IBRANCE

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
IAIN/0044	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/05/2024		SmPC and PL	
IA/0043	B.II.c.3.z - Change in source of an excipient or reagent with TSE risk - Other variation	17/01/2024	n/a		

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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PSUSA/10544 /202208	Periodic Safety Update EU Single assessment - palbociclib	30/03/2023	26/05/2023	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10544/202208.
II/0040	Update of section 5.1 of the SmPC in order to update efficacy and safety information based on final OS results from study A5481008 (PALOMA-2, "A Randomized, Multicenter, Double-blind Phase 3 Study of PD-0332991 (Oral CDK 4/6 Inhibitor) Plus Letrozole Versus Placebo Plus Letrozole for the Treatment of Postmenopausal Women with ER (+), HER2 (-) Breast Cancer Who Have Not Received Any Prior Systemic Anti-Cancer Treatment For Advanced Disease") to fulfil REC 2. In addition, the MAH took the opportunity to align Annex II with the current QRD template. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	30/03/2023	26/05/2023	SmPC and Annex II	After a median follow-up time of 90 months, the final OS results from study PALOMA-2 were not statistically significant. Events were reported for a total of 405 participants, 273 (61.5%) participants in the palbociclib plus letrozole arm and 132 (59.5%) participants in the placebo plus letrozole arm. The median OS was 53.9 months (95% CI: 49.8, 60.8) in the palbociclib plus letrozole arm and 51.2 months (95% CI: 43.7, 58.9) in the placebo plus letrozole arm. The observed HR was 0.956 (95% CI: 0.777, 1.177) with stratified 2-sided p=0.6755. For more information, please refer to the Summary of Product Characteristics
IA/0041/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 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	13/12/2022	n/a		

	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.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.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				
II/0038/G	This was an application for a group of variations.	21/07/2022	26/05/2023	SmPC and PL	The primary target organ findings following single and/or

	C.I.4: Update of section 5.3 of the SmPC in order to update the primary target organ findings and development toxicity wording. In addition, the MAH took the opportunity to update the list of local representatives (Belgium, Luxembourg, Germany and the Netherlands) in the Package Leaflet. A.6: Update of palbociclib ATC code based on the last revised classification of the Cyclin-dependent kinase (CDK) inhibitors made by the WHO. A.6 - Administrative change - Change in ATC Code/ATC Vet Code C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				repeat dosing included haematolymphopoietic and male reproductive organ effects in rats and dogs, and effects on bone and actively growing incisors in rats only. These systemic toxicities were generally observed at clinically relevant exposures based on AUC. Partial to full reversal of effects on the hematolymphopoietic, male reproductive systems, and incisor teeth were established, whereas the bone effect was not reversed following a 12-week nondosing period. In addition, cardiovascular effects (QTc prolongation, decreased heart rate, and increased RR interval and systolic blood pressure) were identified in telemetered dogs at ≥ 4 times human clinical exposure based on Cmax. For more information, please refer to the Summary of Product Characteristics.
II/0037	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	07/04/2022	n/a		
PSUSA/10544 /202108	Periodic Safety Update EU Single assessment - palbociclib	10/03/2022	n/a		PRAC Recommendation - maintenance
R/0034	Renewal of the marketing authorisation.	20/05/2021	16/07/2021	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of IBRANCE in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.

IAIN/0035/G	This was an application for a group of variations. B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.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.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	14/06/2021	n/a		
PSUSA/10544 /202008	Periodic Safety Update EU Single assessment - palbociclib	25/03/2021	19/05/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10544/202008.
N/0031	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/11/2020	19/05/2021	Labelling and PL	
IB/0032	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	09/11/2020	19/05/2021	SmPC and PL	
IB/0030	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	15/10/2020	n/a		

IA/0029	B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	20/07/2020	n/a		
IB/0028/G	This was an application for a group of variations. B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information	26/06/2020	19/05/2021	SmPC, Labelling and PL	
IG/1245/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new/updated or	29/05/2020	n/a		

	deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material)				
PSUSA/10544 /201908	Periodic Safety Update EU Single assessment - palbociclib	13/02/2020	n/a		PRAC Recommendation - maintenance
X/0018	Extension application to introduce a new pharmaceutical form (film-coated tablets) associated with new strengths. Annex I_2.(d) Change or addition of a new pharmaceutical form	12/12/2019	13/02/2020	SmPC, Labelling and PL	
II/0019/G	This was an application for a group of variations. Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to add ILD/pneumonitis as ADRs together with relevant discontinuation recommendations and a warning based on a safety cumulative review. The Package Leaflet is updated accordingly. The RMP is updated to reclassify the risk of ILD/pneumonitis from an important potential to an important	17/10/2019	19/11/2019	SmPC and PL	Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with Ibrance when taken in combination with endocrine therapy. Across clinical trials, 1.4% of Ibrance-treated patients had ILD/pneumonitis of any grade, 0.1% had Grade 3, and no Grade 4 or fatal cases were reported. Additional cases of ILD/pneumonitis have been observed in the post-marketing setting, with fatalities reported. Patients should be monitored for pulmonary symptoms indicative of

	identified risk. Furthermore, long term use has been removed from missing information in the list of safety concerns. In addition, the due date for submission of the final CSR of study A5481027 listed as a Category 3 study in the RMP is updated. The updated RMP version 1.6 is agreed. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data 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				ILD/pneumonitis (e.g. hypoxia, cough, dyspneoa). In patients who have new or worsening respiratory symptoms and are suspected to have developed ILD/pneumonitis, Ibrance should be interrupted immediately and the patient evaluated. In patients with severe interstitial lung disease (ILD)/pneumonitis, Ibrance should be permanently discontinued.
II/0016	Update of sections 4.8 and 5.1 of the SmPC based on the final results from the pivotal Study A5481023 (A double blind, Phase 3 trial of fulvestrant with or without palbociclib in pre- and postmenopausal women with hormone receptor positive, HER2-negative metastatic breast cancer that progressed on prior endocrine therapy) listed as a recommendation at the time of initial MA. The package leaflet is updated accordingly. The MAH also took the opportunity to update the list of local representatives in the PL. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	14/11/2019	13/02/2020	SmPC and PL	After a median follow-up time of 45 months, the final OS analysis was performed based on 310 events (60% of randomised patients). A 6.9-month difference in median OS in the palbociclib plus fulvestrant arm compared with the placebo plus fulvestrant arm was observed; this result was not statistically significant at the pre-specified significance level of 0.0235 (1-sided). In the placebo plus fulvestrant arm, 15.5% of randomised patients received palbociclib and other CDK inhibitors as post progression subsequent treatments. For more information, please refer to the Summary of Product Characteristics.

	data				
N/0026	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/11/2019	13/02/2020	PL	
II/0024	Update of section 5.1 of the SmPC based on the final report from a non-clinical study (PD-0332991) evaluating the correlation of palbociclib response to RB1 status. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	31/10/2019	13/02/2020	SmPC	In a follow-up study with fresh tumour samples, no relation between RB1 expression and tumour response was observed. Similarly, no relation was observed when studying the response to palbociclib in in vivo models with patient-derived xenografts (PDX models).
PSUSA/10544 /201902	Periodic Safety Update EU Single assessment - palbociclib	05/09/2019	n/a		PRAC Recommendation - maintenance
IB/0023/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	03/07/2019	24/10/2019	SmPC	
IA/0022	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	14/06/2019	n/a		

II/0017/G	This was an application for a group of variations. Update of section 5.3 of the SmPC in order to include information from two completed non-clinical studies: a 6-month carcinogenicity study in mice (20084764), and a 2-year carcinogenicity study in rats (20066483). Furthermore, the MAH submitted the final report from the non-clinical study 20084675, a Pre- and Postnatal Developmental Toxicity Study in rats. The MAH took the opportunity to introduce minor editorial changes in SmPC and PL. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/02/2019	24/10/2019	SmPC and PL	Palbociclib was assessed for carcinogenicity in a 6-month transgenic mouse study and in a 2 year rat study. Palbociclib was negative for carcinogenicity in transgenic mice at doses up to 60 mg/kg/day (No Observed Effect Level [NOEL] approximately 11 times human clinical exposure based on AUC). Palbociclib-related neoplastic finding in rats included an increased incidence of microglial cell tumours in the central nervous system of males at 30 mg/kg/day; there were no neoplastic findings in female rats at any dose up to 200 mg/kg/day. The NOEL for palbociclib-related carcinogenicity effects was 10 mg/kg/day (approximately 2 times the human clinical exposure based on AUC) and 200 mg/kg/day (approximately 4 times the human clinical exposure based on AUC) in males and females, respectively. The relevance of the male rat neoplastic finding to humans is unknown.
PSUSA/10544 /201808	Periodic Safety Update EU Single assessment - palbociclib	14/02/2019	n/a		PRAC Recommendation - maintenance
II/0011	Update of section 5.1 of the SmPC to update the clinical efficacy data from pivotal Phase 3 Study A5481008 (PALOMA-2), a study of IBRANCE in combination with letrozole to, to include the results from recent analyses of the study with a data cut-off date of 31 May 2017; in addition, the MAH took the opportunity to update section 4.2 to include a clarification that when co-administered with an aromatase inhibitor, the latter should be	29/11/2018	24/10/2019	SmPC	An updated analysis of the primary and secondary endpoints was performed in the PALOMA-2 study after an additional 15 months of follow up (data cut-off date: 31-May-2017). A total of 405 PFS events were observed; 245 events (55.2%) in the palbociclib plus letrozole arm and 160 (72.1%) in the comparator arm respectively. The assessed updated results are in line with previous results (e.g. HR 0.653 vs. HR 0.611 for the primary vs. updated PFS analysis).

	administered according to the dose schedule reported in the Summary of Product Characteristics. In addition, minor editorial typos have been corrected in the SmPC and PL. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				For more information please refer to the Summary of Product Characteristics.
PSUSA/10544 /201802	Periodic Safety Update EU Single assessment - palbociclib	06/09/2018	n/a		PRAC Recommendation - maintenance
T/0014	Transfer of Marketing Authorisation	11/07/2018	30/07/2018	SmPC, Labelling and PL	
IG/0938/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or	13/07/2018	n/a		

	deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material)				
PSUSA/10544 /201708	Periodic Safety Update EU Single assessment - palbociclib	08/02/2018	n/a		PRAC Recommendation - maintenance
IB/0010/G	This was an application for a group of variations. 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 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 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	06/02/2018	30/07/2018	SmPC, Labelling and PL	
II/0007	Update of sections 4.2, 4.4 and 5.2 of the SmPC to reflect the results of PK studies on the impact of hepatic impairment (Study A5481013) and the impact of renal impairment (Study A5481014). The RMP (version 1.4) is amended to reflect the	14/12/2017	24/01/2018	SmPC	Recommendations for patients with hepatic and renal impairment have been updated. No dose adjustment of IBRANCE is required for patients with mild or moderate hepatic impairment. However, for patients with severe hepatic impairment (Child-Pugh class

	completion of these studies. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				C), the recommended dose of IBRANCE is 75 mg once daily on Schedule 3/1. IBRANCE should be administered with caution to patients with moderate or severe hepatic impairment, with close monitoring of signs of toxicity. For patients with mild, moderate or severe renal impairment, no dose adjustment is required. IBRANCE should be administered with caution to patients with moderate or severe renal impairment, with close monitoring of signs of toxicity. For more information please refer to the Summary of Product Characteristics.
II/0006	Update of sections 4.2, 4.8 and 5.1 of the SmPC in order to reflect independently-reviewed PFS results of study A5481008 (PALOMA-2) and of the Phase 2 portion of the A5481010 single-arm study; the information on ethnicity was also updated in Section 5.2 of the SmPC based on the results of the A5481010 study in Japanese patients. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/12/2017	24/01/2018	SmPC and PL	For patients who experience a maximum of Grade 1 or 2 neutropenia in the first 6 cycles, complete blood counts for subsequent cycles should be monitored every 3 months, prior to the beginning of a cycle and as clinically indicated. The effect of palbociclib on the QT interval corrected for heart rate (QTc) interval was evaluated using time matched electrocardiogram (ECG) evaluating the change from baseline and corresponding pharmacokinetic data in 77 patients with advanced breast cancer. Palbociclib did not prolong the QTc to any clinically relevant extent at the recommended dose of 125 mg daily. Based on an analysis of the cumulative pharmacokinetic, safety, and efficacy data across Asian and non-Asian populations, no dose adjustment based on Asian race is considered necessary. For more information, including a table of laboratory abnormalities observed with palbociclib treatment, please refer to the Summary of Product Characteristics.
PSUSA/10544	Periodic Safety Update EU Single assessment -	30/11/2017	n/a		PRAC Recommendation - maintenance

/201705	palbociclib				
IB/0004	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)	28/03/2017	24/01/2018	SmPC	
IA/0005	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size	15/03/2017	n/a		
IB/0003	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/02/2017	n/a		
IB/0002	B.II.g.5.b - Implementation of changes foreseen in an approved change management protocol - Requires further supporting data	16/02/2017	n/a		
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/11/2016	24/01/2018	PL	