



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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 |
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| PSUSA/10379 /202407 | Periodic Safety Update EU Single assessment - nivolumab | 27/02/2025 | 23/04/2025 | SmPC and PL | Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10379/202407. |
| II/0149 | Submission of the final clinical study report (CSR) for the PASS study CA209234 listed as a category 3 study in the RMP. This is an observational, | 13/03/2025 | 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).



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| | <p>multicenter, prospective study in patients treated with nivolumab for melanoma and lung cancer in order assess the safety experience, survival, adverse event management, and outcomes of adverse events associated with nivolumab (monotherapy or with ipilimumab) in routine oncology care facilities. The RMP version 42.1 has also been submitted.</p> <p>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority</p> | | | | |
| WS/2717 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>A Worksharing application for OPDIVO and YERVOY, as follows:</p> <p>Extension of indication to include a new indication for OPDIVO in combination with ipilimumab as first line treatment of adult patients with unresectable or advanced hepatocellular carcinoma (HCC) based on study CA2099DW. This is a phase 3 randomised, multi-centre, open label study of Nivolumab in combination with Ipilimumab compared to Sorafenib or Lenvatinib as first-line treatment in participants with advanced HCC. 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 41.1 of the RMP has also been submitted.</p> | 30/01/2025 | 28/02/2025 | SmPC, Annex II and PL | Please refer to Scientific Discussion 'Opdivo-Yervoy WS-2717' |

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| | <p>Extension of indication to include a new indication for YERVOY in combination with ipilimumab as first line treatment of adult patients with unresectable or advanced hepatocellular carcinoma (HCC) based on study CA2099DW. This is a phase 3 randomised, multi-centre, open label study of Nivolumab in combination with Ipilimumab compared to Sorafenib or Lenvatinib as first-line treatment in participants with advanced HCC. 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 44.2 of the RMP has also been submitted. In addition the MAH implemented some minor changes to annex II.D.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p> | | | | |
| WS/2672 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>A Worksharing application for OPDIVO and YERVOY, as follows:</p> <p>Extension of indication to include OPDIVO in combination with ipilimumab in the first-line treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) unresectable or metastatic colorectal cancer, based on interim results from study CA2098HW; this</p> | 14/11/2024 | 19/12/2024 | SmPC and PL | Please refer to Scientific Discussion "WS-2672 - Opdivo-Yervoy" |

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| | <p>is a phase 3 randomised clinical trial of nivolumab alone, nivolumab in combination with ipilimumab, or investigator's choice chemotherapy in participants with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer. 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 37.2 of the RMP has also been submitted.</p> <p>Extension of indication to include YERVOY in combination with nivolumab in the first-line treatment of adult patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) unresectable or metastatic colorectal cancer, based on interim results from study CA2098HW; this is a phase 3 randomised clinical trial of nivolumab alone, nivolumab in combination with ipilimumab, or investigator's choice chemotherapy in participants with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer. 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 42.1 of the RMP has also been submitted. The worksharing procedure leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p> | | | | |
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| IB/0150 | C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | 17/12/2024 | n/a | | |
| IAIN/0152 | B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site | 28/11/2024 | n/a | | |
| IB/0147 | B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS | 20/09/2024 | n/a | | |
| IB/0143 | C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | 03/07/2024 | 19/12/2024 | Annex II | |
| IAIN/0145/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 | 28/06/2024 | 19/12/2024 | SmPC and PL | |
| 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 | 19/12/2024 | Annex II | |
| II/0137 | Extension of indication to include OPDIVO in combination with cisplatin and gemcitabine for the first-line treatment of adult patients with unresectable or metastatic urothelial carcinoma, | 25/04/2024 | 23/05/2024 | SmPC and PL | Please refer to Scientific Discussion: Opdivo-H-C-3985-II-0137. |

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| | <p>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.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p> | | | | |
| 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 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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 accordingly. In addition, the MAH took the opportunity to implement editorial changes to the SmPC in line with the QRD.</p> | 15/02/2024 | 23/05/2024 | SmPC and PL | |

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| | 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 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 | 20/07/2023 | 21/08/2023 | SmPC, Annex II and PL | Please refer to Scientific Discussion 'Opdivo-H-C-3985-II-0130' |

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| | <p>Package Leaflet are updated in accordance. Version 33.1 of the RMP has also been submitted.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p> | | | | |
| II/0117 | <p>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.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p> | 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 | <p>This was an application for a group of variations.</p> <p>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</p> | 26/04/2023 | 31/05/2023 | SmPC and PL | Please refer to Scientific Discussion 'Opdivo-H-C-3985-II-0125' |

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| | <p>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.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p> | | | | |
| 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 | 16/03/2023 | n/a | | Not applicable |

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| | <p>registry study in patients who underwent post-nivolumab allogeneic haematopoietic 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.</p> <p>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority</p> | | | | |
| 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 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p> | 27/10/2022 | 24/04/2023 | SmPC and PL | <p>Not applicable</p> <p>Please refer to the Summary of Product Characteristics.</p> |

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| | <p>has been previously reviewed by the CHMP.</p> <p>The updated Opdivo RMP version 29.0 and Yervoy RMP version 37.0 have also been submitted.</p> <p>The MAH took the opportunity to introduce editorial changes.</p> <p>The Package Leaflet was updated accordingly.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> | | | | |
| II/0124/G | <p>This was an application for a group of variations.</p> <p>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</p> <p>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS</p> | 06/10/2022 | n/a | | |
| WS/2289 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p> | 01/09/2022 | 24/04/2023 | SmPC | <p>A statistically significant improvement in OS was observed with nivolumab monotherapy (HR 0.63 [95% CI: 0.52, 0.77]) and the combination of nivolumab + ipilimumab (HR 0.53 [95% CI: 0.44, 0.65]) over ipilimumab. Median OS for all randomized subjects was 72.08 months (95% CI: 38.18, 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%),</p> |

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| | <p>ipilimumab versus ipilimumab monotherapy in subjects with previously untreated, unresectable melanoma.</p> <p>MAH has taken the opportunity to introduce minor editorial revisions in the SmPC.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> | | | | <p>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.</p> <p>For more information, please refer to the Summary of Product Characteristics.</p> |
| 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 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of sections 4.2 and 6.6 of the SmPC to</p> | 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 |

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| | <p>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.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> | | | | to the Summary of Product Characteristics. |
| WS/2113 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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 $\geq 1\%$ 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 Yervoy RMP have also been submitted.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p> | 24/02/2022 | 01/04/2022 | SmPC and PL | OPDIVO/Yervoy-H-C-3985/2213/WS/2113' |
| II/0107 | <p>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</p> | 24/02/2022 | 01/04/2022 | SmPC and PL | Please refer to Scientific Discussion 'OPDIVO-H-C/003985/II-0107' |

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| | <p>metastatic oesophageal squamous cell carcinoma (OSCC) with tumour cell PD-L1 expression $\geq 1\%$ 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.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p> | | | | |
| II/0100 | <p>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 $\geq 1\%$, 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 RMP has also been submitted.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p> | 24/02/2022 | 01/04/2022 | SmPC, Annex II and PL | Please refer to Scientific Discussion 'OPDIVO-H-C-3985-II-0100' |
| 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 | | |

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| IAIN/0116/G | <p>This was an application for a group of variations.</p> <p>A.6 - Administrative change - Change in ATC Code/ATC Vet Code</p> <p>A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release</p> | 09/02/2022 | 01/04/2022 | SmPC, Annex II and PL | |
| WS/2170 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> | 13/01/2022 | 01/04/2022 | SmPC | <p>SmPC new text:</p> <p>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.</p> <p>For more information, please refer to the Summary of Product Characteristics.</p> |
| 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 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of sections 4.2, 4.8, and 5.1 of the SmPC</p> | 28/10/2021 | 01/04/2022 | SmPC | <p>SmPC new text:</p> <p>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.</p> |

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| | <p>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.</p> <p>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</p> | | | | <p>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.</p> |
| II/0106/G | <p>This was an application for a group of variations.</p> <p>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</p> <p>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</p> <p>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</p> <p>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</p> <p>B.II.b.5.b - Change to in-process tests or limits</p> | 28/10/2021 | 01/04/2022 | SmPC, Labelling and PL | <p>The SmPC section 2 has been updated as follows: One vial of 12 mL contains 120 mg of nivolumab.</p> <p>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 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.</p> <p>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.</p> <p>The SmPC section 8 has been updated as follows: EU/1/15/1014/004</p> |

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| | applied during the manufacture of the finished product - Addition of a new test(s) and limits | | | | The Labelling and PL have been updated accordingly. |
| II/0096 | <p>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.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p> | 16/09/2021 | 19/10/2021 | SmPC and PL | Please refer to Scientific Discussion 'Opdivo-H-C-3985-II-0096' |
| IA/0113/G | <p>This was an application for a group of variations.</p> <p>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</p> <p>A.7 - Administrative change - Deletion of manufacturing sites</p> | 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 | 02/09/2021 | 19/10/2021 | SmPC and | Cases of acute graft versus host disease (GVHD) and transplant related mortality (TRM) have been observed |

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| | <p>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.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> | | | Annex II | <p>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).</p> <p>For more information, please refer to the Summary of Product Characteristics.</p> |
| 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 | <p>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 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.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p> | 24/06/2021 | 28/07/2021 | SmPC, Annex II and PL | Please refer to Scientific Discussion 'Opdivo-H-C-3985-II-0095'. |
| 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 | | |

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| WS/1840 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p> | 20/05/2021 | 24/06/2021 | SmPC and PL | Please refer to Scientific Discussion 'Opdivo, Yervoy-H-C-3985 & 2213-WS-1840' |
| 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 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation</p> | 10/06/2021 | 28/07/2021 | Annex II | |

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| WS/1881 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p> | 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 |
| 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 | 25/02/2021 | 13/04/2021 | SmPC and PL | Please refer to Scientific Discussion 'Opdivo-H-C-3985-II-0092' |

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| | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | | | | |
| II/0098 | <p>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 IIb/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 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.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> | 11/03/2021 | 01/06/2021 | SmPC, Annex II and PL | <p>SmPC new text</p> <p>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.</p> <p>For more information, please refer to the Summary of Product Characteristics.</p> |
| 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 | 14/01/2021 | n/a | | |

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| | the AS -replacement or addition of a site where batch control/testing takes place | | | | |
| 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 | <p>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. 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.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p> | 15/10/2020 | 20/11/2020 | SmPC and PL | Please refer to Scientific Discussion "Opdivo-H-C-3985-II-0080". |
| WS/1783 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p> | 17/09/2020 | 05/11/2020 | SmPC and PL | Please refer to Scientific Discussion 'OPDIVO-H-C-3985 & Yervoy-H-C-2213-WS-1783. |

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| | <p>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.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p> | | | | |
| 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 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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).</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> | 23/07/2020 | 05/11/2020 | SmPC | <p>SmPC new text</p> <p>After 60 months of follow-up, median durations of response for patients with tumour PD L1 expression level $\geq 5\%$ 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.</p> <p>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%</p> |

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| | | | | | <p>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.</p> <p>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).</p> <p>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.</p> <p>For more information, please refer to the Summary of</p> |
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| 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 | Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of |

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| | | | | and PL | <p>OPDIVO in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.</p> <p>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.</p> |
| 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 | <p>This was an application for a group of variations.</p> <p>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</p> <p>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</p> <p>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</p> | 23/01/2020 | 23/04/2020 | Annex II | <p>The Annex II has been updated with the inclusion of the following new active substance manufacturer:</p> <p>Swords Laboratories t/a Bristol-Myers Squibb Cruiserath Biologics, Cruiserath Road, Mulhuddart, Dublin</p> |

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| WS/1714 | <p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> | 12/12/2019 | 20/01/2020 | SmPC | The diagnosis of myocarditis requires a high index of suspicion. Patients with cardiac or cardio-pulmonary symptoms should be assessed for potential myocarditis. If myocarditis is suspected, prompt initiation of a high dose of steroids (prednisone 1 to 2 mg/kg/day or methylprednisolone 1 to 2 mg/kg/day) and prompt cardiology consultation with diagnostic workup according to current clinical guidelines should be initiated. Once a diagnosis of myocarditis is established, nivolumab or nivolumab in combination with ipilimumab should be withheld (grade 2 myocarditis) until symptoms resolve and management with corticosteroids is complete or permanently discontinued (grade 3 myocarditis). |
| PSUSA/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 | 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. |

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| | <p>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).</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> | | | | For more information, please refer to the Summary of Product Characteristics. |
| II/0069 | <p>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.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> | 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 | <p>This was an application for a group of variations.</p> <p>B.II.b.5.c - Change to in-process tests or limits</p> | 12/09/2019 | n/a | | |

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| | <p>applied during the manufacture of the finished product - Deletion of a non-significant in-process test</p> <p>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</p> | | | | |
| IA/0072/G | <p>This was an application for a group of variations.</p> <p>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)</p> <p>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)</p> | 30/08/2019 | n/a | | |
| IB/0071 | <p>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</p> | 08/08/2019 | n/a | | |
| IAIN/0070 | <p>B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site</p> | 11/06/2019 | n/a | | |

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| 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 | <p>This was an application for a group of variations.</p> <p>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 (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).</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> | 26/04/2019 | 27/05/2019 | SmPC and Annex II | <p>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 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.</p> <p>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</p> |

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| | | | | | 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 | 15/11/2018 | 11/01/2019 | SmPC and PL | Please refer to the published assessment report Opdivo- |

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| | <p>worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Extension of indication to include the combination treatment with nivolumab and ipilimumab of adult patients with intermediate/poor-risk advanced renal cell carcinoma. As a consequence sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the Opdivo and Yervoy SmPCs were proposed to be updated. The Package Leaflet and the Risk Management Plan (version 19.0 for Yervoy and version 13.0 for Opdivo) were proposed to be updated in accordance. In addition, the Worksharing applicant (WSA) would take the opportunity to correct some typos throughout the Yervoy and Opdivo product information.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p> | | | | Yervoy H-C-WS-1278: EPAR – Assessment Report - Variation |
| II/0057 | <p>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).</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> | 13/12/2018 | 28/03/2019 | SmPC | <p>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.</p> <p>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.</p> |

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| IB/0058/G | <p>This was an application for a group of variations.</p> <p>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS</p> <p>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</p> | 23/11/2018 | n/a | | |
| IB/0059/G | <p>This was an application for a group of variations.</p> <p>B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation</p> <p>B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure</p> | 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, | 28/06/2018 | 30/07/2018 | SmPC and PL | Please refer to Scientific Discussion 'Opdivo-H-C-003985-II-41' |

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| | <p>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.</p> <p>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.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p> | | | | |
| IB/0054/G | <p>This was an application for a group of variations.</p> <p>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits</p> <p>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits</p> <p>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</p> | 19/06/2018 | n/a | | |

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| II/0051/G | <p>This was an application for a group of variations.</p> <p>A.7 - Administrative change - Deletion of manufacturing sites</p> <p>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</p> <p>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</p> <p>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</p> <p>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</p> | 17/05/2018 | 30/07/2018 | SmPC, Labelling and PL | <p>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.</p> <p>Annex A, Labelling and Package Leaflet (PL) are updated accordingly.</p> |
| II/0047 | <p>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.</p> <p>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"</p> | 26/04/2018 | 30/07/2018 | SmPC, Annex II and PL | <p>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.</p> <p>Section 4.4 of the SmPC has been modified as follows: Complications of allogeneic Haematopoietic Stem Cell Transplant (HSCT) in classical Hodgkin Lymphoma</p> |

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| | <p>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.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> | | | | <p>(...) 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).</p> <p>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.</p> |
| II/0036/G | <p>This was an application for a group of variations.</p> <p>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:</p> <ul style="list-style-type: none"> - 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. <p>These changes are based on comparison of the</p> | 22/03/2018 | 23/04/2018 | SmPC and PL | <p>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.</p> <p>See sections 4.2, 5.1, 5.2 and 6.6 of the SmPC for details. The PL has been updated accordingly.</p> |

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| | <p>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.</p> <p>The Package Leaflet is updated accordingly.</p> <p>An updated RMP (version 10.1) has also been presented</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> | | | | |
| 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 | |

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| 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 | <p>This was an application for a group of variations.</p> <p>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</p> <p>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</p> | 22/12/2017 | 23/03/2018 | SmPC | |
| IB/0044/G | <p>This was an application for a group of variations.</p> <p>B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure</p> <p>B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure</p> <p>B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure</p> | 20/12/2017 | n/a | | |

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| II/0037/G | <p>This was an application for a group of variations.</p> <p>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</p> <p>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS</p> <p>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</p> <p>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</p> <p>B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits</p> <p>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</p> <p>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</p> | 14/12/2017 | n/a | | |
| IB/0043/G | <p>This was an application for a group of variations.</p> <p>B.I.b.1.b - Change in the specification parameters</p> | 12/12/2017 | n/a | | |

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| | 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 | | | | |
| 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 | 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 |

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| | <p>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.</p> <p>The RMP version 7.6 has also been submitted. This submission fulfils ANX 016 and Annex II is updated accordingly.</p> <p>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.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> | | | | <p>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</p> |
| 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 | <p>For further information please refer to the published Assessment Report</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p> | 21/04/2017 | 02/06/2017 | SmPC, Annex II and PL | <p>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.</p> <p>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</p> |

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| | | | | | 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 | <p>This was an application for a group of variations.</p> <p>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation</p> <p>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation</p> <p>C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation</p> | 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 | <p>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.</p> <p>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</p> | 23/03/2017 | 28/04/2017 | SmPC and PL | For further information please refer to the published Assessment Report: |

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| | <p>sites) and update the undesirable effect and safety information. Labelling is updated in accordance. Moreover, the updated RMP version 6.3 has been submitted.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p> | | | | |
| II/0024 | <p>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.</p> <p>This application fulfils ANX 001 and 003.1. Annex II has been updated accordingly.</p> <p>RMP version 5.5 has been submitted within this application.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> | 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 | <p>This was an application for a group of variations.</p> <p>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 bio/immunol product and any of the test methods at the site is a</p> | 30/03/2017 | 02/06/2017 | Annex II and PL | |

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| | <p>biol/immunol method</p> <p>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</p> | | | | |
| 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 | <p>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.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> | 23/02/2017 | 28/04/2017 | SmPC | <p>The following text was added in sections 4.8 and 5.1 of SmPC</p> <p>4.8 Undesirable effects</p> <p>Summary of the safety profile</p> <p>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 ($\geq 10\%$) 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.</p> <p>5.1 Pharmacodynamic properties</p> <p>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</p> |

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| | | | | | of 24.2 months follow-up, OS benefit remains consistently demonstrated across subgroups. |
| II/0022/G | <p>This was an application for a group of variations.</p> <p>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</p> <p>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</p> <p>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</p> <p>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</p> <p>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</p> | 02/02/2017 | n/a | | |

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| | <p>B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation</p> <p>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</p> <p>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</p> | | | | |
| II/0018 | <p>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.</p> <p>In addition, the RMP is updated to version 5.6 to reflect this new safety information.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> | 15/12/2016 | 27/01/2017 | SmPC, Annex II and PL | <p>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 Rhabdomyolysis 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.</p> |
| II/0026 | <p>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</p> | 19/01/2017 | n/a | | |

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| | 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 | <p>This was an application for a group of variations.</p> <p>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</p> <p>B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation</p> | 12/12/2016 | n/a | | |
| IB/0025/G | <p>This was an application for a group of variations.</p> <p>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits</p> <p>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of</p> | 05/12/2016 | n/a | | |

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| | <p>specification limits</p> <p>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits</p> <p>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits</p> <p>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits</p> <p>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits</p> <p>B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits</p> <p>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</p> | | | | |
| 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 |

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| 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 | <p>This was an application for a group of variations.</p> <p>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</p> <p>B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits</p> <p>B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation</p> <p>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</p> <p>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</p> <p>B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement</p> | 14/07/2016 | 21/11/2016 | Annex II | |

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| | 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 | <p>This was an application for a group of variations.</p> <p>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits</p> <p>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</p> <p>B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)</p> <p>B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)</p> | 16/06/2016 | n/a | | |
| 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 | 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. |

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| | <p>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.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p> | | | | |
| II/0008 | <p>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 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</p> | 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 |

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| | <p>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.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p> | | | | |
| II/0002 | <p>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.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p> | 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. |

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| IB/0010/G | <p>This was an application for a group of variations.</p> <p>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)</p> <p>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process</p> | 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 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. | 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, 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 |

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| | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | nivolumab is recommended. |
| II/0001 | <p>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.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p> | 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 | | |