Keytruda

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
II/0154	Extension of indication to include in combination with pemetrexed and platinum chemotherapy the first-line treatment of adults with unresectable non-epithelioid malignant pleural mesothelioma for Keytruda, based on final results from study KEYNOTE-483; this is a multicenter, open-label,	27/02/2025	04/04/2025	SmPC and PL	Please refer to Scientific Discussion 'Keytruda-II-0154'

[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).

	Phase 2/3 randomized study to evaluate the efficacy and safety of pembrolizumab in combination with pemetrexed/platinum chemotherapy in participants with unresectable advanced or metastatic malignant pleural mesothelioma (MPM). As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 45.0 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0165	C.I.13: Submission of the final safety analysis report of participants with hematologic malignancies enrolled in MSD Sponsored studies who received an allogenic hematopoietic stem cell transplantation (HSCT) following therapy with pembrolizumab. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	13/03/2025	n/a		
IB/0164	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	31/01/2025	04/04/2025	SmPC, Labelling and PL	
II/0162	B.I.a.4.e - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of an in-process test which may have a significant effect on the overall quality of the AS	05/12/2024	04/04/2025	SmPC and PL	The SmPC section 6.3 has been updated to delete the instruction 'Protect from light'. The Package Leaflet (PL) is updated accordingly.

II/0161	Update of sections 4.4 and 4.8 of the SmPC in order to update information on pericarditis and include the risk of pericarditis under the section "Other immune-mediated adverse reactions" based on post-marketing data and literature. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	05/12/2024	04/04/2025	SmPC and PL	
II/0160	Update of section 5.1 of the SmPC in order to update information based on the Interim Analysis 7 (IA7) results from the P522V05MK3475 (KEYNOTE-522) study. This is a Phase 3 randomized, double-blind study to evaluate pembrolizumab plus chemotherapy vs placebo plus chemotherapy as neoadjuvant therapy and pembrolizumab vs placebo as adjuvant therapy for triple negative breast cancer (TNBC). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/11/2024	04/04/2025	SmPC	SmPC new text At a median follow up time for all patients of 73.1 months (range: 2.7 - 83.9 months), statistical significance was reached in the secondary endpoint OS with HR 0.66; 95%CI: 0.50, 0.87; p=0.00150. Updated descriptive EFS analysis at IA7 was also provided with HR 0.65; 95%CI: 0.51, 0.83. For more information, please refer to the Summary of Product Characteristics.
II/0153	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	19/09/2024	21/10/2024	SmPC and PL	
II/0145	Extension of indication to include in combination with chemoradiotherapy (external beam radiation therapy followed by brachytherapy), the treatment of FIGO	19/09/2024	21/10/2024	SmPC and PL	

	2014 Stage III - IVA locally advanced cervical cancer in adults who have not received prior definitive therapy for Keytruda, based on the results from pivotal Phase III study KEYNOTE-A18. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet and the Risk Management Plan version 44 are updated in accordance. The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0155	B.I.e.2 - Introduction of a post approval change management protocol related to the AS	10/10/2024	n/a		
IB/0158	B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	03/10/2024	n/a		
IB/0159/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor	25/09/2024	n/a		

	changes to an approved test procedure				
II/0150	Extension of indication to include Keytruda in combination with enfortumab vedotin for the first-line treatment of locally advanced or metastatic urothelial carcinoma in adults, based on the final results from KEYNOTE-A39/EV-302: "An open label, randomized, controlled phase 3 study of enfortumab vedotin in combination with pembrolizumab versus chemotherapy alone in previously untreated locally advanced (LA) or metastatic urothelial cancer (mUC)". 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 45.1 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	25/07/2024	29/08/2024	SmPC and PL	Please refer to Scientific Discussion 'Keytruda EMEA/H/C/003820/II/0150'.
IB/0156	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)	08/07/2024	29/08/2024	SmPC, Labelling and PL	
IAIN/0157	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/06/2024	29/08/2024	SmPC and PL	
II/0152	Update of section 5.1 of the SmPC in order to update efficacy information based on interim results from study KEYNOTE-564; this is a phase 3, randomized, double-blind, placebo-controlled clinical trial of pembrolizumab as monotherapy in the adjuvant	02/05/2024	29/08/2024	SmPC	Efficacy results from KEYNOTE-564, with a median follow up time of 55.8 months, confirmed the improvement in DFS compared with placebo (HR: 0.72 [95% CI: 0.59, 0.87]), and showed a statistically significant improvement in OS with an HR of 0.62 (95% CI: 0.44, 0.87; p=0.0024, 1-

	treatment of renal cell carcinoma post nephrectomy. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				sided). For more information, please refer to the Summary of Product Characteristics.
II/0149	B.I.e.2 - Introduction of a post approval change management protocol related to the AS	02/05/2024	n/a		
PSUSA/10403 /202309	Periodic Safety Update EU Single assessment - pembrolizumab	11/04/2024	n/a		PRAC Recommendation - maintenance
II/0134	Extension of indication to include in combination with platinum-containing chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant, for the treatment of resectable non small cell lung carcinoma at high risk of recurrence in adults ,for Keytruda based on study KEYNOTE-671, a phase III, randomized, double-blind trial of platinum doublet chemotherapy +/- pembrolizumab as neoadjuvant/adjuvant therapy for participants with resectable stage II, IIIA, and resectable IIIB (T3-4N2) non-small cell lung 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 42 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	22/02/2024	25/03/2024	SmPC and PL	Please refer to Scientific Discussion 'Keytruda-3820-II-0134'

II/0147	Update of section 5.1 of the SmPC in order to update efficacy information based on final results from study KEYNOTE-B61; this is a Phase 2, Single-arm, Open-label Clinical Trial of Pembrolizumab Plus Lenvatinib in Participants with First-line Advanced/Metastatic Non-clear Cell Renal Cell Carcinoma (nccRCC). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/03/2024	29/08/2024	SmPC	Additional data are available from the open-label single arm Phase II study KEYNOTE-B61 of pembrolizumab (400 mg every 6 weeks) in combination with lenvatinib (20 mg OD) for the first-line treatment of patients with advanced or metastatic RCC with non-clear cell histology (n=158), including 59% papillary, 18% chromophobe, 4% translocation, 1% medullary, 13% unclassified, and 6% other. The ORR was 50.6% (95% CI: 42.6, 58.7) and the median duration of response was 19.5 months (95% CI: 15.3, NR).
IB/0148	B.I.z - Quality change - Active substance - Other variation	29/02/2024	n/a		
IB/0151/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.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	15/02/2024	n/a		
II/0144	B.II.h.1.b.1 - Update to the Adventitious Agents Safety Evaluation information - Replacement of obsolete studies related to manufacturing steps and adventitious agents already reported in the dossier -	15/02/2024	n/a		

	with modifications of risk assessment				
II/0138	Extension of indication to include KEYTRUDA in combination with gemcitabine and cisplatin for the first-line treatment of locally advanced unresectable or metastatic biliary tract carcinoma in adults, based on final results from study KEYNOTE-966; this is a Phase 3 randomized, double blind study of Pembrolizumab plus Gemcitabine/Cisplatin versus Placebo plus Gemcitabine/Cisplatin as first-line therapy in participants with advanced and/or unresectable biliary tract carcinoma. As a consequence, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 41.0 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	09/11/2023	11/12/2023	SmPC and PL	Please refer to Scientific Discussion 'Keytruda-H-C-3820-II-0138'
II/0143	B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method	07/12/2023	n/a		
II/0135	Extension of indication to include in combination with chemotherapy the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastrooesophageal junction adenocarcinoma in adults whose tumours express PD	12/10/2023	23/11/2023	SmPC and PL	Please refer to Scientific Discussion 'Keytruda-H-C-003820-II-0135'

	L1 with a CPS ≥ 1 based on study KEYNOTE-859, a randomised, double-blind phase 3 trial, evaluating KEYTRUDA in combination with chemotherapy compared to placebo in combination with chemotherapy for the first-line treatment of patients with HER2-negative locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma. As a consequence sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 40.0 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0139	Update of section 5.1 of the SmPC in order to update clinical information, based on results from study KEYNOTE-716 listed as a PAES in the Annex II. This is a randomized, double-blind phase 3 study of adjuvant therapy with pembrolizumab versus placebo in resected high-risk stage II melanoma. The Annex II is updated accordingly C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/11/2023	11/12/2023	SmPC and Annex II	SmPC new text Results reported from the pre-specified final analysis for DMFS at a median follow-up time of 38.5 months showed a Hazard ratio of 0.59 (95% CI 0.44, 0.79). For more information, please refer to the Summary of Product Characteristics.
II/0121	Extension of indication to include Keytruda as monotherapy for the adjuvant treatment of adults with non-small cell lung carcinoma who are at high risk of recurrence following complete resection and	14/09/2023	12/10/2023	SmPC, Annex II and PL	Please refer to Scientific Discussion 'Keytruda-H-C-003820-II-0121'

	platinum-based chemotherapy based on study KEYNOTE-091; an ongoing Phase 3, randomized, triple-blinded, placebo-controlled, multicentre study of pembrolizumab versus placebo in patients with early-stage NSCLC after resection and completion of standard adjuvant therapy. As a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC are being updated and the Annex II and the Package Leaflet are updated in accordance. An updated RMP version 39.0 was also submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0141	Update of section 5.1 of the SmPC in order to update efficacy information based on final results from study KEYNOTE-826; this is a phase 3 randomized, double-blind, placebo-controlled trial of pembrolizumab (MK-3475) plus chemotherapy versus chemotherapy plus placebo for the first-line treatment of persistent, recurrent, or metastatic cervical cancer. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/09/2023	12/10/2023	SmPC	SmPC new text: In the final analysis of KEYNOTE 826 with a median duration of follow up of 21.3 months, in patients whose tumours expressed PD-L1 with a CPS ≥ 1, PFS HR by investigator was 0.58 (95%CI 0.47, 0.71), with median PFS 10.5 vs 8.2 months and with OS HR of 0.60 (05%CI 0.49, 0.74). For more information, please refer to the Summary of Product Characteristics.
II/0136	Update of sections 5.1 of the SmPC in order to provide the final OS data (including analyses/KM plots from favourable prognosis subgroups) following	31/08/2023	12/10/2023	SmPC and Annex II	SmPC new text: Efficacy results for KEYNOTE 581 (CLEAR) at the protocol specified final analysis with median follow-up time of 49.4

	the assessment of procedure II/0104, based on results from study E7080-G000-307/KEYNOTE 581 (REC); A Multicenter, Open-label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Everolimus or Pembrolizumab Versus Sunitinib Alone in First-Line Treatment of Subjects with Advanced Renal Cell Carcinoma (CLEAR). In addition, the due date for the final study report of Keynote 054 was updated in Annex II. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				months showed an OS HR for lenvatinib plus pembrolizumab vs sunitinib of 0.79 (95% CI: 0.63, 0.99). Updated PFS and ORR results were overall consistent with the initial data. For more information, please refer to the Summary of Product Characteristics.
II/0133	Extension of indication to include in combination with trastuzumab, fluoropyrimidine and platinum-containing chemotherapy for treatment of locally advanced unresectable or metastatic HER2- positive gastric or gastro-oesophageal junction adenocarcinoma for Keytruda, based on interim results from study KEYNOTE-811, an ongoing Phase 3, double-blind trial comparing trastuzumab plus chemotherapy and pembrolizumab with trastuzumab plus chemotherapy and placebo as first-line treatment in participants with HER2-positive advanced gastric or gastro-oesophageal junction adenocarcinoma; As a consequence, sections 4.1, 4.8, and 5.1 of the SmPC are updated. The Annex II, Package Leaflet and Labelling are updated in accordance. Version 38 of the RMP has also been submitted.	20/07/2023	23/08/2023	SmPC, Annex II and PL	Please refer to Scientific Discussion 'Keytruda-H-C-3820-II-0133'

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IB/0137/G	This was an application for a group of variations. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.z - Quality change - Active substance - Other variation B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product 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	04/08/2023	12/10/2023	Annex II	
IA/0142	A.7 - Administrative change - Deletion of manufacturing sites	26/07/2023	n/a		

IB/0140/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test	11/07/2023	n/a		
PSUSA/10403 /202209	Periodic Safety Update EU Single assessment - pembrolizumab	14/04/2023	n/a		PRAC Recommendation - maintenance
II/0132	Update of section 4.8 of the SmPC in order to add optic neuritis to the list of adverse drug reactions (ADRs) with frequency rare based on literature review. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to introduce editorial changes to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	16/03/2023	23/08/2023	SmPC and PL	
II/0128	Update of section 5.1 of the SmPC in order to update information based on the final OS data for the overall population as well as for MMR subgroups from study 309/KEYNOTE-775 in order to fulfil the Recommendation: REC/033. This Recommendation was agreed to with the approval of study 309/KEYNOTE-775; this is a multicenter, open-label, randomized, phase 3 trial to compare the efficacy	09/03/2023	23/08/2023	SmPC	The results from the final analysis, with additional 16 months of follow-up, are overall consistent with the interim data submitted for Study 309/KEYNOTE-775. For more information, please refer to the Summary of Product Characteristics.

	and safety of lenvatinib in combination with pembrolizumab versus treatment of physician's choice in participants with advanced endometrial cancer. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0131	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	09/01/2023	n/a		
IAIN/0130	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	17/11/2022	23/08/2023	Annex II and PL	
II/0126	To update sections 4.2 and 5.2 of the SmPC to include data for patients with moderate hepatic impairment based on KEYNOTE-240 (a double-blind, randomized, Phase 3 study of pembrolizumab in participants with previously systemically treated advanced HCC) and KEYNOTE-224 (a Phase 2 study of pembrolizumab as monotherapy in participants with advanced HCC). The MAH took the opportunity to make some editorial changes. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/09/2022	14/10/2022	SmPC	SmPC new text: No dose adjustment is needed for patients with mild or moderate hepatic impairment. For more information, please refer to the Summary of Product Characteristics.

IA/0127	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	13/07/2022	n/a		
II/0111	Extension of indication to include the adjuvant treatment of adults and adolescents aged 12 years and older with Stage IIB, Stage IIC or stage III melanoma and to inlcude the treatment of adolescents aged 12 years and older with advanced melanoma for Keytruda; 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 37 of the RMP has also been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce editorial improvements in the wording of the indication for MSI-H or dMMR cancers in section 4.1 of the SmPC and update the list of local representatives in the Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	19/05/2022	22/06/2022	SmPC, Annex II and PL	Please refer to Scientific Discussion 'Keytruda-H-C-3820-II-0111'
PSUSA/10403 /202109	Periodic Safety Update EU Single assessment - pembrolizumab	22/04/2022	21/06/2022	PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10403/202109.
II/0122	Update of sections 4.4 and 4.8 of the SmPC in order to add a new warning for 'Hypoparathyroidism' and to add it to the list of adverse drug reactions (ADRs) with frequency rare based on literature references; the Package Leaflet is updated accordingly.	16/06/2022	14/10/2022	SmPC and PL	Not applicable

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0125	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	02/06/2022	n/a		
II/0110	Extension of indication for Keytruda in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery of adults with locally advanced, or early-stage triple-negative breast cancer at high-risk of recurrence; 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 36.0 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	22/04/2022	19/05/2022	SmPC and PL	Please refer to Scientific Discussion 'Keytruda-H-C-3820-II-0110'
IB/0123	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	17/05/2022	n/a		
II/0117	Extension of indication to include a new indication for Keytruda, in combination with chemotherapy, with or	24/03/2022	25/04/2022	SmPC, Annex	Please refer to Scientific Discussion 'Keytruda-H-C-3820-II-

	without bevacizumab, for the treatment of persistent, recurrent, or metastatic cervical cancer in adults; as a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 35 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one			II and PL	0117’
II/0109	Extension of indication for KEYTRUDA as monotherapy for the treatment of the following MSI H or dMMR tumours in adults with: -unresectable or metastatic colorectal cancer after previous fluoropyrimidine based combination therapy; -advanced or recurrent endometrial carcinoma, who have disease progression on or following prior treatment with a platinum containing therapy in any setting and who are not candidates for curative surgery or radiation; -unresectable or metastatic gastric, small intestine, or biliary cancer, who have disease progression on or following at least one prior therapy. The proposed indication is based on the results from the KEYNOTE-164 (KN164) and KEYNOTE-158 (KN158) trials. 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. An updated version of the RMP (Version 35) has been submitted. C.I.6.a - Change(s) to therapeutic indication(s) -	24/03/2022	25/04/2022	SmPC, Annex II and PL	Please refer to Scientific Discussion ‘Keytruda-H-C-3820-II-0109’

	Addition of a new therapeutic indication or modification of an approved one				
IA/0124/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	21/04/2022	n/a		
II/0115	Update of section 5.1 of the SmPC in order to update efficacy information based on final results from study KEYNOTE-426 listed as imposed PAES in the Annex II; this is a Phase III Randomized, Open-label Study to Evaluate Efficacy and Safety of Pembrolizumab (MK-3475) in combination with Axitinib versus Sunitinib Monotherapy as a First-line Treatment for Locally Advanced or Metastatic Renal Cell Carcinoma (mRCC). In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.	24/03/2022	25/04/2022	SmPC, Annex II and PL	SmPC new text: Based on the final analysis with a median follow up time of 37.7 months, the HR for OS and PFS were 0.73 (95% CI 0.60, 0.88; p Value=0.00062) and 0.68 (95% CI: 0.58, 0.80; p Value< 0.00001) respectively. For more information, please refer to the Summary of Product Characteristics.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0114	Update of sections 5.1 of the SmPC in order to update efficacy information based on final results from study KEYNOTE-087 listed as an imposed PAES in the Annex II; this is a multicenter, single-arm, multi-cohort, non-randomized Phase 2 study of IV pembrolizumab in participants with relapsed or refractory classical Hodgkin lymphoma (cHL). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/02/2022	25/04/2022	SmPC and Annex II	Section 5.1 of the SmPC is updated with final results from study KN-087 showing a consistent efficacy and safety profile of pembrolizumab in r/r cHL. Annex IID of the Product Information is updated to remove KEYNOTE-087.
IA/0120	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	08/02/2022	25/04/2022	SmPC	
II/0108	Extension of indication to include the adjuvant treatment in monotherapy of adults with renal cell carcinoma at increased risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions. As a consequence, sections 4.1, 4.2, and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 34.0 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	16/12/2021	24/01/2022	SmPC and PL	Please refer to Scientific Discussion Keytruda EMA/CHMP/702470/2021-II-0108

IB/0119	C.I.7.a - Deletion of - a pharmaceutical form	04/01/2022	25/04/2022	SmPC, Labelling and PL	
II/0116	Update of sections 5.1 of the SmPC in order to update efficacy information based on final results from study KEYNOTE-177 listed as PAES in Annex II of the Product Information; this is a 2-arm, multicenter, international, randomized, open-label, Phase 3 study evaluating the efficacy and safety of pembrolizumab monotherapy versus globally-accepted SOC therapies for Colorectal carcinoma (CRC) in participants with locally confirmed Deficient mismatch repair (dMMR) or Microsatellite instability-high (MSI-H) unresectable or metastatic CRC who have not received prior chemotherapy for their disease. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/12/2021	24/01/2022	SmPC and Annex II	The study demonstrated a statistically significant improvement in PFS (HR 0.60; 95% CI 0.45, 0.80; p Value 0.0002) for patients randomised to the pembrolizumab arm compared with chemotherapy at the pre specified final analysis for PFS. There was no statistically significant difference between pembrolizumab and chemotherapy in the final OS analysis in which 60% of the patients who had been randomized to receive chemotherapy had crossed over to receive subsequent anti-PD-1/PD-L1 therapies including pembrolizumab.
II/0105	Extension of indication to include pembrolizumab in combination with lenvatinib for the treatment of advanced or recurrent endometrial carcinoma in adults who have disease progression on or following prior treatment with a platinum containing therapy in any setting and who are not candidates for curative surgery or radiation; 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 33.0 of the RMP has also been agreed.	14/10/2021	15/11/2021	SmPC and PL	Please refer to Scientific Discussion 'Keytruda -H -C -003820-II-0105'

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0104	Extension of indication to include Keytruda in combination with lenvatinib first line treatment of adults with advanced renal cell carcinoma (RCC); 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 32.1 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	14/10/2021	15/11/2021	SmPC and PL	Please refer to Scientific Discussion 'Keytruda-H-C-Product Number-II-3820-104'
II/0099	Extension of indication for Keytruda to include in combination with chemotherapy, treatment of locally recurrent unresectable or metastatic triple negative breast cancer in adults whose tumours express PD L1 with a CPS ≥ 10 and who have not received prior chemotherapy for metastatic disease; 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 32 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	16/09/2021	19/10/2021	SmPC and PL	Please refer to Scientific Discussion 'Keytruda-H-C-3820-II-99'

IB/0113	B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised	30/09/2021	n/a		
IAIN/0112	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/08/2021	19/10/2021	SmPC and PL	
II/0097	Extension of indication to include in combination with platinum and fluoropyrimidine based chemotherapy, first-line treatment of locally advanced unresectable or metastatic carcinoma of the oesophagus or HER-2 negative gastroesophageal junction adenocarcinoma in adults whose tumours express PD L1 with a CPS ≥ 10, based on the results from the pivotal KEYNOTE-590 (KN590) trial. As a consequence, sections 4.1, 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Minor updates are also included in Annex II of the Product Information. Version of the RMP (Version 31.0) has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	20/05/2021	24/06/2021	SmPC, Annex II and PL	Please refer to Scientific Discussion Keytruda-H-C-3820-II-97
PSUSA/10403 /202009	Periodic Safety Update EU Single assessment - pembrolizumab	22/04/2021	17/06/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10403/202009.
II/0107	B.II.g.2 - Introduction of a post approval change	03/06/2021	n/a		

	management protocol related to the finished product				
II/0106/G	This was an application for a group of variations. B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method B.II.b.2.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	28/05/2021	n/a		
II/0102	Update of sections 4.2, and 5.1 of the SmPC in order to introduce an alternative dosing regimen of 400 mg every 6 weeks (Q6W) for all approved indications based on interim results from study KEYNOTE-555; this is an interventional, PK study in patients with advanced melanoma. Additonal data/analysis from studies KEYNOTE-021, -048, -189, -407 and -426 were provided. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/04/2021	21/05/2021	SmPC	The recommended dose of KEYTRUDA in adults is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes.
II/0100	Update of section 5.1 of the SmPC in order to update efficacy data based on interim results from study KEYNOTE-054 listed as a PAES in the Annex II; this is a randomized, double-blind, placebo-controlled	15/04/2021	21/05/2021	SmPC	SmPC new text Updated efficacy results with a median follow-up time of 45.5 months were provided, including distant metastases free survival (DMFS) analysis in the whole population and

	phase 3 study evaluating pembrolizumab in the adjuvant therapy of patients with resected high-risk melanoma. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				in the population with PD-L1 positive tumours (secondary outcome measure). RFS and DMFS benefit was consistently demonstrated across subgroups, including tumour PD-L1 expression, BRAF mutation status, and stage of disease (using AJCC 7th edition). These results were consistent when reclassified in a post-hoc analysis according to the current AJCC 8th edition staging system.
II/0094	Update of sections 4.4 and 5.1 of the SmPC in order to update efficacy information based on final results from study KEYNOTE-361 listed as a PAES in the Annex II; this is a Phase III Randomised, Controlled Clinical Trial of Pembrolizumab with or without Platinum-based Combination Chemotherapy versus Chemotherapy in Subjects with Advanced or Metastatic Urothelial Carcinoma; Annex IID is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/03/2021	21/05/2021	SmPC and Annex II	SmPC new text In KEYNOTE-361, a higher number of deaths within 6 months of treatment initiation followed by a long-term survival benefit was observed with pembrolizumab monotherapy compared to chemotherapy (see section 5.1). No specific factor(s) associated with early deaths could be identified. Physicians should consider the delayed onset of pembrolizumab effect before initiating treatment in patients with urothelial carcinoma who are considered eligible for carboplatin-based combination chemotherapy. Results of KEYNOTE 361 for pembrolizumab in combination with chemotherapy did not show statistically significant improvement in PFS as assessed by BICR using RECIST 1.1 (HR 0.78; 95% CI: 0.65, 0.93; p=0.0033), and OS (HR 0.86; 95% CI: 0.72, 1.02; p=0.0407) versus chemotherapy alone. Per the pre specified hierarchical testing order no formal tests for statistical significance of pembrolizumab versus chemotherapy could be performed. The key efficacy results of pembrolizumab monotherapy in patients for whom carboplatin rather than cisplatin was selected by the investigator as the better choice of chemotherapy were consistent with KEYNOTE 052 results. Efficacy results in patients whose tumours express PD L1 with CPS ≥ 10 were similar to the overall population for

					whom carboplatin was selected as the choice of chemotherapy.
IA/0103	A.7 - Administrative change - Deletion of manufacturing sites	04/03/2021	n/a		
II/0090	Extension of the currently approved therapeutic indication for the treatment of relapsed or refractory classical Hodgkin lymphoma (rrcHL) in adults to an earlier line of therapy and to include paediatric patients - as follows: KEYTRUDA as monotherapy is indicated for the treatment of adult and paediatric patients aged 3 years and older with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant (ASCT) or following at least two prior therapies when ASCT is not a treatment option. 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. The Annex II was revised to reflect extended deadline for the submission of the PAES KN-204. Revised RMP Version 30 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	28/01/2021	09/03/2021	SmPC, Annex II and PL	Please refer to Scientific Discussion Keytruda-H-C-3820-II-0090.
II/0091	Extension of indication to include first-line treatment of metastatic microsatellite instability-high (MSI H) or mismatch repair deficient (dMMR) colorectal cancer in adults for Keytruda based on the results	10/12/2020	21/01/2021	SmPC, Annex II and PL	Please refer to Scientific Discussion Keytruda-H-C-3820-II-0091.

	from KEYNOTE-177 (an international, randomised, open-label Phase 3 trial of pembrolizumab versus chemotherapy in MSI-H or dMMR Stage IV Colorectal Carcinoma). 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. In addition, a minor correction has been made in section 4.4, "Immune related endocrinopathies" subsection. Version 29.0 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IAIN/0101	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/01/2021	09/03/2021	SmPC and PL	
IAIN/0098	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	02/12/2020	21/01/2021	SmPC and PL	
IA/0095/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.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	10/11/2020	21/01/2021	Annex II and PL	

	manufacturer of a novel excipient A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)				
IAIN/0093/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	09/10/2020	21/01/2021	Annex II and PL	
IA/0092/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.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	18/09/2020	n/a		
IB/0089	B.I.c.2.d - Change in the specification parameters and/or limits of the immediate packaging of the AS -	17/07/2020	n/a		

	Addition or replacement of a specification parameter as a result of a safety or quality issue				
II/0088	B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products	09/07/2020	21/01/2021	SmPC	The SmPC section 6.5 has been updated as follows: 4 mL of concentrate in a 10 mL Type I clear glass vial, with a coated grey chlorobutyl or bromobutyl stopper and an aluminium seal with a dark blue coloured flip off cap, containing 100 mg pembrolizumab.
II/0087/G	This was an application for a group of variations. Update of section 5.1 of the SmPC in order to update efficacy information based on final results from three interventional efficacy studies in non-small cell lung cancer; study KEYNOTE-407 listed as a PAES in the Annex II, study KEYNOTE-189 listed as a category 3 study in the RMP and KEYNOTE-021 (cohort A, C and G1) listed as a category 3 study in the RMP. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	02/07/2020	21/01/2021	SmPC and Annex II	SmPC changes introduced with this variation concerns section 5.1 with an update of efficacy data from the interventional Phase 3 studies KEYNOTE-189 and KEYNOTE-407. For more information, please refer to the Summary of Product Characteristics.
IB/0086/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of	10/06/2020	21/01/2021	Annex II	

	manufacturing sites B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product				
PSUSA/10403 /201909	Periodic Safety Update EU Single assessment - pembrolizumab	26/03/2020	02/06/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10403/201909.
II/0057	Update of sections 4.4, 4.8 and 5.1 of the SmPC to reflect the results from study KEYNOTE-042; an international, randomized, open-label Phase 3 study investigating KEYTRUDA monotherapy compared to standard of care platinum-based chemotherapy in patients with locally advanced or metastatic PD-L1 positive (TPS ≥ 1%) NSCLC. An updated RMP version	30/04/2020	21/01/2021	SmPC and Annex II	Please refer to the Scientific Discussion Keytruda-H-C-3820/II/0057.

	28.0 was submitted as part of the application. In addition, the MAH revised the due date for the submission of Annex II study P361 to Q4 2020. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
R/0081	Renewal of the marketing authorisation.	30/01/2020	24/03/2020	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Keytruda in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0084	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	05/03/2020	n/a		
IA/0082/G	This was an application for a group of variations. B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	29/11/2019	n/a		

II/0080	To update sections 4.2, 4.4 and 4.8 of the SmPC on the safety information for immune-related endocrinopathies following a safety review for Addison's disease/primary adrenal insufficiency. The updated RMP version 27.0 has also been agreed. The MAH also took the opportunity to include the changes in Annex II related to the new EMA QRD template version 10.1 and to update the details of the local representative of Portugal in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/10/2019	14/11/2019	SmPC, Annex II and PL	Adrenal insufficiency (primary and secondary) has been reported in patients receiving pembrolizumab. Adrenal insufficiency occurred in 46 (0.8%) patients, including Grade 2, 3 or 4 cases in 19 (0.3%), 20 (0.3%) and 3 (0.1%) patients, respectively, receiving pembrolizumab, and the median time to onset was 5.4 months (range 1 day to 17.7 months). Patients should be monitored for signs and symptoms of adrenal insufficiency and other causes excluded. Corticosteroids to treat adrenal insufficiency and other hormone replacement should be administered as clinically indicated, and pembrolizumab should be withheld for adrenal insufficiency until the event is controlled with hormone replacement. Continuation of pembrolizumab may be considered, after corticosteroid taper, if needed.
II/0065	Extension of indication to include, as monotherapy or in combination with platinum and 5-fluorouracil (5-FU) chemotherapy, the first-line treatment of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults whose disease expresses PD-L1 with CPS score ≥1, based on the results from KEYNOTE-048, a randomized, multi-centre, open-label phase 3 study investigating pembrolizumab, or pembrolizumab plus platinum plus 5-FU chemotherapy versus platinum plus 5-FU plus cetuximab in subjects with first-line recurrent or metastatic HNSCC. 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. An updated version of the RMP (Version 27.0) has also been agreed.	17/10/2019	14/11/2019	SmPC and PL	Please refer to the Scientific Discussion Keytruda-EMEA-H-C-3820-II-0065.

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IB/0078/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	08/10/2019	14/11/2019	Annex II	
II/0069	Extension of Indication to include first line treatment of advanced or metastatic renal cell carcinoma (RCC) as combination therapy of pembrolizumab together with axitinib based on the results of the first Interim	25/07/2019	26/08/2019	SmPC, Annex II and PL	Please refer to the Scientific Discussion EMEA/H/C/003820/II/0069.

	Analysis (IA1) from the pivotal study, KN426, an ongoing, Phase 3, randomized, open-label, multicenter, global study, to evaluate the efficacy and safety of pembrolizumab in combination with axitinib versus sunitinib in previously untreated subjects with advanced/metastatic RCC. It also includes supportive data from KEYNOTE-427 Cohort A (pembrolizumab monotherapy) and a Sponsored Study A4061051 (axitinib monotherapy). 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. The MAH took the opportunity to update the educational materials in Annex II of the Product Information in relation to the adopted variation procedure EMEA/H/C/003820/II/0068. Furthermore, the due date of the Post-authorisation efficacy study P361 is updated to 2Q 2020. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. The risk management plan (RMP) Version 25 is submitted. The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				

IB/0079/G	This was an application for a group of variations. 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) C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/08/2019	14/11/2019	SmPC, Labelling and PL	
II/0074	Update of section 5.1 of the SmPC based on the CSR version 03 for study KEYNOTE-013 summarising final data from the relapsed or refractory classical Hodgkin lymphoma (r/r/cHL) cohort; the Annex II is updated with removal of the relevant obligation. The MAH also took the opportunity to introduce minor editorial changes in the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/07/2019	26/08/2019	SmPC and Annex II	Updated long-term results from study KEYNOTE-013 confirm the known efficacy profile of pembrolizumab in relapsed-refractory classical Hodgkin lymphoma (cHL): treatment with pembrolizumab in advanced r/r cHL can result in long-lasting response, yet only a minority of subjects is able to achieve disease eradication. No new safety risk have been identified, and the limited data in subjects receiving post-pembrolizumab HSCT do not raise additional concerns. For more information, please refer to the Summary of Product Characteristics.
II/0068	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	11/07/2019	n/a		
II/0076	To update section 5.1 of the SmPC based on final results from study KEYNOTE-052 (KN052) listed as a PAES in Annex II; this is a single arm Phase II Clinical Trial of pembrolizumab in subjects with advanced/unresectable or metastatic urothelial	27/06/2019	26/08/2019	SmPC and Annex II	The SmPC section 5.1 was updated to reflect final results from study KEYNOTE-052, which were in line with the interim results previously reported.

	cancer (1st line). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0075	Update of section 5.1 of the SmPC in order to reflect the updated results from study KEYNOTE-010 listed as a category 3 study in the RMP with a data cutoff of 16 March 2018. Study KEYNOTE-010 is a controlled phase II/III trial that randomized a total of 1034 previously-treated subjects with advanced or metastatic NSCLC whose tumours express PD-L1 to receive pembrolizumab at 2 mg/kg Q3W or 10 mg/kg Q3W or docetaxel at 75 mg/m2 Q3W. In addition, the MAH took the opportunity of this variation to include additional instructions in section 4.5 of the SmPC to clarify the use of corticosteroids in subjects treated with pembrolizumab in combination with other chemotherapeutic agents. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	27/06/2019	26/08/2019	SmPC and PL	The updated efficacy results from study KEYNOTE-010 with a median follow-up of 42.6 months are consistent with those reported at the time of initial approval. The safety results were also consistent with those reported at the time of initial approval and with the established safety profile of pembrolizumab monotherapy. Corticosteroids can be used as premedication, when pembrolizumab is used in combination with chemotherapy, as antiemetic prophylaxis and/or to alleviate chemotherapy-related adverse reactions.
II/0073	B.I.e.2 - Introduction of a post approval change management protocol related to the AS	27/06/2019	n/a		
II/0071	To update sections 4.2, 4.8, 5.1 and 5.2 of the SmPC based on interim results from study KEYNOTE-051; this is an ongoing Phase I/II, single-arm study to	27/06/2019	26/08/2019	SmPC	In KEYNOTE-051, 154 paediatric patients were administered pembrolizumab 2 mg/kg every 3 weeks. Pembrolizumab concentrations in these patients were

	evaluate the PK, pharmacodynamics, toxicity, safety, and anti-tumour activity of pembrolizumab in paediatric participants (Measure 2 of PIP01). Additionally, the results of study Study PD018 / PA-0064; evaluation of expression of PD-1, PD-L1, and PD-L2 in archival paediatric tumour tissues, were submitted (Measure 1 of PIP01). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				comparable to those of adults at the same dose. Participants were enrolled across 28 tumour types by primary diagnosis. The most common tumour types by histology were Hodgkin lymphoma (11.7%), glioblastoma multiforme (9.1%), neuroblastoma (6.5%), osteosarcoma (6.5%) and melanoma (5.2%). In patients with solid tumours and other lymphomas, the ORR was 5.9%, no patient had a complete response and 8 patients (5.9%) had a partial response. In the Hodgkin lymphoma population, the ORR was 50.0%, 2 patients (11.1%) had a complete response and 7 patients (38.9%) had a partial response. The safety profile in these paediatric patients was generally similar to that seen in adults treated with pembrolizumab. The most common adverse reactions (reported in at least 20% of paediatric patients) were pyrexia (31%), vomiting (26%), headache (22%), abdominal pain (21%), anaemia (21%) and constipation (20%). For more information, please refer to the Summary of Product Characteristics.
PSUSA/10403 /201809	Periodic Safety Update EU Single assessment - pembrolizumab	28/03/2019	22/05/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10403/201809.
IA/0077	A.7 - Administrative change - Deletion of manufacturing sites	15/05/2019	n/a		
II/0062	Update of sections 4.2 and 5.1 of the SmPC to add an alternative dosing regimen of 400 mg every 6 weeks (Q6W) for all approved monotherapy indications and indications currently under review in addition to the currently approved 200 mg every Q3W, based on modelling and simulation analysis.	28/02/2019	28/03/2019	SmPC and PL	The recommended dose of KEYTRUDA as monotherapy is either 200 mg every 3 weeks or 400 mg every 6 weeks administered as an intravenous infusion over 30 minutes. The recommended dose of KEYTRUDA as part of combination therapy is 200 mg every 3 weeks administered as an intravenous infusion over 30 minutes.

	No new clinical or pre-clinical studies are being submitted as part of the current application. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Pembrolizumab doses of 2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks, and 10 mg/kg every 2 weeks were evaluated in melanoma or previously treated NSCLC clinical trials. Based on the modelling and simulation of dose/exposure relationships for efficacy and safety for pembrolizumab, there are no clinically significant differences in efficacy or safety among the doses of 200 mg every 3 weeks, 2 mg/kg every 3 weeks, and 400 mg every 6 weeks as monotherapy.
II/0066/G	This was an application for a group of variations. B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	21/03/2019	n/a		

	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation				
IB/0070	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	12/03/2019	n/a		
II/0060	Extension of indication to include, in combination with carboplatin and either paclitaxel or nab-paclitaxel, for the first-line treatment of metastatic squamous NSCLC in adults for Keytruda; 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. Additionally, editorial corrections to section 5.1 of the SmPC are introduced (concerning the procedure EMEA/H/C/003820/II/0052). The RMP version 23 has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	31/01/2019	11/03/2019	SmPC, Annex II and PL	Please refer to the Scientific Discussion EMEA/H/C/003820/II/0060.
II/0067/G	This was an application for a group of variations. B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is	14/02/2019	n/a		

	a biological/immunological medicinal product and the change requires an assessment of comparability B.II.b.4.c - Change in the batch size (including batch size ranges) of the finished product - The change requires assessment of the comparability of a biological/immunological medicinal product or a new bioequivalence study				
PSUSA/10403 /201803	Periodic Safety Update EU Single assessment - pembrolizumab	18/10/2018	11/01/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10403/201803.
IB/0063/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	17/12/2018	n/a		
II/0047	Extension of Indication to include (as monotherapy) adjuvant treatment of adults with Stage III melanoma and lymph node involvement who have undergone complete resection, based on study KEYNOTE-054; a randomized, double-blind, phase 3 study conducted in collaboration with the European Organisation for Research and Treatment of Cancer (EORTC), undertaken to evaluate adjuvant therapy with pembrolizumab compared to placebo in patients with resected high-risk melanoma (Stage IIIA [> 1 mm lymph node metastasis], IIIB and IIIC). As a	18/10/2018	12/12/2018	SmPC, Annex II and PL	Please refer to the Scientific Discussion EMEA/H/C/003820/II/0047.

	consequence, sections 4.1, 4.2 and 5.1 of the SmPC have been updated and the Package Leaflet has been updated accordingly. The RMP version 22.0 was agreed. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0054	Update of section 5.1 of the SmPC based on the final clinical study report (CSR) for KEYNOTE-045 (KN045); a phase III randomized clinical trial of pembrolizumab (MK-3475) versus paclitaxel, docetaxel or vinflunine in subjects with recurrent or progressive metastatic urothelial cancer. The submission addresses the post-authorisation measure 'ANX 020' and Annex IID has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	08/11/2018	11/03/2019	SmPC and Annex II	The MAH has provided the updated efficacy and safety analyses for KN045 with a data cut-off date of 26 Oct 2017 (versus 07 Sept 2016 which was the data cut-off date in the original submission). Overall, the updated efficacy results with longer follow-up are consistent with the data provided at the previous cut-off date. The updated data from KN045 confirm the previous findings and support the currently authorised indication of Keytruda in locally advanced or metastatic urothelial carcinoma in who have received prior platinum-containing chemotherapy, regardless PD-L1 expression status. It is observed that the Overall Survival Kaplan-Meier curves tend to remain constantly separated also at later time points, confirming the benefit of pembrolizumab over standard chemotherapy with longer follow-up. No new safety signals were found in the updated safety data from KN045.
II/0058	Update of section 4.4 of the SmPC, to include in the existing warning regarding immune-related adverse reactions the fact that these reactions may be fatal in patients treated with pembrolizumab, as well as minor consequential amendments to increase consistency. The Package Leaflet is being updated	04/10/2018	12/12/2018	SmPC and PL	Immune-related adverse reactions, including severe and fatal cases, have occurred in patients receiving pembrolizumab.

	accordingly, and for consistency with the already existing statement in the SmPC section 4.4, the Package Leaflet is also being updated to include the fact that immune-related adverse reactions can occur after discontinuation of pembrolizumab treatment. An updated RMP version 20.0 was agreed during the procedure. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IA/0061	B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	26/09/2018	n/a		
II/0051/G	This was an application for a group of variations. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	13/09/2018	n/a		
II/0043	Extension of Indication to include 1st line treatment of metastatic non-squamous non-small cell lung cancer (NSCLC) in adults whose tumours have no EGFR or ALK positive mutations, in combination with pemetrexed and platinum chemotherapy, based on the efficacy and safety data from pivotal study	26/07/2018	04/09/2018	SmPC and PL	Please refer to Scientific Discussion 'Keytruda-H-C-3820-II-43'.

	KEYNOTE-189, supported by data from KEYNOTE-021 cohorts C and G. KEYNOTE-189 is a phase 3, randomized, placebo-controlled study undertaken to evaluate the efficacy and safety of pembrolizumab +pemetrexed + carboplatin or cisplatin (pembro combo) versus saline placebo + pemetrexed + carboplatin or cisplatin (control) in previously untreated subjects with advanced/metastatic nonsquamous NSCLC with no EGFR or ALK genomic tumor aberrations. As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated and the Package Leaflet is updated in accordance. An updated RMP version 17.0 was agreed during the procedure. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0042	Extension of Indication to include treatment as monotherapy of recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a ≥ 50% TPS and progressing on or after platinum-containing chemotherapy based on the results from KEYNOTE-040 (KN040) with supportive data from two additional single arm studies (KEYNOTE-012/ KEYNOTE-055). KN040 is a randomized, multi-	26/07/2018	04/09/2018	SmPC and PL	Please refer to Scientific Discussion 'Keytruda-H-C-3820-II-42'

	center, pivotal phase III study investigating KEYTRUDA as a monotherapy versus standard treatment (methotrexate, docetaxel or cetuximab) in 495 patients with recurrent or metastatic HNSCC who have previously progressed on prior platinum. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to include in SmPC section 5.2 the description of pembrolizumab PK results on time-dependent change in clearance using a time-dependent pharmacokinetic (TDPK) model structure rather than the static PK model structure. Furthermore, the existing obligation in the Annex II with regard to the further exploration of the value of biomarkers to predict the efficacy of pembrolizumab has been updated to include also the HNSCC study (KN040). An updated RMP version 16 was agreed during the procedure. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IB/0056	B.II.z - Quality change - Finished product - Other variation	08/08/2018	n/a		
IB/0055	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/08/2018	12/12/2018	SmPC and PL	

II/0048	Update of sections 4.2, 5.1 and 5.3 of the SmPC in order to align the posology of Keytruda for the melanoma and 2nd line NSCLC indications from 2 mg/kg Q3W to a 200 mg Q3W fixed dose regimen already approved for more recent indications (1st line NSCLC, classical Hodgkin lymphoma and urothelial carcinoma) based on the available overall PK and exposure data. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the contact details of the local representative in Belgium in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/06/2018	02/08/2018	SmPC and PL	Pembrolizumab doses of 2 mg/kg every 3 weeks, 10 mg/kg every 3 weeks, and 10 mg/kg every 2 weeks were evaluated in melanoma or previously treated NSCLC clinical trials. Based on the dose/exposure relationships for efficacy and safety for pembrolizumab, there are no clinically significant differences in efficacy and safety between the doses of 200 mg or 2 mg/kg every 3 weeks in patients with melanoma or NSCLC. The recommended dose of pembrolizumab is 200 mg every 3 weeks.
II/0046	B.II.c.3.b - Change in source of an excipient or reagent with TSE risk - Change or introduction of a TSE risk material or replacement of a TSE risk material from a different TSE risk material, not covered by a TSE certificate of suitability	26/07/2018	n/a		
IB/0049	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	18/07/2018	n/a		
II/0052	Restriction of indication in cisplatin-ineligible urothelial carcinoma patients to exclude patients whose tumours express PD-L1 with a combined positive score (CPS) <10, based on the review of interim analysis data by the independent data	31/05/2018	06/07/2018	SmPC	Please refer to Scientific Discussion 'Keytruda-H-C-3820-II-52'

	monitoring committee (iDMC) from study KEYNOTE-361 listed as a PAES in the Annex II; this is a Phase III randomised, active-controlled, parallel-group, open-label trial to determine the efficacy and safety of pembrolizumab with or without chemotherapy versus chemotherapy alone as first line treatment in subjects with advanced or metastatic urothelial carcinoma. Sections 4.1, 4.2, 4.4 and 5.1 of the SmPC have been revised accordingly. A DHPC was considered necessary to communicate on the restricted indication. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0044	Update of section 5.1 of the SmPC in order to reflect the final overall survival efficacy data from study Keynote-024; a randomized, open-label phase III trial of pembrolizumab versus platinum based chemotherapy in 1L subjects with PD-L1 strong metastatic non-small cell lung cancer (NSCLC). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/06/2018	02/08/2018	SmPC	Overall survival (OS) results from the KEYNOTE-24 study were provided from the final analysis at a median follow-up of 25 months. The data confirmed the survival improvement of pembrolizumab (200 mg every 3 weeks) compared to chemotherapy (HR=0.63, median OS 30 vs 14.2 months).
PSUSA/10403 /201709	Periodic Safety Update EU Single assessment - pembrolizumab	26/04/2018	21/06/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10403/201709.
T/0045	Transfer of Marketing Authorisation	16/04/2018	08/05/2018	SmPC,	

				Labelling and PL	
II/0037/G	This was an application for a group of variations. Update of section 4.4 of the SmPC to add information regarding the risks of encephalitis, sarcoidosis and graft versus host disease (GVHD), including the occurrence of fatal GVDH events that have been reported with pembrolizumab in patients with a history of allogeneic Haematopoietic Stem Cell Transplantation (HSCT), and update of section 4.8 of the SmPC to add encephalitis as a 'rare' new ADR. Further, section 4.2 of the SmPC has been updated to include the recommendation to permanently discontinue pembrolizumab at the first occurrence of Grade 3 or 4 encephalitis and Grade 3 or 4 Guillain-Barré syndrome (GBS). The Package Leaflet has been updated accordingly as well as the Annex II; the information regarding educational material in the section 'additional risk minimisation measures'. In addition, the MAH took the opportunity to implement minor changes in the SmPC section 5.1 and editorial changes in the SmPC and Package Leaflet. An updated RMP version 14.0 was agreed during the procedure. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	22/02/2018	23/03/2018	SmPC, Annex II and PL	Clinically significant cases of sarcoidosis and encephalitis, including severe and fatal cases, have been reported in clinical trials or in post-marketing experience. Allogeneic Haematopoietic Stem Cell Transplantation (HSCT) after treatment with pembrolizumab: Cases of graft-versus-host-disease (GVHD) and hepatic veno-occlusive disease (VOD) have been observed in patients with classical Hodgkin lymphoma undergoing allogeneic HSCT after previous exposure to pembrolizumab. Until further data become available, careful consideration to the potential benefits of HSCT and the possible increased risk of transplant-related complications should be made case by case. Allogeneic HSCT prior to treatment with pembrolizumab: In patients with a history of allogeneic HSCT, acute GVHD, including fatal GVHD, has been reported after treatment with pembrolizumab. Patients who experienced GVHD after their transplant procedure may be at an increased risk for GVHD after treatment with pembrolizumab. Consider the benefit of treatment with pembrolizumab versus the risk of possible GVHD in patients with a history of allogeneic HSCT.

	data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0041	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	19/02/2018	n/a		
IB/0040	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	21/12/2017	n/a		
IB/0036	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	13/12/2017	n/a		
PSUSA/10403 /201703	Periodic Safety Update EU Single assessment - pembrolizumab	12/10/2017	08/12/2017	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10403/201703.
IB/0038	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	20/11/2017	n/a		
II/0031/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished	14/09/2017	n/a		

	product - Minor changes to an approved test procedure B.II.d.2.c - Change in test procedure for the finished product - Substantial change to or replacement of a biol/immunol/immunochemical test method or a method using a biol. reagent or replacement of a biol. reference preparation not covered by an approved protocol				
II/0030	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	14/09/2017	n/a		
IB/0035	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	05/09/2017	n/a		
II/0028	Update of sections 4.2, 4.4 and 4.8 of the SmPC to include the risk of myocarditis that has been reported in patients treated with pembrolizumab. The Package Leaflet has been updated accordingly. An updated RMP version 10.0 was agreed during the procedure. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/07/2017	24/08/2017	SmPC and PL	The SmPC has been updated to include 'myocarditis' as a new ADR in section 4.8 under 'cardiac disorders' with a frequency of uncommon; under the heading 'other immune-related adverse reactions' in section 4.4 mentioning the fact that severe and fatal cases have been reported in patients treated with pembrolizumab in clinical trials or in post-marketing experience, and under the heading 'other immune-related adverse reactions' in section 4.2 including guidance regarding recommended treatment modification depending on the severity of the reaction.
II/0023/G	This was an application for a group of variations. Grouped application including:	20/07/2017	24/08/2017	SmPC, Annex II and PL	For further information please refer to the published Assessment Report: Keytruda H-3820-II-23-G-AR

	Extension of Indication to add treatment as monotherapy of locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy based on the results from study KEYNOTE-045; a phase 3, randomized, active-controlled, multi-site, open-label trial evaluating pembrolizumab administered at 200 mg Q3W versus investigators' choice of paclitaxel, docetaxel, or vinflunine in patients previously treated with chemotherapy. Extension of Indication to add treatment as monotherapy of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy based on the results from study KEYNOTE-52; a phase 2, single-arm, multisite, open-label trial of pembrolizumab at 200 mg Q3W in the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy. 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, the MAH is taking the opportunity to implement a change to section 4.4 of the SmPC adding possible hypersensitivity and anaphylaxis as part of infusion reactions. In addition, Annex II has been updated to include new Post-authorisation efficacy studies (PAES) as obligations under 'conditions or restrictions with regard to the safe and effective use of the medicinal product'. An updated RMP version 7.2 was agreed during the procedure.				

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0026/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.II.d.2.a - Change in test procedure for the finished	13/07/2017	n/a		

	product - Minor changes to an approved test procedure				
II/0029	Submission of the final study report for non-clinical study "Anti-Murine PD-1 Antibody (muDX400 L-005571333): Exploratory Multiple-Dose Subcutaneous Immunotoxicity Study in Mice with Hepatitis B Vaccine (L-005552770)". An updated RMP version 11.0 was agreed during the procedure. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	06/07/2017	n/a		n/a
II/0025	Update of sections 4.2, 4.4 and 4.8 of the SmPC to add posology recommendations and a warning for the risk of severe skin reactions and to communicate that Stevens - Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), including fatal cases, have been reported in patients treated with pembrolizumab. The requirements for the physician educational material in Annex II and the Package Leaflet have been updated accordingly. An updated RMP version 8.2 was agreed during the procedure. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/05/2017	23/06/2017	SmPC and PL	Immune-related severe skin reactions have been reported in patients receiving pembrolizumab; in 53 (1.7%) patients, including Grade 2 or 3 cases in 3 (0.1%) and 45 (1.4%) patients, respectively. The median time to onset of severe skin reactions was 2.4 months (range 4 days to 21.5 months). The median duration was 1.2 months (range 3 days to 17.8+ months). Severe skin reactions led to discontinuation of pembrolizumab in 5 (0.2%) patients. Severe skin reactions resolved in 36 patients. Patients should be monitored for suspected severe skin reactions and other causes should be excluded. Based on the severity of the adverse reaction, pembrolizumab should be withheld or permanently discontinued, and corticosteroids should be administered. Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some with fatal outcome, have been reported in patients receiving pembrolizumab. For signs or symptoms of SJS or TEN, pembrolizumab should

					be withheld and the patient should be referred to a specialised unit for assessment and treatment. If SJS or TEN is confirmed, pembrolizumab should be permanently discontinued. Caution should be used when considering the use of pembrolizumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune- stimulatory anticancer agents.
IA/0034	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	19/06/2017	24/08/2017	Annex II	
PSUSA/10403 /201609	Periodic Safety Update EU Single assessment - pembrolizumab	21/04/2017	16/06/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10403/201609.
IB/0033	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	12/06/2017	24/08/2017	SmPC, Annex II and PL	
II/0014	Extension of Indication to include monotherapy treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma (cHL) who have failed autologous stem cell transplant (ASCT) and brentuximab vedotin (BV), or who are transplant-ineligible and have failed BV, based on the results from study KEYNOTE-087, an open-label Phase II trial of pembrolizumab in subjects with relapsed or refractory cHL and study KEYNOTE-013, a Phase Ib multi-cohort trial of pembrolizumab in	23/03/2017	02/05/2017	SmPC, Annex II and PL	For further information please refer to the published Assessment Report: Keytruda H-3820-II-14-AR

	subjects with hematologic malignancies. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated and the Package Leaflet is updated accordingly. Annex II has been updated to include changes to the 'additional risk minimisation measures' and the 'obligation to conduct post-authorisation measures'. An updated RMP version 5.3 was agreed during the procedure. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0018/G	This was an application for a group of variations. Update of section 5.1 of the SmPC to reflect the data from three post-authorisation efficacy studies (PAES) in melanoma, studies P001, P002 and P006; the Annex II has been revised to reflect that the relevant data have been submitted and that the Annex II conditions for the submission of the P002 and P006 CSRs, of a comparison between two dosing regimens and of biomarker analyses in the melanoma indication have been fulfilled. An updated RMP version 6.2 was agreed during the procedure. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/04/2017	16/06/2017	SmPC and Annex II	The MAH has provided the final study reports for: Study P002: A randomized, phase II study of MK-3475 versus chemotherapy in patients with advanced melanoma. Study P006: A multicenter, randomized, controlled, three-arm, phase III study to evaluate the safety and efficacy of two dosing schedules of MK-3475 compared to ipilimumab in patients with advanced Melanoma. Study P001: A phase I study of single agent MK-3475 in patients with progressive locally advanced or metastatic carcinoma, melanoma, and non-small cell lung carcinoma. As well as the following data in the melanoma indication: - Updated efficacy data in subgroups comparing 2 vs 10 mg/kg Q3W from the P002 final analysis. - Evaluation of the value of biomarkers other than PD-L1 expression status by Immunohistochemistry (IHC) (e.g. PD-L2, RNA signature, etc.) to predict the efficacy of pembrolizumab. The data and the updated results are reflected in the

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				revised section 5.1 of the SmPC.
IB/0024/G	This was an application for a group of variations. B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data) B.II.f.1.e - Stability of FP - Change to an approved stability protocol	20/04/2017	16/06/2017	SmPC	
II/0020/G	This was an application for a group of variations. B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS B.II.d.2.c - Change in test procedure for the finished product - Substantial change to or replacement of a biol/immunol/immunochemical test method or a method using a biol. reagent or replacement of a biol. reference preparation not covered by an approved protocol	09/03/2017	n/a		
II/0013	Update of section 4.4 of the SmPC to reflect that immune-related adverse reactions affecting more than one body system can occur simultaneously, and the fact that immune-related adverse reactions, including severe and fatal cases, have been reported	02/02/2017	02/05/2017	SmPC and PL	N/A

	in clinical trials or in post-marketing experience. In addition, the MAH took the opportunity to revise the instructions for handling and storage after reconstitution in SmPC sections 6.3 and 6.6 for increased clarity. The Package Leaflet has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0021	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	30/01/2017	n/a		
II/0011	Extension of Indication to include first-line treatment of metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a ≥50% tumour proportion score (TPS) with no EGFR or ALK positive tumour mutations; 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. An updated RMP version 4.2 was agreed during the procedure. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	15/12/2016	27/01/2017	SmPC and PL	For further information please refer to the published Assessment Report: Keytruda H-3820-II-11-AR
IB/0022	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	04/01/2017	n/a		

IA/0019/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	16/12/2016	n/a		
IB/0015/G	This was an application for a group of variations. B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data B.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	23/11/2016	n/a		
IA/0016	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	11/11/2016	n/a		
PSUSA/10403 /201603	Periodic Safety Update EU Single assessment - pembrolizumab	29/09/2016	n/a		PRAC Recommendation - maintenance

IA/0012	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	14/09/2016	n/a		
X/0001/G	This was an application for a group of variations. Annex I_2.(d) Change or addition of a new pharmaceutical form B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	23/06/2016	18/08/2016	SmPC, Annex II, Labelling and PL	
II/0007	Extension of Indication to include a new indication for Keytruda in second line Non-Small Cell Lung Cancer (NSCLC); as a consequence, sections 4.1, 4.2, 4.4, 4.6, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC are updated. Annex II is updated in order to include NSCLC on-going studies among the study designed to explore value of the biomarkers to predict efficacy	23/06/2016	29/07/2016	SmPC, Annex II and PL	For further information please refer to the published Assessment Report: Keytruda H-3820-II-07-AR.

	of pembralizumab. The Package Leaflet and the RMP (final version 3.3) is updated in accordance. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IA/0009/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.d.2.e - Change in test procedure for the finished product - Update of the test procedure to comply with the updated general monograph in the Ph. Eur.	27/05/2016	n/a		
II/0008	B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method	28/04/2016	n/a		
II/0004	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	01/04/2016	n/a		

II/0002	Update of sections 4.8, 5.1 and 5.2 of the SmPC with safety and PK data based on the CSR of Study P006v01. Further, the ADR Guillain-Barré Syndrome has been added to sections 4.4 and 4.8 of the SmPC. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to revise the text referring to fatal cases of pneumonitis in section 4.4 of the SmPC, to implement minor editorial changes in the annexes, to align the SmPC, Annex II, labelling and Package Leaflet with the latest QRD template version 9.1, and to update the contact details of the local representative in Luxemburg in the Package Leaflet. A revised RMP version 2.0 was provided as part of the application. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/04/2016	29/07/2016	SmPC, Annex II, Labelling and PL	The new data and analyses confirm the previous immunogenicity, PK and exposure-response results for pembrolizumab. The new PK parameter estimates are very similar to those previously calculated. Immunogenicity is confirmed to be very low, with an observed incidence of treatment emergent ADA in evaluable subjects of 0.3% (1 out of 376). Exposure-response analysis confirmed the lack of a significant exposure-response relationship. Available efficacy results of Study P006 show a clinically meaningful advantage of pembrolizumab over ipilimumab in IPI-naive patients with unresectable advanced melanoma. Regarding efficacy results in subgroups, it is acknowledged that the study was not sufficiently powered. Efficacy data of study P006 are already included in the Keytruda SmPC. Based on comparative safety data from study P006, no differences between pembrolizumab and ipilimumab treated patients in the rate of Grade ≥3 AEs (36.7% vs 35.5%), but a lower rate of Grade ≥3 drug-related AEs (11.7% vs 19.9%), SAEs (25.2% vs 30.1%) and serious drug-related AEs (8.8% vs 17.6%) was reported with pembrolizumab. In addition, fewer patients in the pembrolizumab group discontinued treatment due to AEs (9% vs 13.3%). Since the exposure to pembrolizumab was three-fold longer than to IPI, comparison of arms during active treatment (i.e. week 0 - week 12) were provided showing a lower rate of drug-related AEs, including Grade ≥3 drug-related AEs and serious drug-related AEs, in patients treated with pembrolizumab. The safety profile of the 2 drugs was slightly different from a quantitative point of view, with a higher incidence of colitis with IPI and more commonly reported thyroid disorders (hyperthyroidism,

					hypothyroidism) and pneumonitis with pembrolizumab. In addition, the time to Grade ≥3 AEs onset was shorter in the IPI arm and treatment interruption or discontinuation was required in a lower number of patients in the pembrolizumab arms. A new safety concern was identified based on data from study P006. At the cut-off date for safety analysis (3 Sep 2014), 1 case of Grade 4 Guillan-Barré syndrome was reported in the pembrolizumab 10 mg/kg Q3W arm. Subsequently, one case of acute motor axonal neuropathy, a form of Guillan-Barré syndrome (Grade 2) was diagnosed in the pembrolizumab 10 mg/kg Q2W arm and remained ongoing at the time of the interim analysis 2. Based on these events, the Guillan-Barré syndrome is now considered as an Important Identified Risk. In addition, new AEs reported in the study, such as optic neuritis (Grade 2), scleritis (Grade 2), Sjogren's syndrome (Grade 1), ankylosing spondylitis (Grade 1), rheumatoid arthritis (Grade 2) and Systemic inflammatory response syndrome (1 Grade 1, 1 Grade 2 and 1 grade 3) are added to the SmPC.
PSUSA/10403 /201509	Periodic Safety Update EU Single assessment - pembrolizumab	17/03/2016	n/a		PRAC Recommendation - maintenance
IB/0006	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	23/02/2016	n/a		
IB/0005	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological	03/02/2016	29/07/2016	SmPC	

	medicinal product in accordance with an approved stability protocol				