult patients with advanced (unresectable or metastatic) melanoma. Consequently, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the Summary of Product Characteristics (SmPC) have been updated. The Package Leaflet has been updated accordingly. Editorial changes were also made to the SmPC 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	24/10/2013	31/10/2013	SmPC and PL	Please refer to Scientific Discussion Yervoy-H-2213-II-08-AR.

IB/0019/G	This was an application for a group of variations. 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 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	23/10/2013	n/a		
IA/0017	B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	08/08/2013	n/a		
IB/0016	B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test	29/07/2013	n/a		
IB/0015	B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test	24/06/2013	n/a		
IB/0013/G	This was an application for a group of variations. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting	13/06/2013	n/a		

	material/intermediate/reagent - Tightening of specification limits				
II/0014	Update of section 4.4 of the SmPC to add a warning with regard to the combined use of ipilimumab and vemurafenib at the request of the CHMP following information on results of a clinical trial. The Package leaflet has been updated accordingly. The product information has also been updated in line with QRD template version 9 and the list of local representatives in the package leaflet has been revised to add the contact in Croatia. C.I.3.z - 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 - Other variation	30/05/2013	31/10/2013	SmPC, Annex II and PL	In a Phase 1 trial, asymptomatic grade 3 increases in transaminases (ALT/AST > 5 × ULN) and bilirubin (total bilirubin > 3 × ULN) were reported with concurrent administration of ipilimumab (3 mg/kg) and vemurafenib (960 mg BID or 720 mg BID). Based on these preliminary data, the concurrent administration of ipilimumab and vemurafenib is not recommended.
II/0012	Changes in the bioassay method. B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS	30/05/2013	n/a		
II/0009/G	This was an application for a group of variations. This was an application for a group of variations to add two quality control testing sites for Yervoy drug	21/02/2013	n/a		

	product and changes in the quality control testing arrangements for drug substance. B.II.b.2.z - Change to batch release arrangements and quality control testing of the FP - Other variation B.II.b.2.z - Change to batch release arrangements and quality control testing of the FP - Other variation 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				
IB/0011	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	30/01/2013	n/a		
IG/0254	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		
IB/0006	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	13/08/2012	n/a		
IA/0007	A.7 - Administrative change - Deletion of manufacturing sites	03/08/2012	n/a		
II/0002	Update of sections 4.6 and 5.3 of the SmPC with the results of a pre- and post-natal development study in cynomolgus monkeys conducted at the request of the CHMP (FUM 013). The MAH also took the	24/05/2012	21/06/2012	SmPC, Annex II, Labelling and PL	At the time of the initial marketing authorisation, the applicant committed to submit the final report for study DN10020, an intravenous study of pre- and post-natal development in cynomolgus monkeys with a 6-month post-

	opportunity to update the product information in line with the QRD template version 8.1 and to make minor corrections to the SmPC. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				natal evaluation (FUM 013). The effects of ipilimumab on prenatal and postnatal development were investigated in a study in cynomolgus monkeys. Pregnant monkeys received ipilimumab every 3 weeks from the onset of organogenesis in the first trimester through delivery, at exposure (AUC) levels either similar to or higher than those associated with the clinical dose of 3 mg/kg of ipilimumab. No treatment-related adverse effects on reproduction were detected during the first two trimesters of pregnancy. Beginning in the third trimester, both ipilimumab groups experienced higher incidences of abortion, stillbirth, premature delivery (with corresponding lower birth weight), and infant mortality relative to control animals; these findings were dose-dependent. Additionally, developmental external or visceral abnormalities were identified in the urogenital system of 2 infants exposed in utero to ipilimumab. One female infant had unilateral renal agenesis of the left kidney and ureter, and one male infant had an imperforate urethra with associated urinary obstruction and subcutaneous scrotal edema. The relationship of these malformations to treatment is unclear. The product information has been updated accordingly.
IB/0004/G	This was an application for a group of variations. B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	20/06/2012	n/a		

II/0001	To replace the current method used to determine host cell protein (HCP) levels in unformulated bulk drug substance by a new process specific HCP method. This type II variation addresses Quality Obligation 001. B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological AS	15/03/2012	26/04/2012	Annex II	
IB/0003	B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)	25/04/2012	n/a		