OPDIVO

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/0142	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	12/06/2024		Annex II	
II/0137	Extension of indication to include OPDIVO in combination with cisplatin and gemcitabine for the	25/04/2024	23/05/2024	SmPC and PL	Please refer to Scientific Discussion: Opdivo-H-C-3985-II-

[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).

	first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma, based on interim results from study CA209901 (CheckMate901). This is a Phase 3, open-label, randomised study of nivolumab combined with ipilimumab, or with standard of care chemotherapy, versus standard of care chemotherapy in participants with previously untreated unresectable or metastatic urothelial cancer. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 35.1 of the RMP has 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				0137.
X/0132	Annex I_1.(c) Replacement of a biological AS with one of a slightly different molecular structure	25/01/2024	25/03/2024	Annex II	Please refer to Scientific Discussion OPIVO EMEA/H/C/003985/X/0132.
WS/2597	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 4.4 and 4.8 of the SmPC in order to add 'myelitis' as a warning under the subsection "Other immune-mediated adverse reactions" and to the list of adverse drug reactions (ADRs) with their calculated frequencies for monotherapy (not known) and in combination (rare), based on post marketing data and literature; the Package Leaflet is updated	15/02/2024	23/05/2024	SmPC and PL	

	accordingly. In addition, the MAH took the opportunity to implement editorial changes to the SmPC in line with the QRD. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IA/0139	A.7 - Administrative change - Deletion of manufacturing sites	08/12/2023	n/a		
IB/0133	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/10/2023	25/03/2024	SmPC	
IA/0136	B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits	16/10/2023	n/a		
IA/0135	B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits	08/09/2023	n/a		
IB/0134	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	08/09/2023	n/a		
II/0130	Extension of indication to include OPDIVO for the adjuvant treatment of adults and adolescents 12 years of age and older with stage IIB or IIC melanoma who have undergone complete resection, based on results from study CA20976K; This is a phase III, randomized, double-blind study of	20/07/2023	21/08/2023	SmPC, Annex II and PL	Please refer to Scientific Discussion 'Opdivo-H-C-3985-II-0130'

	adjuvant immunotherapy with nivolumab versus placebo after complete resection of stage IIB/C melanoma. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Annex II and Package Leaflet are updated in accordance. Version 33.1 of the RMP has 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/0117	Extension of indication to include OPDIVO in combination with platinum-based chemotherapy for neoadjuvant treatment of adult patients with resectable Stage IB-IIIA non-small cell lung cancer (NSCLC), based on results from study CA209816; a randomised, open-label, phase 3 trial of nivolumab plus ipilimumab or nivolumab plus platinum-doublet chemotherapy versus platinum-doublet chemotherapy in early-stage NSCLC. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 27.4 of the RMP has 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	25/05/2023	26/06/2023	SmPC, Annex II and PL	Please refer to Scientific Discussion 'Opdivo-H-C-3985-II-0117'
II/0125/G	This was an application for a group of variations.	26/04/2023	31/05/2023	SmPC and PL	Please refer to Scientific Discussion 'Opdivo-H-C-3985-II-0125'

	Extension of indication to include adolescent patients aged 12 years and older in treatment of advanced (unresectable or metastatic) melanoma (nivolumab monotherapy), treatment of advanced (unresectable or metastatic) melanoma (nivolumab in combination with ipilimumab) and adjuvant treatment of melanoma (nivolumab monotherapy) for Opdivo, based on results from a nonclinical biomarker study (Expression of PD-L1 (CD274), and characterization of tumor infiltrating immune cells in tumors of pediatric origin), also based on results from a Phase 1/2 clinical study (CA209070, A Phase 1/2 Study of Nivolumab (Ind# 124729) In Children, Adolescents, And Young Adults With Recurrent Or Refractory Solid Tumors As A Single Agent And In Combination With Ipilimumab) and a modelling and simulation study. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 30.1 of the RMP has 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 C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				

IB/0129	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	21/03/2023	24/04/2023	Annex II	
II/0127	Submission of the final report from the post-authorisation safety study (PASS) CA209835: A registry study in patients who underwent post-nivolumab allogeneic haematopoetic stem-cell transplantation (HSCT). This study is listed as a Category 3 study in the RMP. An updated RMP version 31.0 has also been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	16/03/2023	n/a		Not applicable
IA/0131	A.7 - Administrative change - Deletion of manufacturing sites	15/03/2023	n/a		
IA/0128	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	02/02/2023	24/04/2023	Annex II	
IB/0126	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	04/01/2023	n/a		
WS/2187	This was an application for a variation following a worksharing procedure according to Article 20 of	27/10/2022	24/04/2023	SmPC and PL	Not applicable Please refer to the Summary of Product Characteristics.

	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				
II/0124/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 material [-] used in the manufacture of a biological/immunological product B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	06/10/2022	n/a		
WS/2289	This was an application for a variation following a worksharing procedure according to Article 20 of	01/09/2022	24/04/2023	SmPC	A statistically significant improvement in OS was observed with nivolumab monotherapy (HR 0.63 [95% CI: 0.52,

	Commission Regulation (EC) No 1234/2008. To update sections 4.8 and 5.1 of the SmPC to 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				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, 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.
IB/0123	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	06/07/2022	n/a		
IB/0119	B.II.z - Quality change - Finished product - Other variation	10/06/2022	n/a		
PSUSA/10379 /202107	Periodic Safety Update EU Single assessment - nivolumab	24/02/2022	25/04/2022	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10379/202107.

IB/0120	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	24/04/2023	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 26.2 of the Opdivo RMP and version 35.0 of the	24/02/2022	01/04/2022	SmPC and PL	OPDIVO/Yervoy-H-C-3985/2213/WS/2113’

	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				
II/0107	Extension of indication to include in combination with fluoropyrimidine- and platinum-based combination chemotherapy the 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 based on study CA209648; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 26.2 of the RMP has 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	24/02/2022	01/04/2022	SmPC and PL	Please refer to Scientific Discussion 'OPDIVO-H-C/003985/II-0107'
II/0100	Extension of indication for Opdivo to include as monotherapy for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC (see section 5.1); as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC and Annex II are updated. The Package Leaflet is updated in accordance. Version 26.2 of the	24/02/2022	01/04/2022	SmPC, Annex II and PL	Please refer to Scientific Discussion 'OPDIVO-H-C-3985-II-0100'

	RMP has 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				
IA/0118	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	21/03/2022	n/a		
IAIN/0116/G	This was an application for a group of variations. A.6 - Administrative change - Change in ATC Code/ATC Vet Code A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	09/02/2022	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	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.

	new quality, preclinical, clinical or pharmacovigilance data				
IB/0115	B.II.f.1.b.3 - Stability of FP - Extension of the shelf life of the finished product - After dilution or reconstitution (supported by real time data)	07/12/2021	01/04/2022	SmPC and PL	
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	01/04/2022	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.
II/0106/G	This was an application for a group of variations. B.II.e.5.c - Change in pack size of the finished product - Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including	28/10/2021	01/04/2022	SmPC, Labelling and PL	The SmPC section 2 has been updated as follows: One vial of 12 mL contains 120 mg of nivolumab. The SmPC section 4.4 has been updated as follows: Patients on controlled sodium diet Each mL of this medicinal product contains 0.1 mmol (or 2.5 mg) sodium. This medicinal product contains 10 mg

	biological/immunological medicinal products 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.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.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits				sodium per 4 ml vial, 25 mg sodium per 10 ml vial, 30 mg sodium per 12 ml vial or 60 mg sodium per 24 ml vial, which is equivalent to 0.5%, 1.25%, 1.5% or 3% respectively, of the WHO recommended maximum daily intake of 2 g sodium for an adult. The SmPC section 6.5 has been updated as follows: 12 mL of concentrate in a 25 mL vial (Type I glass) with a stopper (coated butyl rubber) and a blue flip off seal (aluminium). Pack size of 1 vial. The SmPC section 8 has been updated as follows: EU/1/15/1014/004 The Labelling and PL have been updated accordingly.
II/0096	Extension of indication to use OPDIVO (nivolumab) in combination with fluoropyrimidine- and platinum-based combination chemotherapy, in first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, gastro-oesophageal junction (GEJ) or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) ≥ 5 (Study CA209649); as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 6.6 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 21.2 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or	16/09/2021	19/10/2021	SmPC and PL	Please refer to Scientific Discussion 'Opdivo-H-C-3985-II-0096'

	modification of an approved one				
IA/0113/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	11/10/2021	n/a		
II/0105	Update of sections 4.4, 4.8, and 5.1 of the SmPC based on final results from study CA209205 listed as a PAES in the Annex II; this is a Phase 2, open-label, multi-cohort, single-arm study of nivolumab in patients with classical Hodgkin's Lymphoma; The RMP version 20.3 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	02/09/2021	19/10/2021	SmPC and Annex II	Cases of acute graft versus host disease (GVHD) and transplant related mortality (TRM) have been observed from the follow-up of patients with cHL undergoing allogeneic HSCT after previous exposure to nivolumab. Nineteen of 4962 patients (30.6%) died from complications of allogeneic HSCT after nivolumab. The 62 patients had a median follow up from subsequent allogeneic HSCT of 38.5 months (range: 0-68 months). For more information, please refer to the Summary of Product Characteristics.
IAIN/0110	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/08/2021	19/10/2021	SmPC and PL	
II/0095	Extension of indication to include adjuvant treatment of adult patients with oesophageal, or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy for OPDIVO (study CA209577) as	24/06/2021	28/07/2021	SmPC, Annex II and PL	Please refer to Scientific Discussion 'Opdivo-H-C-3985-II-0095'.

	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 22.0 of the RMP has 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/0103	B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP	15/07/2021	n/a		
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 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.	20/05/2021	24/06/2021	SmPC and PL	Please refer to Scientific Discussion 'Opdivo, Yervoy-H-C-3985 & 2213-WS-1840'

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IB/0104	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	18/06/2021	n/a		
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	28/07/2021	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, 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) -	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

	Addition of a new therapeutic indication or modification of an approved one				
PSUSA/10379 /202007	Periodic Safety Update EU Single assessment - nivolumab	25/02/2021	21/04/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10379/202007.
IA/0101	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	16/04/2021	n/a		
II/0092	Extension of indication to include in combination with cabozantinib for the first line treatment of advanced renal cell carcinoma for Opdivo; 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 19.1 of the RMP has 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	25/02/2021	13/04/2021	SmPC and PL	Please refer to Scientific Discussion 'Opdivo-H-C-3985-II-0092'
II/0098	Update of section 5.1 of the SmPC in order to update overall survival information based on the final OS data for study CA209238, listed as an obligation in the Annex II and in the RMP; study CA 209238 is a Phase 3, randomised double-blind study of OPDIVO versus Yervoy in patients who have undergone complete resection of Stage IIIb/c or Stage IV melanoma; the MAH took also the occasion to update section 4.8 of the SmPC to pull the safety data sets	11/03/2021	01/06/2021	SmPC, Annex II and PL	SmPC new text With a minimum follow up of 48 months, the trial continued to demonstrate improvement in Recurrence free survival in the nivolumab arm compared with the ipilimumab arm [HR 0.71 (95% CI: 0.60, 0.86)]. RFS benefit was sustained across all subgroups. Median OS was not reached in either group (HR = 0.87, 95.03% CI: 0.66, 1.14; p-value: 0.3148), as OS data are confounded by the effects of effective subsequent anti-cancer therapies.

	of nivolumab as monotherapy across advanced metastatic and adjuvant settings. The Package Leaflet is updated accordingly. The RMP version 17.2 has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial and formatting revisions in the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				For more information, please refer to the Summary of Product Characteristics.
IA/0099	A.7 - Administrative change - Deletion of manufacturing sites	12/02/2021	13/04/2021	Annex II and PL	
IB/0094	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	14/01/2021	n/a		
IB/0097	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	06/01/2021	n/a		
II/0080	Extension of indication to include treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) after prior fluoropyrimidine- and platinum-based 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.	15/10/2020	20/11/2020	SmPC and PL	Please refer to Scientific Discussion "Opdivo-H-C-3985-II-0080".

	Version 16.2 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives for Sweden and Denmark 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				
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 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	17/09/2020	05/11/2020	SmPC and PL	Please refer to Scientific Discussion 'OPDIVO-H-C-3985 & Yervoy-H-C-2213-WS-1783.
IA/0090	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	02/09/2020	n/a		

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 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	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 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.
IB/0088	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	21/07/2020	n/a		
IB/0085	B.II.f.1.b.3 - Stability of FP - Extension of the shelf life of the finished product - After dilution or reconstitution (supported by real time data)	14/07/2020	05/11/2020	SmPC and PL	

IB/0087	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	25/06/2020	n/a		
IB/0086/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	24/06/2020	n/a		
IAIN/0084	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/05/2020	05/11/2020	SmPC and PL	
R/0074	Renewal of the marketing authorisation.	27/02/2020	23/04/2020	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 OPDIVO in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity. Updates to the Product Information were made in line with the SmPC guideline and the latest QRD template (version 10.1). Annex IID has been updated in line with the proposed changes to the Risk minimisation measures as per RMP version 15.2. The MAH has also taken the opportunity to implement changes of the local representative for Malta and Latvia in the package leaflet.

IAIN/0083	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	20/04/2020	05/11/2020	Annex II and PL	
II/0076/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer 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	23/01/2020	23/04/2020	Annex II	The Annex II has been updated with the inclusion of the following new active substance manufacturer: Swords Laboratories t/a Bristol-Myers Squibb Cruiserath Biologics, Cruiserath Road, Mulhuddart, Dublin
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.	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

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				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/10379 /201907	Periodic Safety Update EU Single assessment - nivolumab	16/01/2020	n/a		PRAC Recommendation - maintenance
IB/0079	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	20/12/2019	23/04/2020	SmPC	
II/0078	B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability	12/12/2019	n/a		
II/0073	To update sections 4.8 and 5.1 of the SmPC based on the final results from two studies: CA209017 (Open-label Randomized Phase III Trial comparing Nivolumab Versus Docetaxel in Previously Treated Advanced or Metastatic Squamous Cell Non-small Cell Lung Cancer) and CA209057 (Open-label Randomized Phase III Trial comparing Nivolumab Versus Docetaxel in Previously Treated Metastatic Non-Squamous Non-small Cell Lung Cancer). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/10/2019	20/01/2020	SmPC	With a minimum of 62.6 months follow-up in non-small cell lung cancer, Overall Survival benefit remained consistently demonstrated across subgroups and no new safety signals were identified. For more information, please refer to the Summary of Product Characteristics.

II/0069	Update of section 4.2, 5.1 and 6.6 of the SmPC in order to replace the current weight-based dosing regimen for the adjuvant treatment of melanoma by the flat dose regimens of 240 mg every 2 weeks (Q2W) administered intravenously (IV) over 30 minutes or 480 mg every 4 weeks (Q4W) administered IV over 60 minutes based on population pharmacokinetic data and an exposure-response efficacy analysis. The Package leaflet has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/09/2019	21/10/2019	SmPC and PL	
PSUSA/10379 /201901	Periodic Safety Update EU Single assessment - nivolumab	25/07/2019	26/09/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10379/201901.
II/0067/G	This was an application for a group of variations. B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.d - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of an in-process test which may have a significant effect on the overall quality of the finished product	12/09/2019	n/a		
IA/0072/G	This was an application for a group of variations.	30/08/2019	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.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)				
IB/0071	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	08/08/2019	n/a		
IAIN/0070	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	11/06/2019	n/a		
IAIN/0068	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	07/06/2019	26/09/2019	SmPC and PL	
II/0060/G	This was an application for a group of variations. Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to include information from studies CA209171 (A Phase 2, single-arm, open-label, multicentre clinical trial with nivolumab monotherapy in subjects with advanced or metastatic squamous	26/04/2019	27/05/2019	SmPC and Annex II	Study CA209171 was a single-arm, open label study of nivolumab monotherapy in patients with previously treated advanced or metastatic squamous NSCLC. No new safety signals were identified in all treated patients and the overall safety profile of nivolumab was similar across subgroups. The efficacy in terms of ORR of nivolumab in elderly patients (≥75 years old) was comparable to that observed

	(Sq) cell non-small cell lung cancer (NSCLC) who have received at least one prior systemic regimen for the treatment of Stage IIIb/IV Sq NSCLC) and CA209172 (A Phase 2, single-arm, open-label, multicentre clinical trial with nivolumab monotherapy in subjects with histologically confirmed Stage III (unresectable) or Stage IV melanoma progressing after prior treatment containing an anti-CTLA-4 monoclonal antibody). In addition, the MAH takes the occasion to update Annex II to reflect already fulfilled requirement regarding biomarkers (ANX 005.3, ANX 006, ANX 023, ANX 024, ANX 026 and ANX 027). The RMP has been updated accordingly (final version 13.6). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				in younger patients and the overall population within the study CA209171. These data appear to confirm the lower efficacy of nivolumab in elderly patients (>75) and in ECOG PS 2 patients where the antitumor activity of nivolumab is clearly lower than in the overall population. Patients with baseline performance score of 2 were included in study CA209171. In the absence of data for patients with autoimmune disease, symptomatic interstitial lung disease, active brain metastases and patients who had been receiving systemic immunosuppressants prior to study entry, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis. Study CA209172 was a single-arm, open label study of nivolumab monotherapy in patients with stage III (unresectable) or stage IV metastatic melanoma after prior treatment containing an anti-CTLA-4 monoclonal antibody.No new safety signals were identified in all treated patients and the overall safety profile of nivolumab was similar across subgroups. Patients with baseline performance score of 2, treated leptomeningeal metastases, ocular/uveal melanoma, autoimmune disease and patients who have had a Grade 3 4 adverse reaction that was related to prior anti CTLA 4 therapy were included in study CA209172. In the absence of data for patients who had been receiving systemic immunosuppressants prior to study entry, and for patients with active brain or leptomeningeal metastases, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

IB/0066	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	22/05/2019	n/a		
PSUSA/10379 /201807	Periodic Safety Update EU Single assessment - nivolumab	31/01/2019	28/03/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10379/201807.
II/0061/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)	14/03/2019	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	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

	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				
II/0057	Update of section 5.1 of the SmPC in order to include descriptive efficacy data available from study CA209374 (A Phase 3b/4 Safety Trial of Nivolumab (BMS-936558) in Subjects With Advanced or Metastatic Renal Cell Carcinoma). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/12/2018	28/03/2019	SmPC	Additional safety and descriptive efficacy data are available from study CA209374, an open-label Phase 3b/4 safety study of nivolumab monotherapy (treated with 240 mg every 2 weeks) for the treatment of patients with advanced or metastatic RCC (n = 142), including 44 patients with non-clear cell histology. In subjects with non-clear cell histology, at a minimum follow-up of approximately 16.7 months ORR and median duration of response were 13.6% and 10.2 months, respectively. Clinical activity was observed regardless of tumour PD-L1 expression status.
IB/0058/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the 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	23/11/2018	n/a		

	or addition) for the AS or a starting material/intermediate				
IB/0059/G	This was an application for a group of variations. 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.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	13/11/2018	n/a		
PSUSA/10379 /201801	Periodic Safety Update EU Single assessment - nivolumab	26/07/2018	20/09/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10379/201801.
IB/0055	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	28/08/2018	n/a		
II/0041	Extension of Indication to include adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add efficacy and safety information from the pivotal Study CA209238. The Package Leaflet is updated in accordance. In addition, the already authorised indication in squamous cell cancer of the head and neck has been further clarified. Furthermore, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial	28/06/2018	30/07/2018	SmPC and PL	Please refer to Scientific Discussion 'Opdivo-H-C-003985-II-41'

	changes to the PI. Annex II has been updated to reflect new conditions. The RMP has been updated to version 12.3. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IB/0054/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.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.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	19/06/2018	n/a		
II/0051/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits	17/05/2018	30/07/2018	SmPC, Labelling and PL	Sections 2, 6.3, 6.5 and 8 of the SmPC are being updated to reflect the addition of a new presentation: one vial of 24 mL containing 240 mg of nivolumab concentrate for solution for infusion. Annex A, Labelling and Package Leaflet (PL) are updated accordingly.

	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.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.5.c - Change in pack size of the finished product - Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/immunological medicinal products				
II/0047	Update of sections 4.4 and 4.8 of the SmPC in order to add a warning on the nivolumab use in patients who have previously undergone allogeneic HSCT and the increased risk of rapid onset and severe Graft versus Host Disease (GVHD) based on evidence from spontaneous case reports, literature case reports, and from 2 multicenter case series. Annex II.D and the Package Leaflet are updated accordingly. The RMP version 10.2 has also been submitted to include the "risk of GVHD with nivolumab after allogeneic HSCT" as an "Important Potential Risk" based on the RMP template (Revision 2). In addition, the Marketing authorisation holder (MAH) took the opportunity to make some minor editorial corrections to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to	26/04/2018	30/07/2018	SmPC, Annex II and PL	The MAH has updated the Product Information to add a warning on the nivolumab use in patients who have previously undergone allogeneic haematopoietic stem cell transplant (HSCT) and the increased risk of rapid onset and severe Graft versus Host Disease (GVHD) based on evidence from spontaneous case reports, literature case reports, and from 2 multicenter case series. Section 4.4 of the SmPC has been modified as follows: Complications of allogeneic Haematopoietic Stem Cell Transplant (HSCT) in classical Hodgkin Lymphoma (…) In patients treated with nivolumab after allogeneic HSCT, rapid-onset and severe GVHD, some with fatal outcome, have been reported in the post-marketing setting. Treatment with nivolumab may increase the risk of severe GVHD and death in patients who have had prior allogeneic HSCT, mainly in those with prior history of

	new quality, preclinical, clinical or pharmacovigilance data				GVHD. The benefit of treatment with nivolumab versus the possible risk should be considered in these patients (see section 4.8). Section 4.8 of the SmPC has been modified as follows: Complications of allogeneic HSCT in classical Hodgkin Lymphoma Rapid onset of GVHD has been reported with nivolumab use before and after allogeneic HSCT (see section 4.4). Annex II and PL have been modified accordingly.
II/0036/G	This was an application for a group of variations. Update of sections 4.2, 5.1, 5.2 and 6.6 of the SmPC in order to introduce new dosing regimens (240 mg every 2 weeks and 480 mg every 4 weeks) and infusion time (30-minutes) depending on the dose: - The 240 mg every 2 weeks regimen in combination with the 30-minute infusion time is recommended for currently approved indications (melanoma, renal cell carcinoma, non-small lung cancer, classical Hodgkin lymphoma, squamous cell cancer of the head and neck, urothelial carcinoma). - The 480 mg every 4 weeks regimen in combination with the 60-minute infusion time is recommended for melanoma and renal cell carcinoma indications. These changes are based on comparison of the exposure-response and safety of nivolumab 3 mg/kg Q2W, 240 mg Q2W, and 480 mg Q4W in melanoma, NSCLC, RCC, SCCHN, cHL, and UC. The analyses to support the 30 minute infusion time were conducted across different indications and from study CA209153; this is a phase IIIb/IV safety trial of	22/03/2018	23/04/2018	SmPC and PL	With this grouping of variations new dosing regimens (240 mg every 2 weeks and 480 mg every 4 weeks) and infusion time (30-minutes) have been introduced. The 240 mg every 2 weeks regimen in combination with the 30-minute infusion time is recommended for currently approved indications (melanoma, renal cell carcinoma, non-small lung cancer, classical Hodgkin lymphoma, squamous cell cancer of the head and neck, urothelial carcinoma). The 480 mg every 4 weeks regimen in combination with the 60-minute infusion time is recommended for melanoma and renal cell carcinoma indications. See sections 4.2, 5.1, 5.2 and 6.6 of the SmPC for details. The PL has been updated accordingly.

	nivolumab in subjects with advanced or metastatic non-small cell Lung cancer who have progressed during or after receiving at least one prior systemic regimen. The Package Leaflet is updated accordingly. An updated RMP (version 10.1) has also been presented C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10379 /201707	Periodic Safety Update EU Single assessment - nivolumab	25/01/2018	23/03/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10379/201707.
IB/0050	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	07/03/2018	n/a		
IB/0048	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	21/02/2018	23/04/2018	Annex II	
IB/0049	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	20/02/2018	n/a		

IB/0046	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	12/01/2018	23/03/2018	SmPC and PL	
IB/0045/G	This was an application for a group of variations. 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 B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	22/12/2017	23/03/2018	SmPC	
IB/0044/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	20/12/2017	n/a		
II/0037/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS -	14/12/2017	n/a		

	Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place 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.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits 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.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits				
IB/0043/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	12/12/2017	n/a		

	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits				
II/0038	Update of section 4.8 of the SmPC with longer follow-up for subjects proceeding to allogeneic transplant following nivolumab treatment, of section 5.1 of the SmPC with efficacy data from longer follow-up based on final results from study CA209205 listed as a PAES in the Annex II; this is a Phase 2, non-comparative, multi-cohort, single-arm, open-label study of nivolumab (BMS-936558) in cHL subjects after failure of ASCT. Annex II is updated accordingly. Version 7.7 of the RMP has been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/11/2017	23/03/2018	SmPC and Annex II	
II/0032	Update of sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to update the statement on outcome benefit, to add administration guidance, to update the safety information and updated overall survival data based on final results from study CA209067 (listed as an imposed PAES in the Annex II). Study CA209067 is an interventional, randomized, double-blind study of nivolumab monotherapy or nivolumab combined with ipilimumab versus ipilimumab monotherapy in adult	14/09/2017	19/10/2017	SmPC, Annex II and PL	The MAH presented additional efficacy and safety data, including the co-primary endpoint of OS, from Study CA209067 in adult subjects with previously untreated, unresectable or metastatic Stage III or Stage IV melanoma. The product information has been updated in 4.1 to update the statement on outcome benefit, to add the final OS analysis with a minimum 36 months (section 5.1) along with updated safety information with the longer follow-up (4.4, 4.8, 5.1, 5.2). For nivolumab and ipilimumab combination therapy, it is proposed to update

	subjects with previously untreated, unresectable or metastatic Stage III or Stage IV melanoma. The Package Leaflet is updated accordingly. The RMP version 7.6 has also been submitted. This submission fulfils ANX 016 and Annex II is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make other changes to the Annex II conditions to reflect the fact that ANX/005 has been fulfilled, i.e. the initial ANX 005 commitment has been removed and was replaced by the new ANX 005.1 and ANX005.2 commitments. Moreover, the MAH took the opportunity to introduce minor editorial and formatting revisions in the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				posology and method of administration to provide clarity for physicians regarding timing of the first dose of nivolumab monotherapy following the last dose of nivolumab and ipilimumab combination therapy (section 4.2). The package leaflet is updated accordingly
PSUSA/10379 /201701	Periodic Safety Update EU Single assessment - nivolumab	20/07/2017	18/09/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10379/201701.
II/0019	For further information please refer to the published Assessment Report C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	21/04/2017	02/06/2017	SmPC, Annex II and PL	Extension of Indication to include the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy for OPDIVO. As a consequence, sections 4.1, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to add the proposed indication, add a warning about the patient populations excluded from the clinical trial, and update the safety information. The Package Leaflet is updated in accordance.

					Moreover, the updated RMP version 7.2 has been submitted
IB/0035/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - 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	16/05/2017	18/09/2017	SmPC and PL	
IB/0034	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	02/05/2017	n/a		
II/0017	Extension of Indication to include treatment of squamous cell cancer of the head and neck (SCCHN) in adults progressing on or after platinum-based therapy for OPDIVO as monotherapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, of the SmPC are updated in order to add the proposed new indication, add a warning to recommend careful consideration before initiating treatment with nivolumab in patients excluded from the SCCHN clinical trial (patients with a baseline performance score ≥ 2, untreated brain metastasis, active autoimmune disease, medical conditions requiring systemic immunosuppression, or carcinoma of the nasopharynx or salivary gland as the primary tumour sites) and update the undesirable effect and safety information. Labelling is updated in accordance.	23/03/2017	28/04/2017	SmPC and PL	For further information please refer to the published Assessment Report:

	Moreover, the updated RMP version 6.3 has 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/0024	duration of response with longer follow-up, following completion of PAES CA209037 (Randomized, Open-Label, Phase 3 Trial of nivolumab vs Investigator's Choice in Advanced (Unresectable or Metastatic) Melanoma Patients Progressing Post Anti-CTLA-4 Therapy) and its addendum on predictability of efficacy with biomarkers. This application fulfils ANX 001 and 003.1. Annex II has been updated accordingly. RMP version 5.5 has been submitted within this application. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/04/2017	02/06/2017	SmPC and Annex II	Updated subgroup analysis (24-month follow-up) has been reflected in section 5.1 Pharmacodynamic properties.
II/0031/G	This was an application for a group of variations. 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	30/03/2017	02/06/2017	Annex II and PL	

	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				
PSUSA/10379 /201607	Periodic Safety Update EU Single assessment - nivolumab	26/01/2017	24/03/2017		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10379/201607.
II/0023	Update of sections 4.8 and 5.1 of the SmPC in order to update the safety and pharmacological information with the 24 months data from the completed NSCLC studies CA209017 and CA209057. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/02/2017	28/04/2017	SmPC	The following text was added in sections 4.8 and 5.1 of SmPC 4.8 Undesirable effects Summary of the safety profile In the pooled dataset of nivolumab 3 mg/kg as monotherapy across tumour types (CA209066, CA209037, CA209067 [monotherapy group], CA209017, CA209057, CA209063, CA209025, CA209205, and CA209039), the most frequent adverse reactions (≥ 10%) were fatigue (32%), rash (18%), pruritus (13%), diarrhoea (13%), and nausea (13%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). With a minimum of 24 months follow-up in NSCLC, no new safety signals were identified. 5.1 Pharmacodynamic properties The observed OS benefit was consistently demonstrated across subgroups of patients. Survival benefit was observed regardless of whether patients had tumours that were designated PD-L1 negative or PD-L1 positive (tumour membrane expression cut off of 1%, 5% or 10%). However, the role of this biomarker (tumour PD-L1 expression) has not been fully elucidated. With a minimum of 24.2 months follow-up, OS benefit remains consistently

					demonstrated across subgroups.
II/0022/G	This was an application for a group of variations. 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.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.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.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.e.2.z - Change in the specification parameters	02/02/2017	n/a		

	and/or limits of the immediate packaging of the finished product - Other variation 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.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				
II/0018	Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to update the safety information for toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), myositis, myocarditis and rhabdomyolysis based on findings from routine pharmacovigilance activities. The Package Leaflet is updated accordingly. In addition, the RMP is updated to version 5.6 to reflect this new safety information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/12/2016	27/01/2017	SmPC, Annex II and PL	Following the assessment of causality of individual case reports presented and taking into account the incidence in clinical trials, there is a reasonable possibility that Stevens-Johnson syndrome, Myositis, Myocarditis and Rhabdomyolisis could be associated with the use of nivolumab therapy. Warnings informing of the precaution for use of these risks and specific risk minimization guidance have been in section 4.4. In addition Section 4.2 has been updated to reflect that nivolumab treatment should be discontinued in case of Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or Grade 3 myocarditis.
II/0026	B.I.a.4.d - Change to in-process tests or limits applied during the manufacture of the AS - Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the	19/01/2017	n/a		

	AS				
II/0020	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	22/12/2016	n/a		
IB/0028	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	20/12/2016	24/03/2017	SmPC and PL	
IB/0027/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.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	12/12/2016	n/a		
IB/0025/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.1.b - Change in the specification parameters and/or limits of an AS, starting	05/12/2016	n/a		

	material/intermediate/reagent - Tightening of specification limits 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.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits 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.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits 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				
II/0012	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	13/10/2016	21/11/2016	SmPC, Labelling and PL	For further information please refer to the published Assessment Report: Opdivo H-3985-II-12-AR
PSUSA/10379	Periodic Safety Update EU Single assessment -	02/09/2016	n/a		PRAC Recommendation - maintenance

/201601	nivolumab				
II/0014	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	28/07/2016	21/11/2016	Annex II	
II/0011/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 material [-] used in the manufacture of a biological/immunological product B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - 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.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	14/07/2016	21/11/2016	Annex II	

	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/0016	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	20/06/2016	21/11/2016	Annex II	
II/0015/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.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.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	16/06/2016	n/a		
II/0003	Extension of Indication to include treatment in combination with ipilimumab of advanced	01/04/2016	11/05/2016	SmPC, Annex II and PL	Please refer to the published assessment report Opdivo-H-C-3985-II-0003-AR.

	(unresectable or metastatic) melanoma in adults based on interim data from study CA209067 and the final CSR of study CA209069. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been revised accordingly. In addition, the MAH took the opportunity to implement minor editorial changes in the SmPC, Annex II and Package Leaflet, and to provide a paediatric non-clinical biomarker study as part of the application to fulfil paediatric requirements. Further, an updated RMP version 4.3 was agreed during the procedure and two efficacy measures were added to Annex II upon request by the CHMP. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0008	Extension of Indication to add treatment as monotherapy of patients with advanced renal cell carcinoma (RCC) after prior therapy in adults, based on Study CA209025; a phase 3 study of nivolumab vs. everolimus in subjects with advanced or metastatic clear-cell RCC who have received prior anti-angiogenic therapy, and the CA209010 addendum study report; phase 2 dose-ranging study of nivolumab in subjects with progressive advanced/metastatic clear-cell RCC who have received prior anti-angiogenic therapy. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the	25/02/2016	04/04/2016	SmPC and PL	For further information please refer to the published Assessment Report: Opdivo H-3985-II-08-AR

	SmPC have been updated, and the Package Leaflet and the descriptions and timelines of the 'obligations to conduct post-authorisation measures' in the Annex II have been updated accordingly. In addition, the MAH took the opportunity to make editorial changes in the SmPC and Package Leaflet and to update the contact details of the local representative in France in the Package Leaflet. An updated RMP version 4.1 was agreed during the procedure. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0002	Extension of Indication to include treatment as monotherapy of locally advanced or metastatic non-squamous NSCLC after prior chemotherapy in adults based on study CA209057. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated and the Package Leaflet has been updated accordingly. Further, SmPC section 4.8 has been revised with updated combined clinical trial exposure numbers to reflect inclusion of studies in non-squamous NSCLC and in nivolumab in combination with ipilimumab in advanced melanoma. In addition, the MAH took the opportunity to align the annexes with the latest QRD template version 9.1, to update the agreed post-authorisation measures in Annex II and to implement minor editorial changes. A revised RMP version 4.2 was agreed during the procedure.	25/02/2016	04/04/2016	SmPC, Annex II, Labelling and PL	For further information please refer to the published Assessment Report: Opdivo H-3985-II-02-AR.

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IB/0010/G	This was an application for a group of variations. 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.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	24/02/2016	n/a		
II/0006	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol	04/02/2016	n/a		
IB/0009	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	02/02/2016	n/a		
PSUSA/10379 /201507	Periodic Safety Update EU Single assessment - nivolumab	14/01/2016	n/a		PRAC Recommendation - maintenance
II/0004	Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information with reference to	17/12/2015	04/04/2016	SmPC and PL	Rare cases of toxic epidermal necrolysis (TEN) some of them with fatal outcome have been observed. If symptoms

	the ADR toxic epidermal necrolysis (TEN). The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the contact details of the local representatives in the Package Leaflet. A revised RMP version 2.1 was agreed during the procedure. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				or signs of Stevens-Johnson Syndrome (SJS) or TEN appear, nivolumab treatment should be discontinued and the patient referred to a specialised unit for assessment and treatment. If the patient has developed SJS or TEN with the use of nivolumab, permanent discontinuation of nivolumab is recommended.
II/0001	Extension of indication to include treatment of locally advanced or metastatic squamous non-small cell lung cancer (NSCLC) after prior chemotherapy in adults (in line with the Nivolumab BMS MAA, procedure EMEA/H/C/003840). As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated and the Package Leaflet has been revised accordingly. Further, Annex II has been updated to include a post-authorisation efficacy study as a new obligation in line with the agreed Annex II for Nivolumab BMS. In addition, the MAH took the opportunity to make editorial changes in the SmPC, Annex II, labelling and Package Leaflet. A revised RMP version 2.0 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	24/09/2015	28/10/2015	SmPC, Annex II, Labelling and PL	For further information please refer to the published Assessment Report: Opdivo H-3985-II-01-AR.

IB/0005	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	02/10/2015	n/a		