Kadcyla

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/0071/G	This was an application for a group of variations. A grouped application consisting of: - C.I.4 (Type II): Update of sections 4.8 and 5.1 of the SmPC in order to update efficacy and safety information based on the interim results from study	20/02/2025		SmPC, Annex II, Labelling and PL	Description of selected adverse reactions Immunogenicity […] In the KATHERINE (BO27938) study, 4.0% (16/401) of patients tested positive for anti-trastuzumab emtansine antibodies, of which 5 were also positive for neutralizing

[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).

	BO27938 (KATHERINE), a PAES included in annex II.D as well as a category 3 study in the RMP, in order to fulfil ANX 021; This is a randomized, multicentre, open label phase III study to evaluate the efficacy and safety of trastuzumab emtansine versus trastuzumab as adjuvant therapy for patients with HER2-positive primary breast cancer who have residual tumour present pathologically in the breast or axillary lymph nodes following preoperative therapy. The Package Leaflet is updated in accordance. The RMP version 16.0 has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet, to bring the PI in line with the latest QRD template version 10.4, to update the PI in accordance with the latest EMA excipients guideline, and to implement editorial changes throughout the PI. - A.4 (Type I): To update the address of the site F. Hoffmann La Roche AG responsible for manufacture, quality control testing, release and storage of the active substance trastuzumab emtansine from Grenzacherstrasse 124, 4070 Basel, Switzerland, to Grenzacherstrasse 124, 4058 Basel, Switzerland. There is no change in the location of the site. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data 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				antibodies. Due to the low occurrence of anti-drug antibodies, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, and/or effectiveness of trastuzumab emtansine is unknown. Clinical efficacy Early Breast Cancer BO27938 (KATHERINE) […] At the time of primary analysis, a statistically significant improvement in IDFS was observed in patients who received trastuzumab emtansine compared with trastuzumab, see Table 6. The final descriptive IDFS analysis was conducted when 385 IDFS events had been observed and showed results which are consistent with the primary analysis (HR = 0.54, 95% CI: 0.44 – 0.66), see Figure 1. The second interim OS analysis was performed after a median follow-up of 101 months and showed a statistically significant improvement in OS in patients who received trastuzumab emtansine compared with trastuzumab (unstratified HR = 0.66, 95% CI: 0.51 – 0.87, p = 0.0027). See Table 6 and Figure 2. For more information, please refer to the Summary of Product Characteristics.

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
PSUSA/10136 /202402	Periodic Safety Update EU Single assessment - trastuzumab emtansine	03/10/2024	n/a		PRAC Recommendation - maintenance
II/0069/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.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes	11/01/2024	n/a		
WS/2419/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	13/07/2023	n/a		

	biological 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				
N/0067	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/03/2023	15/09/2023	PL	
PSUSA/10136 /202202	Periodic Safety Update EU Single assessment - trastuzumab emtansine	29/09/2022	n/a		PRAC Recommendation - maintenance
II/0066/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.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.c.1.c - Change in immediate packaging of the AS - Liquid ASs (non sterile) 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	08/09/2022	15/09/2023	Annex II and Labelling	
II/0064	Submission of the final report from study BO28407 (KAITLIN): A randomized, multicenter, open-label, Phase III trial comparing trastuzumab plus	07/07/2022	n/a		

	pertuzumab plus a taxane following anthracyclines versus trastuzumab emtansine plus pertuzumab following anthracyclines as adjuvant therapy in patients with operable HER2-positive primary breast cancer listed as a category 3 study in the RMP. The RMP version 15.0 has also been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IG/1496	A.7 - Administrative change - Deletion of manufacturing sites	18/03/2022	n/a		
IA/0062/G	This was an application for a group of variations. B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.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)	14/03/2022	n/a		

II/0061/G	This was an application for a group of variations. 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.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.f.1.b.5 - Stability of FP - Extension of the shelf	27/01/2022	08/07/2022	SmPC	

	life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol 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.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.II.f.1.e - Stability of FP - Change to an approved stability protocol B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
WS/2131	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	25/11/2021	n/a		

PSUSA/10136 /202102	Periodic Safety Update EU Single assessment - trastuzumab emtansine	30/09/2021	n/a		PRAC Recommendation - maintenance
IB/0059/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/08/2021	08/07/2022	SmPC, Annex II and PL	
IB/0058	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/07/2021	08/07/2022	SmPC, Labelling and PL	
II/0055	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	10/06/2021	n/a		
IB/0056/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement	31/05/2021	n/a		

	or addition) for the AS or a starting material/intermediate B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method 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)				
II/0053	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	18/02/2021	n/a		
IAIN/0054/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites 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	08/02/2021	n/a		

PSUSA/10136 /202002	Periodic Safety Update EU Single assessment - trastuzumab emtansine	01/10/2020	n/a		PRAC Recommendation - maintenance
IG/1224	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	10/04/2020	n/a		
II/0045	Extension of indication to include the use of Kadcyla as a single agent for the adjuvant treatment of adult patients with HER2-positive early breast cancer who have invasive residual disease, in the breast and/or lymph nodes, after neoadjuvant taxane-based and HER2-targeted therapy; as a consequence, sections 4.1, 4.2, 4.4, 4.7, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to introduce editorial changes throughout the product information. An updated RMP version 9.2 has been agreed. The variation leads to amendments to the Summary of Product Characteristics, Annex II 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	14/11/2019	16/12/2019	SmPC, Annex II and PL	Please refer to the Scientific Discussion Kadcyla-H-2389-II-0045
II/0048/G	This was an application for a group of variations. C.1.4: Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information on the risk of	12/12/2019	09/12/2020	SmPC	In an observational study (BO39807), approximately 22% (7 out of 32) of MBC patients initiating trastuzumab emtansine with LVEF of 40-49% at baseline, experienced a LVEF drop of >10% from baseline and/or CHF; most of

	Left ventricular dysfunction (LVD) based on the final results from study BO39807 listed as a category 3 study in the RMP. This is an observational study of cardiac events in patients with HER2-positive metastatic breast cancer who have a Left Ventricular Ejection Fraction (LVEF) between 40%-49% prior to initiating treatment with Kadcyla; the RMP version 11.1 is approved. C.I.13: Submission of the final report from study BO28408 listed as a category 3 study in the RMP addressing cardiac safety, safety in elderly patients, and immunogenicity. This is a randomised, multicenter, open-label, two-arm, phase III neoadjuvant study evaluating the efficacy and safety of trastuzumab emtansine plus pertuzumab compared with chemotherapy plus trastuzumab and pertuzumab for patients with HER2-Positive Breast Cancer. 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				these patients had other cardiovascular risk factors. The decision to administer trastuzumab emtansine in MBC patients with low LVEF must be made only after careful benefit risk assessment and cardiac function should be closely monitored in these patients.
WS/1612/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.z - Change in the manufacturer of AS or of a	07/11/2019	n/a		

	starting material/reagent/intermediate for 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 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.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.II.d.z - Change in control of the Finished Product - Other variation B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.2.z - Change in test procedure for the finished product - Other variation				
PSUSA/10136 /201902	Periodic Safety Update EU Single assessment - trastuzumab emtansine	05/09/2019	n/a		PRAC Recommendation - maintenance
IB/0049/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of	04/09/2019	n/a		

	specification limits B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
WS/1531	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.e.5.b - Implementation of changes foreseen in an approved change management protocol - Requires further supportive data	14/03/2019	n/a		
II/0042/G	This was an application for a group of variations. 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 C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	14/02/2019	n/a		
IA/0044	B.II.c.3.z - Change in source of an excipient or reagent with TSE risk - Other variation	04/01/2019	n/a		

R/0039	Renewal of the marketing authorisation.	26/07/2018	17/09/2018	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Kadcyla in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10136 /201802	Periodic Safety Update EU Single assessment - trastuzumab emtansine	06/09/2018	n/a		PRAC Recommendation - maintenance
T/0038	Transfer of Marketing Authorisation	20/02/2018	16/03/2018	SmPC, Labelling and PL	
PSUSA/10136 /201702	Periodic Safety Update EU Single assessment - trastuzumab emtansine	28/09/2017	n/a		PRAC Recommendation - maintenance
WS/1204/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	14/09/2017	n/a		

II/0034	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	14/09/2017	n/a		
II/0033	Submission of the final clinical study results from study TDM4788g/ BO22589 (MARIANNE) listed as a specific obligation in Annex II.D; this is an interventional randomised, 3-arm, phase III study to evaluate the efficacy and safety of trastuzumab emtansine combined with pertuzumab, or trastuzumab emtansine combined with pertuzumab-placebo versus trastuzumab plus taxane, as first line treatment in HER2-positive progressive or recurrent locally advanced breast cancer or previously untreated metastatic breast cancer. Consequently, Annex II of the product information is updated to remove this study as a specific obligation. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/07/2017	16/03/2018	Annex II	Results from for Study TDM4788g/BO22589 (MARIANNE) showed the final overall survival analysis indicated no clear treatment benefit in terms of overall survival for the trastuzumab emtansine □□containing regimens, compared with trastuzumab □□taxane. No new risks were identified beyond those already known for trastuzumab emtansine with or without pertuzumab. No new safety signals were identified with longer follow-up time and the safety profile of trastuzumab emtansine was consistent with previously reported findings. Overall these results did not warrant changes to the approved product information.
IAIN/0036	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	23/06/2017	n/a		
IB/0032/G	This was an application for a group of variations. B.I.a.4.f - Change to in-process tests or limits applied during the manufacture of the AS - Addition	16/05/2017	n/a		

	or replacement of an in-process test as a result of a safety or quality issue B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method 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.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
II/0031	To update the SmPC sections 4.4 and 4.8 to introduce a new warning and a detailed description regarding haemorrhage (not necessarily associated with thrombocytopenia) based on a safety review following the assessment of PSUR 4. The package leaflet is amended accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	11/05/2017	16/03/2018	SmPC and PL	Cases of haemorrhagic events, including central nervous system, respiratory and gastrointestinal haemorrhage, have been reported with trastuzumab emtansine treatment. Some of these bleeding events resulted in fatal outcomes. The incidence of severe haemorrhagic events (Grade ≥3) occurred in 2.2% of the overall trastuzumab emtansine treated patients in clinical studies. In some of the observed cases the patients had thrombocytopenia, or were also receiving anti-coagulant therapy or antiplatelet therapy; in others there were no known additional risk factors. Use caution with these agents and consider additional monitoring when concomitant use is medically necessary.
IB/0030	B.I.c.1.c - Change in immediate packaging of the AS	10/03/2017	n/a		

	- Liquid ASs (non sterile)				
IB/0029	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	21/12/2016	n/a		
II/0027/G	This was an application for a group of variations. C.I.4 (Type II): Submission of the final study report for the study TDM4997g/BO25734 (TH3RESA study) to address the safety concerns in Left Ventricular Dysfunction and Safety in Elderly patients. The RMP and Annex II.D are updated. C.I.11.z (Type IB): To update the RMP following the submission of the third annual report of study H4621g. The MAH takes the opportunity to implement the following administrative changes to the RMP: - inclusion of standard post-authorization data based on PSUR number 4 (reporting period from 22 February 2015 to 21 February 2016). - change of Herceptin picture in the Kadcyla Educational Material to align the picture with the recently approved version of the Herceptin vial label and carton. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing	15/12/2016	16/02/2017	Annex II	With this variation, the Marketing Authorisation Holder fulfilled an obligation to submit the clinical study report for a study to investigate the safety concerns in Left Ventricular Dysfunction and safety in elderly patients. The results of this study demonstrated that the safety profile of Kadcyla is consistent with that reported previously, and no new safety signals have been identified. By submitting this study report, the Marketing Authorisation Holder fulfilled a condition to the marketing authorisation and therefore Annex II of the marketing authorisation has been updated accordingly.

	authorisation, including the RMP - Other variation				
IA/0028	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	02/12/2016	n/a		
WS/0945/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	22/09/2016	n/a		
PSUSA/10136 /201602	Periodic Safety Update EU Single assessment - trastuzumab emtansine	02/09/2016	n/a		PRAC Recommendation - maintenance
N/0024	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/05/2016	16/02/2017	Labelling	
IA/0023	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	19/04/2016	n/a		
WS/0868	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	25/02/2016	n/a		

	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				
II/0019/G	This was an application for a group of variations. Update of section 5.1 of the SmPC with long-term Overall survival (OS) data from the pivotal study EMILIA (TDM4370g/BO21977). The Annex II of the product information is updated accordingly to delete the relevant condition (ANX006). Furthermore, section 4.8 of the SmPC is updated as a result of a pooled data analysis from several clinical studies including a change in the frequency of dizziness from very common to common. The RMP is updated accordingly. In addition, the RMP is updated with the inclusion and deletion of safety concerns (introduction of enhanced pregnancy program, inclusion of evaluation of cardiac safety in patients with baseline Left Ventricular Ejection Fraction below 50% and deletion of a category 3 study evaluating efficacy of monotherapy versus trastuzumab in combination with docetaxel). Changes of final CSR due dates for study KRISTINE (BO28408) and KAMILLA (mo28231) have been introduced. The MAH also took the opportunity to update the RMP following requests from previously assessed procedures (EMEA/H/C/002389/MEA/011.1 and EMEA/H/C/002389/ANX/007). In addition, the MAH has taken the occasion to include in the RMP some other minor corrections.	25/02/2016	16/02/2017	SmPC and Annex II	

	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.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 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 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 C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing				

	authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
WS/0865	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product	18/02/2016	n/a		
II/0020/G	This was an application for a group of variations. Update of sections 4.2, 4.4 and 5.2 of the SmPC in order to update the safety information on hepatic impaired patients after analysis of study BO25499 in fulfilment of MEA 009. The Package Leaflet and the RMP (final version 5.0) are updated accordingly. The due date for final study report for study BO25499 is also changed retrospectively. In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 9.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.11.z - Introduction of, or change(s) to, the	17/12/2015	22/01/2016	SmPC, Annex II and PL	No adjustment to the starting dose is required for patients with mild or moderate hepatic impairment. Trastuzumab emtansine was not studied in patients with severe hepatic impairment. Treatment of patients with hepatic impairment should be undertaken with caution due to known hepatotoxicity observed with trastuzumab emtansine.

	obligations and conditions of a marketing authorisation, including the RMP - Other variation				
WS/0833	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.e.2 - Introduction of a post approval change management protocol related to the AS	03/12/2015	n/a		
IB/0017	B.II.z - Quality change - Finished product - Other variation	23/10/2015	22/01/2016	SmPC, Annex II and PL	
PSUSA/10136 /201502	Periodic Safety Update EU Single assessment - trastuzumab emtansine	10/09/2015	n/a		PRAC Recommendation - maintenance
IA/0016	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	25/08/2015	n/a		
IG/0573	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	01/07/2015	n/a		
II/0013/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	21/05/2015	n/a		

	biological/immunological product B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate 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.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				
PSUSA/10136 /201408	Periodic Safety Update EU Single assessment - trastuzumab emtansine	12/03/2015	n/a		PRAC Recommendation - maintenance
II/0011/G	This was an application for a group of variations. B.II.b.1.d - Replacement or addition of a manufacturing site for the FP - Site which requires an initial or product specific inspection B.II.b.2.c.3 - Change to importer, batch release arrangements and quality control testing of the FP -	26/02/2015	n/a		

	Including batch control/testing for a biol/immunol product and any of the test methods is a biol/immunol/immunochemical method B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) 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) B.II.b.z - Change in manufacture of the Finished Product - Other variation				
IB/0010/G	This was an application for a group of variations. 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.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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.e - Change in test procedure for AS or starting material/reagent/intermediate - Other	08/01/2015	n/a		

	changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IG/0497	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	18/11/2014	n/a		
II/0006/G	This was an application for a group of variations. The MAh submitted a grouped variation application as follows: - Type II variation to update section 4.6 of the SmPC and section 2 of the Package Leaflet in order to change the duration of contraception to be used after concluding Kadcyla (trastuzumab emtansine) treatment, and the period before starting breast feeding, from 6 to 7 months in line with the Herceptin (trastuzumab) product information. Further, the MAH took the opportunity to make minor editorial changes in the Package Leaflet. - Type IB variation to update the due dates concerning the submission of the overall survival outcome data from the pivotal study BO21977 (EMILIA) in Annex II of the product information and the RMP.	23/10/2014	15/10/2015	SmPC, Annex II and PL	The MAH has submitted the variation application in order to update the SmPC and Package Leaflet with regards to the timelines for use of contraception and for start of breast feeding after concluding treatment with Kadcyla. In addition, updates to the RMP have been proposed, as a consequence of the update to the SmPC but also in order to amend the due dates for three studies included in the RMP. The due date for one of these studies is reflected in Annex II and hence Annex II has been updated in accordance with the changes to the RMP. The changes to the product information and RMP are acceptable. This variation application does not influence the benefit / risk balance of Kadcyla, which remains unchanged in the authorised indication(s).

	- Type IB variation to update the due date in the RMP concerning the submission of data from the study BO25499. - Type IB variation to update the due date in the RMP concerning the submission of data for the study BO28407 (KAITLIN). A revised RMP version 4.1 has been provided. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
II/0005	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/09/2014	n/a		
PSUV/0004	Periodic Safety Update	11/09/2014	n/a		PRAC Recommendation - maintenance
IA/0008	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	15/08/2014	n/a		

IB/0007	B.I.a.z - Change in manufacture of the AS - Other variation	29/07/2014	n/a		
II/0003	change in batch size of the AS B.I.a.3.c - Change in batch size (including batch size ranges) of AS or intermediate - The change requires assessment of the comparability of a biological/immunological AS	24/07/2014	n/a		
IA/0002	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	12/05/2014	n/a		
IB/0001	B.I.a.z - Change in manufacture of the AS - Other variation	18/03/2014	n/a		