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
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	14/03/2019	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).

	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)				
IG/1059	A.1 - Administrative change - Change in the name and/or address of the MAH	15/02/2019		SmPC, Labelling and PL	
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 or addition) for the AS or a starting material/intermediate	23/11/2018	n/a		
IB/0059/G	This was an application for a group of variations.	13/11/2018	n/a		

	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				
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 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	28/06/2018	30/07/2018	SmPC and PL	Please refer to Scientific Discussion 'Opdivo-H-C-003985-II-41'

	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 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	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.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 new quality, preclinical, clinical or pharmacovigilance data	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 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 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	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.

	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	22/12/2017	23/03/2018	SmPC	

	medicinal product in accordance with an approved stability protocol				
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 - 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	14/12/2017	n/a		

	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 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		
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.	09/11/2017	23/03/2018	SmPC and Annex II	

	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				
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 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	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 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

	new quality, preclinical, clinical or pharmacovigilance data				
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. 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	23/03/2017	28/04/2017	SmPC and PL	For further information please refer to the published Assessment Report:
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.	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.

	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				
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 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	30/03/2017	02/06/2017	Annex II and PL	
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	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

	data				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	02/02/2017	n/a		

	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 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	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

	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				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 AS	19/01/2017	n/a		
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	12/12/2016	n/a		

	starting material/reagent/intermediate for AS - Other variation				
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 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	05/12/2016	n/a		

	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 /201601	Periodic Safety Update EU Single assessment - nivolumab	02/09/2016	n/a		PRAC Recommendation - maintenance
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	14/07/2016	21/11/2016	Annex II	

	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/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	16/06/2016	n/a		

	replacement or addition)				
II/0003	Extension of Indication to include treatment in combination with ipilimumab of advanced (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	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.
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	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

	consequence, sections 4.1, 4.4, 4.8 and 5.1 of the 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 the ADR toxic epidermal necrolysis (TEN). The Package	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 or signs of Stevens-Johnson Syndrome (SJS) or TEN appear,

	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				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	02/10/2015	n/a		

	the AS or a starting material/intermediate				