Herceptin

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
IB/0193	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	14/08/2024		SmPC, Labelling and PL	
IA/0192	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	30/04/2024	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).

WS/2572/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.II.c.z - Change in control of excipients in the Finished Product - Other variation 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	18/01/2024	n/a		
II/0189	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	21/09/2023	n/a		
WS/2514	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.c.z - Change in control of excipients in the Finished Product - Other variation	31/08/2023	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.	13/07/2023	n/a		

	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.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/0187	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/03/2023		PL	
WS/2276	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	12/01/2023	n/a		
WS/2364/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.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.c.3.a.2 - Change in source of an excipient or reagent with TSE risk - From TSE risk material to vegetable or synthetic origin - For excipients or reagents USED in the manufacture of a biol/immunol	15/12/2022	n/a		

	AS or in a biol/immunol medicinal product				
WS/2243/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.II.c.3.a.2 - Change in source of an excipient or reagent with TSE risk - From TSE risk material to vegetable or synthetic origin - For excipients or reagents USED in the manufacture of a biol/immunol AS or in a biol/immunol medicinal product	10/11/2022	n/a		
WS/2277	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.c.z - Change in control of excipients in the Finished Product - Other variation	01/09/2022	n/a		
IA/0183/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.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	04/07/2022	n/a		

PSUSA/3010/ 202109	Periodic Safety Update EU Single assessment - trastuzumab	10/06/2022	n/a		PRAC Recommendation - maintenance
IB/0181	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	27/04/2022	n/a		
IG/1496	A.7 - Administrative change - Deletion of manufacturing sites	18/03/2022	n/a		
IA/0179/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.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	25/02/2022	n/a		

	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.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				
II/0174/G	This was an application for a group of variations. B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size 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 A.7 - Administrative change - Deletion of manufacturing sites	16/12/2021	n/a		
WS/2131	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	25/11/2021	n/a		

	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation				
IA/0177	B.II.c.4.a - Change in synthesis or recovery of a non-pharmacopoeial or novel excipient - Minor change	22/11/2021	n/a		
II/0173	B.I.e.2 - Introduction of a post approval change management protocol related to the AS	28/10/2021	n/a		
WS/2044	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.c.4.c - Change in synthesis or recovery of a non-pharmacopoeial or novel excipient excipient - The excipient is a biological/immunological substance	23/09/2021	n/a		
IB/0175/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	20/08/2021	08/07/2022	SmPC, Annex II, Labelling and PL	
N/0172	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/07/2021	08/07/2022	PL	
II/0168	Update of sections 4.2 and 4.4 of the SmPC (SC formulation) in order to modify the administration instructions by shortening observation time and	10/06/2021	08/07/2022	SmPC and PL	SmPC new text This variation amended the instructions for the HCPs and patients in relation to the length of the observation time

	including mild injection-related symptoms management based on final results from study SafeHER (MO28048) listed as a category 3 study in the RMP; this is a Phase III prospective, two Cohort nonrandomized, multicentre, multinational, open label study to assess the safety of assisted- and self-administered subcutaneous Herceptin as adjuvant therapy in patients with operable HER2- positive early breast cancer. The Package Leaflet is updated accordingly. Additionally, the MAH took the opportunity to introduce minor editorial updates throughout the PI. The RMP version 21.1 has also been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				post SC administration and mild injection-related symptoms management. Patients should be observed for ARRs for 30 minutes after the first injection and for 15 minutes after subsequent injections. ARRs considered mild in severity can be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine. For more information, please refer to the Summary of Product Characteristics.
IB/0169	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/03/2021	01/09/2021	SmPC and PL	
IG/1365	B.II.c.2.b - Change in test procedure for an excipient - Deletion of a test procedure if an alternative test procedure is already authorised	03/03/2021	n/a		
II/0166	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	14/01/2021	n/a		

IB/0167/G	This was an application for a group of variations. B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	18/12/2020	n/a		
IB/0164/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.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	06/10/2020	n/a		
IA/0165	A.7 - Administrative change - Deletion of manufacturing sites	24/09/2020	n/a		
II/0160	Update of section 4.7 of the SmPC in order to add "dizziness and somnolence" to the recommendations on the effects on the patient's ability to drive and use machines. Update of section 4.8 of the SmPC to remove Herpes zoster, Erysipelas, Cellulitis Common, Sepsis, Thinking abnormal, Ataxia, Paresis, Brain oedema, Pericarditis, Bradycardia and Hepatic failure as adverse drug reactions. An update of the frequencies of adverse reactions is proposed in	16/07/2020	01/09/2021	SmPC and PL	

	accordance to a change in the company core datasheet (CDS) for Herceptin: Anaphylactic reaction and Anaphylactic shock is changed to frequency Rare, Wheezing is changed to frequency Uncommon, Pneumonitis is changed to frequency Uncommon and Palpitation is changed to frequency Common. The MAH is taking the opportunity to update Section 2 of the Herceptin PL to ensure compliance with the guidance on Excipients in the Labelling and Package Leaflet of medicinal products for Human Use (SANTE 2017-11668). 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				
II/0158	Submission of the final report from study BO29159 (MetaPHER) a post- authorization safety measure Category 3 Non-Imposed Post-Approval Safety Study (NI-PASS), following approval of the Herceptin SC line extension procedure EMEA/H/C/278/X/60 to generate and evaluate additional safety and tolerability data for the approved triplet regimen (Herceptin+Perjeta+docetaxel) in the advanced breast cancer setting. In addition, bioanalytical supportive studies are presented. An updated version of the Herceptin Risk Management Plan (version 21) has also been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission	30/04/2020	n/a		

	of studies to the competent authority				
IA/0163/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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	10/04/2020	n/a		
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		
IB/0161	B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method	02/03/2020	n/a		
IB/0159	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	10/02/2020	n/a		
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 starting material/reagent/intermediate for AS - Other variation	07/11/2019	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 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				
II/0157	To submit the results from biopharmaceutic studies and clinical pharmacology studies on the improved sensitivity of the assay developed and validated to assess rHuPH20, as recommended during extension application EMEA/H/C/000278/X/60. 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	n/a		

IB/0156	B.II.f.1.b.2 - Stability of FP - Extension of the shelf life of the finished product - After first opening (supported by real time data)	27/07/2019	30/09/2020	SmPC	
PSUSA/3010/ 201809	Periodic Safety Update EU Single assessment - trastuzumab	29/05/2019	25/07/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/3010/201809.
IA/0154/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.c.1.z - Change in immediate packaging of the AS - Other variation B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	31/05/2019	n/a		
IB/0152/G	This was an application for a group of variations. B.II.c.z - Change in control of excipients in the Finished Product - Other variation B.II.c.z - Change in control of excipients in the	12/04/2019	n/a		

	Finished Product - Other variation				
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		
IB/0149	B.II.f.1.b.3 - Stability of FP - Extension of the shelf life of the finished product - After dilution or reconstitution (supported by real time data)	14/03/2019	25/07/2019	SmPC and PL	
IG/1070	B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	04/03/2019	n/a		
WS/1508/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.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	07/02/2019	n/a		

II/0147	Submission of the final report from the pregnancy registry (H4621g, MotHER), study listed as a category 3 study in the RMP. This is an observational study of pregnancy and pregnancy outcome in women with breast cancer treated with trastuzumab, pertuzumab in combination with trastuzumab, or ADO-trastuzumab emtansine during pregnancy or within 7 months prior to conception. The RMP is being updated accordingly (version 20.0) and in response to comments discussed and received in procedure EMEA/H/C/000278/II/140. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	31/10/2018	n/a		
IB/0145	B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)	31/08/2018	n/a		
IB/0144	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)	23/08/2018	11/03/2019	SmPC, Labelling and PL	
N/0146	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/08/2018	11/03/2019	PL	
T/0142	Transfer of Marketing Authorisation	20/02/2018	06/04/2018	SmPC, Labelling and PL	
II/0140	Update of sections 4.4 and 4.8 of the SmPC for	22/03/2018	11/03/2019	SmPC and PL	Results from study BO22227 did not reveal notable

	Herceptin 150mg powder for concentrate for solution for infusion and sections 4.4, 4.8 and 5.1 of the SmPC for Herceptin 600mg solution for injection in vial, in order to update the safety information based on the final results from study BO22227 (Hannah) listed as a category 3 study in the RMP; this is a phase III, randomised, open-label study to compare pharmacokinetics, efficacy and safety of subcutaneous (SC) Herceptin with intravenous (IV) Herceptin administered in women with HER2 positive early breast cancer (EBC). Section 4.7 of the SmPC is also updated to reflect Herceptin has minor influence on the ability to drive or use machines. The package leaflet is updated accordingly. The RMP version 19.0 has also been approved. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				differences in efficacy results and safety assessments for Herceptin IV and SC. The final analysis at a median follow-up exceeding 70 months showed similar event-free-survival (EFS) and overall survival (OS) between patients who received Herceptin IV and those who received Herceptin SC. The 6-year EFS rate was 65% in both arms and the OS rate, 84% in both arms. Data were also updated concerning the incidence of cardiac failure (i.e. 0.3% in the Herceptin IV arm; 0.7% in the Herceptin SC arm is unchanged), the incidence of anti-trastuzumab antibodies (i.e. 10.1%) and neutralizing anti-trastuzumab antibodies (i.e. 2 of 30 patients in the Herceptin IV arm and 3 of 47 in the Herceptin SC arm) which had no impact on EFS.
IB/0143	B.II.z - Quality change - Finished product - Other variation	14/03/2018	n/a		
IB/0136	B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	30/10/2017	16/03/2018	Annex II	
IB/0139	C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation	27/10/2017	16/03/2018	SmPC, Labelling and PL	

IA/0138	B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	20/10/2017	n/a		
IA/0137	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)	05/10/2017	n/a		
II/0135	Submission of the final report from study BO20652 (OHERA), a non-interventional study aimed to determine the incidence of symptomatic congestive heart failure and cardiac death in patients with HER2-positive early breast cancer treated with Herceptin as per routine clinical practice. This study is listed as a category 3 study in the RMP. The RMP version 18.0 has also been updated. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	28/09/2017	n/a		The results from the Study BO20652 (OHERA) final analysis are consistent with prior cardiac safety results reported from Herceptin adjuvant early breast cancer (EBC) studies, such as the HERceptin Adjuvant (HERA) (Study BO16348) but with slightly higher incidences of cardiac related events NYHA class II-IV. This difference may be related to patients with risk factors treated in OHERA and excluded in HERA. In addition, the study had limitation limiting the interpretation of the finding. The results of the study also raised the need to create awareness that cardiac monitoring in patients should be performed in line with the recommendations as per the SmPC.
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	14/09/2017	n/a		

	or addition) for the AS or a starting material/intermediate B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IB/0133	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	19/07/2017	n/a		
IB/0132/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.b.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)	28/06/2017	n/a		
II/0121	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	21/04/2017	n/a		
PSUSA/3010/ 201609	Periodic Safety Update EU Single assessment - trastuzumab	06/04/2017	n/a		PRAC Recommendation - maintenance

IA/0131	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	31/03/2017	n/a		
IB/0130	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	28/03/2017	n/a		
IB/0129	B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	10/03/2017	16/03/2018	SmPC, Labelling and PL	
IB/0128	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	28/02/2017	n/a		
II/0127/G	This was an application for a group of variations. B.II.c.z - Change in control of excipients in the Finished Product - Other variation B.II.c.2.c - Change in test procedure for an excipient - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent	23/02/2017	n/a		
II/0126	C.I.13. - Submission of the final study report for the PrefHer study (MO22982); a category 3 study in the RMP to fulfill a required additional pharmacovigilance activity. The PrefHer study is a Phase II, randomized, multicenter, open-label, two-cohort, two-arm, crossover study designed to investigate patient	23/02/2017	n/a		

	preference for Herceptin intravenous (IV) or Herceptin subcutaneous (SC) administered using the three-weekly (q3w) dosing regimen via the single-use injection device (SID) or from the vial via hand-held syringe, and to compare Health Care professional (HCP) satisfaction and perceived time savings with the two methods of administration in patients with HER2-positive early breast cancer (EBC) in the neoadjuvant/adjuvant setting. The study also evaluated the safety and efficacy (event-free survival) of Herceptin SC and IV. The crossover design of the study also allowed an evaluation of the safety and tolerability of switching between the Herceptin IV and the Herceptin SC formulations, and vice versa. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IB/0120	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	07/02/2017	n/a		
IB/0119	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	22/12/2016	n/a		
IB/0124	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	15/12/2016	n/a		

IB/0123	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	09/12/2016	n/a		
IA/0122	B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure	07/12/2016	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		
IB/0118	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	21/09/2016	n/a		
IB/0116	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	21/09/2016	n/a		
II/0113/G	This was an application for a group of variations. to add a manufacturing site for the finished product 150 mg vials, to increase the finished product batch size and change the finished product test limit. B.II.b.1.c - Replacement or addition of a	15/09/2016	n/a		

	manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line) B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits				
II/0112	Submission of the Heloise (BO27798) final study report. The following changes to the Product Information have been introduced with this variation following a request from the CHMP: Section 4.9 of the SmPC: to mention that a maintenance dose of 10 mg/kg every 3 weeks (q3w) following a loading dose of 8 mg/kg has been studied in a clinical trial with metastatic gastric cancer patients. Section 5.2 of the SmPC: to mention that baseline levels of the shed HER2-ECD receptor observed in metastatic gastric cancer (MGC) patients were comparable to those in metastatic breast cancer (MBC) and early breast cancer (EBC) patients and no apparent impact on trastuzumab clearance was observed.	15/09/2016	11/01/2017	SmPC	The following changes to the Product Information have been introduced with this variation following a request from the CHMP: Section 4.9 of the SmPC: to mention that a maintenance dose of 10 mg/kg every 3 weeks (q3w) following a loading dose of 8 mg/kg has been studied in a clinical trial with metastatic gastric cancer patients. Section 5.2 of the SmPC: to mention that baseline levels of the shed HER2-ECD receptor observed in metastatic gastric cancer (MGC) patients were comparable to those in metastatic breast cancer (MBC) and early breast cancer (EBC) patients and no apparent impact on trastuzumab clearance was observed.

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IB/0117	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	01/09/2016	n/a		
N/0114	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/05/2016	11/01/2017	Labelling	
PSUSA/3010/ 201509	Periodic Safety Update EU Single assessment - trastuzumab	14/04/2016	n/a		PRAC Recommendation - maintenance
IB/0111	B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation	31/03/2016	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. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	25/02/2016	n/a		
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	18/02/2016	n/a		

	impact on the quality, safety or efficacy of the medicinal product				
II/0104	Update of section 5.1 of the SmPC in line with long-term efficacy and safety data based on the 10-year follow-up final CSR for Study BCIRG 006. In addition, the MAH took the opportunity to implement editorial changes and to update the annexes in line with the latest QRD template. The provision of the CSR addresses the post-authorisation measure MEA 082.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/02/2016	11/01/2017	SmPC, Annex II, Labelling and PL	Section 5.1 of the SmPC has been updated and reflects the results from the 10-year follow-up of study BCIRG 006 and the previously obtained Joint Analysis of Studies NSABP B-31 and NCCTG N9831. It is agreed that the exploratory analyses of the patient subgroups were generally consistent with an increased DFS duration in favor of the Herceptin-containing arms compared with the AC→T arm, and were consistent with the patient subgroup findings at the 5-year follow-up. Further, it is agreed that the AC→TH and TCH treatment regimens continue to be important adjuvant therapy regimens for HER2-positive EBC patients with either node-negative or node-positive status. Symptomatic cardiac events included symptomatic congestive heart failure, Grade 3 or 4 arrhythmia, Grade 3-4 ischemia or myocardial infarction, probable cardiac death; clinically significant asymptomatic cardiac events included decline of >15 percentage points in left ventricular ejection fraction compared with baseline and below the lower limit of normal. In this regard it is agreed that long-term follow-up is presented as 5-year data, i.e. exploratory analysis of DFS plus symptomatic cardiac events. The cardiac safety follow-up was not as rigorous between the 5-year and 10-year follow up. Regardless of the regimen used, most symptomatic cardiac events occurred within the first 18 months of treatment.
IB/0110	B.II.c.z - Change in control of excipients in the Finished Product - Other variation	10/02/2016	n/a		

IB/0109	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	02/02/2016	11/01/2017	SmPC	
IB/0103/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 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.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	15/01/2016	n/a		
IB/0102/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	06/01/2016	n/a		

	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				
IB/0106	B.II.c.z - Change in control of excipients in the Finished Product - Other variation	18/12/2015	n/a		
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		
II/0096	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	05/11/2015	22/02/2016	Annex II	
PSUSA/3010/ 201503	Periodic Safety Update EU Single assessment - trastuzumab	08/10/2015	n/a		PRAC Recommendation - maintenance

IB/0100	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	30/09/2015	n/a		
II/0093	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/09/2015	22/02/2016	SmPC	
II/0092	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/09/2015	22/02/2016	SmPC	
IB/0099	B.I.e.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	12/08/2015	n/a		
II/0095	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/07/2015	22/02/2016	SmPC and PL	
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		
IB/0094	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	08/06/2015	n/a		
II/0089/G	This was an application for a group of variations. As requested by the CHMP during the assessment of	23/04/2015	22/02/2016	SmPC	

	the variation II-076 and based on the mega population pharmacokinetic analysis, update of section 4.2 (for Herceptin IV only), 4.4, 4.6 and 5.2 to include the key findings. Update of section 4.5 to include the outcomes of the H4613g/GO01305 study and the updated population pharmacokinetic analysis of PK data from BO22227/HannaH study. 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				
PSUSA/3010/ 201409	Periodic Safety Update EU Single assessment - trastuzumab	10/04/2015	n/a		PRAC Recommendation - maintenance
IA/0091	B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure	16/03/2015	n/a		
II/0085	B.I.e.2 - Introduction of a post approval change management protocol related to the AS	26/02/2015	n/a		
II/0084/G	This was an application for a group of variations. Sections 4.2 and 4.8 of the SmPC have been updated with information on switching between intravenous (IV) and subcutaneous (SC) formulations further to safety data from study MO22982. The Package	26/02/2015	22/02/2016	SmPC and PL	

	Leaflet is updated accordingly. In addition, the MAH took the opportunity make corrections to the SmPC and Package leaflet. 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				
IB/0088/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.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	14/01/2015	n/a		
IA/0090	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)	23/12/2014	n/a		
II/0083/G	This was an application for a group of variations. B.II.f.1.c - Stability of FP - Change in storage conditions for biological medicinal products, when the	18/12/2014	n/a		

	stability studies have not been performed in accordance with an approved stability protocol B.II.f.1.e - Stability of FP - Change to an approved stability protocol				
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		
PSUV/0082	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance
II/0081/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.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.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	25/09/2014	n/a		
II/0076	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		

II/0078/G	This was an application for a group of variations. B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products	24/07/2014	06/02/2015	SmPC, Labelling and PL	
II/0080	Update of section 4.8 of the SmPC in order to add the adverse reactions (ADRs) of stomatitis and palmar-plantar erythrodysaesthesia syndrome with the frequency category of "very common" and to reassign the frequency of existing adverse reactions of the SmPC further to a review of safety information from pivotal clinical studies. Section 4.4 and 4.8 of the SmPC are also updated with regards to the ADRs Interstitial lung disease (ILD), pulmonary hypoplasia and renal hypoplasia reported in the post-marketing setting and currently described in other sections of the SmPC. The data in section 4.8 of the SmPC is also revised to include the information from the 1-year Herceptin treatment arm of Study BO16348 (HERA). 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	26/06/2014	06/02/2015	SmPC and PL	Stomatitis and palmar-plantar erythrodysaesthesia were added to the list of Herceptin adverse drug reactions (ADRs) with the frequency "very common". The frequency category of existing ADRs, nasopharyngitis, thrombocytopenia, insomnia, weight loss, anorexia, paraesthesia and dysgeusia, was updated from the category "common" to very common. The frequency category of ADR pleural effusion has been updated from "uncommon" to "common". Pneumonia and pharyngitis were reclassified according to the MedDRA system organ classification. Finally, three ADRs from the post-marketing setting, ILD, pulmonary hypoplasia and renal hypoplasia (currently described in section 4.4 and 4.6), were added to section 4.8 with the frequency category "not known".

	data				
PSUV/0075	Periodic Safety Update	10/04/2014	n/a		PRAC Recommendation - maintenance
IB/0077	B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)	01/04/2014	n/a		
II/0074	Update of sections 4.8 and 5.1 of the SmPC with the outcomes of the final analysis of efficacy from the Joint Analysis of studies NSABP-B31 and NCCTG N9831. The Package Leaflet is updated accordingly. A statement to avoid confusion with trastuzumab emtansine is added under SmPC section 4.2. Editorial corrections have been made throughout the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/02/2014	06/02/2015	SmPC, Labelling and PL	The purpose of this variation is to update sections 4.8 and 5.1 of the Herceptin SmPC with the outcomes of the final analysis of efficacy and safety data from the Joint Analysis of studies NSABP-B31 and NCCTG N9831. The submission of these results is in accordance with a post authorization measure requested by the CHMP at the approval of the extension of indication to include concurrent use of Herceptin with chemotherapy in the adjuvant treatment of patients with HER2-positive early breast cancer as part of a treatment regimen consisting of doxorubicin and cyclophosphamide followed by combination with paclitaxel or docetaxel, or combination with docetaxel and carboplatin. The primary endpoint of trial NSABP B-31 was Overall Survival (OS), with Disease Free Survival (DFS) and safety as secondary endpoints. When the plan for a joint analysis was approved, DFS was made the primary efficacy endpoint and OS became a secondary efficacy endpoint. Overall survival was a secondary efficacy endpoint in study NCCTG N9831 and the Joint Analysis of Studies NSABP B-31 and NCCTG N9831. Updated information is provided after 8 years of follow up

					for DFS and OS for both studies individually and as joint analysis with a total of 4063 patients (2119 patients from the NSABP B-31 study and 1944 patients from the NCCTG N9831 study) evaluable for efficacy (Joint Efficacy Population) and results confirm the efficacy of Herceptin given for 52 weeks concomitantly with chemotherapy. The Summary of Efficacy results from the joint analysis of the NSABP B-31 and NCCTG N9831 trials will be reported at the time of the definitive DFS analysis and the updated 8 year follow up preplanned overall survival analysis from the joint analysis of trials NSABPB-31 and NCCTG N9831. Post-hoc exploratory analysis Results from the Joint Analysis NSABP B-31/NCCTG, N9831 and BCIRG006 Clinical Studies combining DFS Events and Symptomatic Cardiac Events remains as was previously, i.e. with data up to median of 2 years follow up. No updated information is presented in the SmPC regarding DFS data. Since DFS has been upgraded to be the primary endpoint for each study and the joint analysis, the updated DFS outcomes following 8 years approximately, were also presented in the SmPC as follows: "DFS analysis was also performed at the final analysis of OS from the joint analysis of studies NSABP B-31 and NCCTG N9831. The updated DFS analysis results (stratified HR = 0.61; 95% CI [0.54, 0.69]) showed a similar DFS benefit compared to the definitive primary DFS analysis, despite 24.8% patients in the AC→P arm who crossed over to receive Herceptin. At 8 years, the disease-free survival rate was estimated to be 77.2% (95% CI: 75.4, 79.1) in the AC→PH arm, an absolute benefit of 11.8% compared with the AC→P arm." Furthermore, an updated integrated analysis combining

					DFS Events and Symptomatic Cardiac Events should be performed. The MAH commits to update the SmPC with an analysis combining DFS events and symptomatic cardiac events from the Joint Analysis NSABP B-31/NCCTG N9831 and BCIRG006 clinical studies when the data from BCIRG006 becomes available.
II/0068/G	This was an application for a group of variations. Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to include the outcomes of the final analysis of 8-year follow-up from Study B016348 (HERA) in adjuvant breast cancer. Update section 4.4 to include a statement on the traceability of Herceptin. Update of sections 4.2, 4.5 and 4.8 to harmonise information from the recent assessment of the subcutaneous formulation of Herceptin. The Package Leaflet is updated accordingly. Editorial changes are proposed throughout the PI. Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 9.0. The requested group of variations proposed amendments to the Summary of Product Characteristics and Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/11/2013	18/12/2013	SmPC, Annex II, Labelling and PL	The current submission to support an update to the Herceptin product information is based on the results of the final 8 year median follow up analyses from Study BO16348 (HERA), a randomized, three arm, open-label, multicenter, Phase 3 study in patients randomized upon completion of definitive surgery and systemic adjuvant chemotherapy, to receive no Herceptin (Observation), or Herceptin for 1 year or 2 years, in a 1:1:1 ratio. A final analysis was performed after a median follow-up of 8 years, which showed that 1 year Herceptin treatment is associated with a 24 % risk reduction compared to observation only (HR=0.76, 95 % CI 0.67, 0.86). This translates into an absolute benefit in terms of an 8 year disease free survival rate of 6.4 percentage points in favour of 1 year Herceptin treatment. In this final analysis, extending Herceptin treatment for a duration of two years did not show additional benefit over treatment for 1 year [DFS HR in the intent to treat (ITT) population of 2 years vs 1 year=0.99 (95 % CI: 0.87, 1.13), p-value=0.90 and OS HR=0.98 (0.83, 1.15); p-value= 0.78]. This update confirms the positive benefit – risk ratio of Herceptin in the adjuvant setting. The currently recommended one-year dosing regimen is sufficient for efficacy whereas the rate of cardiac dysfunction is

					increased in the 2-year treatment arm thereby the recommendation for the treatment duration of 1 year, is now emphasized in the SmPC sections 4.2 and 5.1. and recommendations for dose modifications in 4.2 and safety recommendations in section 4.4 are further detailed. The addition of a statement on the traceability of trastuzumab is in accordance with relevant guidelines and also aims to ensure effective pharmacovigilance monitoring. This variation concerns extensive revisions of the product information requested by the CHMP in order to harmonise with changes implemented during the procedure X/60 (subcutaneous formulation) for completeness of the text and to avoid potential medication errors with the currently available two different methods of administration, throughout the product information. The package kleaflet has been updated accordingly. Revisions in compliance with Quality review of documents templates (QRD) and editorial changes have been implemented in the product information.
II/0069/G	This was an application for a group of variations. New manufacturing site for trastuzumab active substance and changes to the manufacturing process of trastuzumab. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other	21/11/2013	18/12/2013	Annex II	

	variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - 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.1.c - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions				
IB/0072	B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)	16/10/2013	n/a		
IB/0071/G	This was an application for a group of variations. B.II.c.4.z - Change in synthesis or recovery of a non-pharmacopoeial or novel excipient - Other variation B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition) B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure	16/10/2013	n/a		
X/0060	Addition of a new pharmaceutical form "solution for injection" for the use of 600mg/5ml (new strength) as subcutaneous use (new route of administration) in	27/06/2013	26/08/2013	SmPC, Labelling and	

	the approved breast cancer indications. Annex I_2.(d) Change or addition of a new pharmaceutical form			PL	
IB/0066/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 B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	12/04/2013	n/a		
IB/0067/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 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 B.I.a.2.a - Changes in the manufacturing process of	05/04/2013	n/a		

	the AS - Minor change in the manufacturing process of the AS				
II/0062	Update of section 4.5 of the SmPC to incorporate information regarding drug-drug interactions (DDI) for Herceptin with various chemotherapeutic agents. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/01/2013	26/08/2013	SmPC	No formal drug interaction studies have been performed. Clinically significant interactions with the concomitant medication used in clinical trials have not been observed based on the results of a population PK analysis (HO407g, HO551g, HO649g, and HO648g). Pharmacokinetic data from studies BO15935 and M77004 in women with HER2-positive MBC suggest that exposure to paclitaxel and doxorubicin (and their major metabolites 6-α hydroxyl-paclitaxel, POH, and doxorubicinol, DOL) is not altered in the presence of trastuzumab (8 mg/kg or 4 mg/kg IV loading dose followed by 6 mg/kg q3w or 2 mg/kg q1w IV,resp.). However, trastuzumab may elevate the overall exposure of one doxorubicin metabolite, (7-deoxy-13 dihydro-doxorubicinone, D7D). The bioactivity of D7D and the clinical impact of the elevation of this metabolite is unclear. Data from study JP16003, a single-arm study of trastuzumab (4 mg/kg IV loading dose and 2 mg/kg IV weekly) and docetaxel (60 mg/m2 IV) in Japanese women with HER2- positive MBC, suggest that concomitant administration of trastuzumab has no effect on the single dose pharmacokinetics of docetaxel. Study JP19959 was a substudy of BO18255 (ToGA) performed in male and female Japanese patients with advanced gastric cancer to study the pharmacokinetics of capecitabine and cisplatin when used with or without trastuzumab. The results of this small substudy suggested that the exposure to the bioactive metabolites (e.g. 5-FU) of capecitabine was not affected by concurrent use of cisplatin or by concurrent use

					of cisplatin plus trastuzumab. However, capecitabine itself showed higher concentrations and a longer half-life when combined with trastuzumab. The data also suggested that the pharmacokinetics of cisplatin were not affected by concurrent use of capecitabine or by concurrent use of capecitabine plus trastuzumab. By comparison of simulated serum trastuzumab concentrations after trastuzumab monotherapy (4 mg/kg loading/2 mg/kg q1w IV) and observed serum concentrations in Japanese women with HER2- positive MBC (study JP16003) no evidence of a PK effect of concurrent administration of docetaxel on the pharmacokinetics of trastuzumab was found. Comparison of PK results from two Phase II studies (BO15935 and M77004) and one Phase III study (H0648g) in which patients were treated concomitantly with Herceptin and paclitaxel and two Phase II studies in which Herceptin was administered as monotherapy (W016229 and MO16982), in women with HER2-positive MBC indicates that individual and mean Herceptin trough serum concentrations varied within and across studies but there was no clear effect of the concomitant administration of paclitaxel on the pharmacokinetics of trastuzumab.
IG/0228	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/11/2012	n/a		
IB/0064	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	03/09/2012	n/a		

IB/0063	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	03/09/2012	n/a		
IAIN/0061	C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV	30/04/2012	n/a		
II/0059	Update of section 4.6 of the SmPC to include foetal renal growth and function impairment in association with oligohydramnios, in pregnant women who had been exposed to trastuzumab. The Package Leaflet has been updated in accordance. Both SmPC and Package Leaflet were also updated with wording to better reflect the potential for unfavourable outcomes in pregnant cancer patients receiving trastuzumab. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/01/2012	17/02/2012	Annex II and PL	The MAH presented a comprehensive search of the global safety database including all data captured cumulatively until 16th May 2010, for pregnant women who had been exposed to Herceptin and in whom predefined foetal adverse events were reported. The search returned 98 adverse events reported in 56 case reports. All case reports were reviewed for any evidence of oligohydramnios and renal hypoplasia. The resulting analysis identified four case reports in which oligohydramnios and evidence of renal hypoplasia were observed. These four cases all originated from literature articles. There were also eleven reports of oligohydramnios in which no renal dysfunction was noted. Five infants were healthy at the time of the most recent reports received and six had died (including therapeutic abortion) of complications due to oligohydramnios/preterm delivery. One pregnancy in which oligohydramnios had been reported was ongoing at the time of the most recent and additional information for this report has been requested. There was also one report of multi-organ failure with a history of oligohydramnios, but there was no information of renal involvement.

					Based on the results presented in this application, section 4.6 of the SmPC was updated to include foetal renal growth and function impairment in association with oligohydramnios, in pregnant women who had been exposed to trastuzumab. The Package Leaflet has been updated in accordance. Both SmPC and Package Leaflet were also updated with wording to better reflect the potential for unfavourable outcomes in pregnant cancer patients receiving trastuzumab.
II/0057	The Extension of indication to include treatment of patients with HER2-positive EBC in combination with neoadjuvant chemotherapy, followed by adjuvant trastuzumab monotherapy, for locally advanced (including inflammatory) breast cancer or tumours > 2 cm in diameter. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	17/11/2011	19/12/2011	SmPC, Annex II and PL	Please refer to Public EPAR Assessment Report (H-278-VAR-II-57-en)
IB/0058/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.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 changes to a test procedure (including replacement	29/07/2011	n/a		

	or addition) for the AS or a starting material/intermediate B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.III.2.a.2 - Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material				
II/0056	C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	19/05/2011	23/06/2011	SmPC	
II/0053	Extension of indication to include concurrent use of Herceptin with chemotherapy in the adjuvant treatment of patients with HER2-positive early breast cancer as part of a treatment regimen consisting of doxorubicin and cyclophosphamide followed by combination with paclitaxel or docetaxel, or as part of a treatment regimen in combination with docetaxel and carboplatin. In addition, the package leaflet has been updated to reflect the results of the user testing further to the assessment of FUM 068. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	17/03/2011	20/04/2011	SmPC, Annex II and PL	Please refer to Public EPAR Assessment Report (H-278-VAR-II-53-en)

II/0055	Inclusion of additional information in section 4.4 of the SmPC with regard to the risk of Interstitial Lung Disease (ILD) further to the assessment of PSUR 16. Furthermore, the MAH has taken the opportunity to include minor editing changes in the SmPC and package leaflet. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	16/12/2010	27/01/2011	SmPC and PL	In the current variation, the MAH has included additional information in section 4.4 of the SmPC with regard to cases of Interstitial Lung Disease (ILD) reported in the safety database. The review was performed following the assessment of PSUR 16. In addition, information on risk factors including prior or concomitant therapy with other anti-neoplastic therapies known to be associated with IDL such as taxanes, gemcitabine, vinorelbine and radiation therapy has been included.
II/0054	Update of the recommendations in section 4.6 of the SmPC and section 2 of the Package Leaflet following the review of cases of oligohydramnios in the post-marketing setting. The review was requested further to the assessment of the renewal procedure (R-48). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	23/09/2010	25/10/2010	SmPC and PL	Following a review in the post-marketing setting requested further to the assessment of the renewal procedure (R-48), cases of oligohydramnios, some associated with fatal pulmonary hypoplasia of the foetus, were reported in pregnant women receiving trastuzumab. The CHMP has concluded that women of childbearing potential should be advised to use effective contraception during treatment with Herceptin and for at least 6 months after treatment has concluded. In addition women who become pregnant should be advised of the possibility of harm to the foetus and if a pregnant woman is treated with Herceptin, close monitoring by a multidisciplinary team is desirable. In this variation the MAH has updated Section 4.6 (Fertility, Pregnancy and Lactation) of the SmPC and Section 2 (Before you use Herceptin) of the Package Leaflet of Herceptin to include these recommendations.
II/0051	Update of Sections 4.4 and 5.2 of the SmPC to reflect follow up data on clinical pharmacology from a number of pharmacokinetic studies available since the first license renewal.	23/09/2010	25/10/2010	SmPC	Section 5.2 of the SmPC has been updated to reflect follow up data on clinical pharmacology from several pharmacokinetic studies available since the first license renewal. The revision included information on the non-

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				linearity of pharmacokinetics on short duration intravenous infusions of trastuzumab once weekly and updated pharmacokinetic data for breast cancer patients such as elimination half-life and washout period, steady state pharmacokinetics, clearance and volume of distribution.
II/0052	To transfer of a trastuzumab production process from Genentech, USA, to Roche Penzberg (PZ), Germany. 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 medicinal product and is not related to a protocol	23/09/2010	01/10/2010		
II/0050	Change to the testing methods used for the determination of HER2 gene amplification in gastric cancer patients to be treated with Herceptin. Sections 4.1 and 5.1 of the SmPC have been updated to broaden the current recommended testing using Fluorescence in situ Hybridisation (FISH) to include Silver-enhanced in situ Hybridisation (SISH). In addition minor editorial changes were included in sections 4.1 and 5.1 of the SmPC. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	24/06/2010	06/08/2010	SmPC	This variation concerns a change to the testing methods used for the determination of HER2 gene amplification in gastric cancer patients to be treated with Herceptin. Sections 4.1 and 5.1 of the SmPC have been updated to broaden the current recommended testing using Fluorescence in situ Hybridisation (FISH) to include Silver-enhanced in situ Hybridisation (SISH).
R/0048	Renewal of the marketing authorisation.	20/05/2010	28/07/2010	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be

					adequately and sufficiently demonstrated and therefore considered that the benefit risk profile of Herceptin continues to be favourable. The CHMP recommends the renewal of the Marketing Authorisation with unlimited validity.
II/0049	To add an alternative manufacturing site for the finished product. 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, batch control, and secondary packaging, for biological/immunological medicinal products.	24/06/2010	06/07/2010		
II/0047	Extension of the indication for use in combination with capecitabine or 5-fluorouracil and cisplatin for the treatment of patients with HER2 positive metastatic adenocarcinoma of the stomach or gastro-esophageal junction who have not received prior anti-cancer treatment for their metastatic disease. Herceptin should only be used in patients with metastatic gastric cancer whose tumours have HER2 overexpression as defined by IHC2+ and a confirmatory FISH+ result, or IHC 3+, as determined by an accurate and validated assay (see Sections 4.4 and 5.1 of the SPC). Editorial changes have been introduced to harmonise information across all indications. The RMP version	17/12/2009	19/01/2010	SmPC, Annex II and PL	Please refer to Assessement Report (Herceptin-H-278-II-47-AR).

	number was updated in Annex II. Minor updates have also been made in the contact details of the local representatives for Latvia in the package leaflet. Extension of Indication				
II/0046	Changes in the testing methods for the drug substance Change(s) to the test method(s) and/or specifications for the active substance	25/06/2009	16/07/2009		
II/0045	Change in shelf life of drug substance Change(s) to shelf-life or storage conditions	25/06/2009	16/07/2009		
II/0044	Changes in a filtration step prior to a cromatographic process used in the purification of the drug substance. Change(s) to the manufacturing process for the active substance	18/12/2008	05/01/2009		
II/0043	Change in the type of bags used in the IV administration of Herceptin Update of or change(s) to the pharmaceutical documentation	23/10/2008	02/12/2008	SmPC and PL	
II/0039	Update of section 4.2 of the SPC with an additional posology of a 3-weekly dosing regimen for patients	24/07/2008	09/09/2008	SmPC and PL	

	with metastatic breast cancer following the assessment of a post-approval follow-up measure (FUM038). The package leaflet has been updated accordingly. In addition, the MAH took the opportunity to update the contact details of some local representatives in the package leaflet. Update of Summary of Product Characteristics and Package Leaflet				
II/0042	To include an additional manufacturing process of the drug substance in a new builiding at one of the production facilities. Change(s) to the manufacturing process for the active substance	30/05/2008	11/06/2008		
II/0040	Changes in the manufacture of the drug substance Change(s) to the manufacturing process for the active substance	24/04/2008	28/04/2008		
IA/0041	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	18/01/2008	n/a	Annex II and PL	
II/0038	Quality changes	20/09/2007	27/09/2007		
II/0037	Change(s) to the manufacturing process for the active substance	26/04/2007	02/05/2007		
II/0033	The MAH applied for an extension of the indication for use in combination with an aromatase inhibitor	22/03/2007	24/04/2007	SmPC and PL	Please see Herceptin-H-C-278-II-33 Scientific Discussion

	for the treatment of patients with HER2-positive and hormone receptor positive metastatic breast cancer, not previously treated with trastuzumab. The EMEA website address has also been updated in the Package Leaflet, in accordcance to the latest QRD template. Extension of Indication				
II/0034	Update of or change(s) to the pharmaceutical documentation	22/02/2007	09/03/2007	Annex II and PL	Inclusion of Roche Diagnostics GmbH, Mannheim, Germany as a second alternative manufacuter for the finished product and also as a manufacturer responsible for the batch release.
II/0035	Change(s) to the test method(s) and/or specifications for the active substance	22/02/2007	27/02/2007		
N/0036	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/02/2007	n/a	PL	
II/0027	Quality changes	21/09/2006	20/10/2006	Annex II	
II/0029	Change(s) to the manufacturing process for the active substance	21/09/2006	28/09/2006		
IA/0032	IA_05_Change in the name and/or address of a manufacturer of the finished product	20/09/2006	n/a	Annex II and PL	
II/0028	Change(s) to the manufacturing process for the active substance	27/07/2006	03/08/2006		
IB/0031	IB_42_a_01_Change in shelf-life of finished product	31/07/2006	n/a	SmPC	

	- as packaged for sale				
IA/0030	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	10/07/2006	n/a		
II/0026	Extension of Indication	27/04/2006	22/05/2006	SmPC, Annex II, Labelling and PL	Extension of indication for use in patients with HER2 positive early breast cancer. Additionally, the MAH has applied to amend section 4.8 of the SPC to include Stevens-Johnson syndrome, as requested by the CHMP following an assessment of the latest PSUR. The MAH has taken this opportunity to update the annexes to bring them in line with the QRD template. The Package Leaflet has also been updated accordingly.
II/0025	Change(s) to the test method(s) and/or specifications for the finished product	27/04/2006	03/05/2006		
IA/0024	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	10/01/2006	n/a		
II/0021	The MAH applies for changes to the manufacturing process of the active substance. Change(s) to the manufacturing process for the active substance	14/12/2005	21/12/2005		
IA/0023	IA_01_Change in the name and/or address of the marketing authorisation holder	01/12/2005	n/a	SmPC, Labelling and PL	
R/0019	Renewal of the marketing authorisation.	23/06/2005	08/09/2005	Annex II	

IA/0022	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	06/09/2005	n/a		
II/0018	Update of Summary of Product Characteristics	26/05/2005	28/06/2005	SmPC	Update of the SPC section 5.1 following the 24 months results of study M7701 (Herceptin + docetaxel).
II/0017	Update of Summary of Product Characteristics	17/03/2005	28/04/2005	SmPC	Update of the SPC following the assessment of the 6th PSUR in order to comply to the information on oligohydramnios in section 4.6 and to amend the wording used to describe certain adverse reactions in 4.4 and 4.8 in harmonisation with MedDra terminology .
IB/0016	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	21/12/2004	n/a	SmPC, Labelling and PL	
II/0015	The Marketing Authorisation Holder applied for a change in the specification of raw materials used in the fermentation and purification process of trastuzumab. Quality changes	18/11/2004	24/11/2004		
II/0013	Update of Summary of Product Characteristics	16/09/2004	22/10/2004	SmPC	
IB/0014	IB_37_a_Change in the specification of the finished product - tightening of specification limits	08/10/2004	n/a		
II/0011	Extension of Indication	22/04/2004	10/06/2004	SmPC and PL	
N/0012	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/05/2004	n/a	Labelling and PL	

I/0009	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	03/10/2003	14/10/2003		
II/0008	Change(s) to the test method(s) and/or specifications for the finished product	20/03/2003	31/03/2003		
I/0007	24_Change in test procedure of active substance 25_Change in test procedures of the medicinal product	20/02/2003	26/02/2003		
I/0006	15_Minor changes in manufacture of the medicinal product	20/02/2003	26/02/2003		
II/0004	Change(s) to the manufacturing process for the active substance	19/09/2002	14/01/2003	Annex II	
I/0005	12_Minor change of manufacturing process of the active substance	22/08/2002	18/09/2002		
II/0002	Update of Summary of Product Characteristics and Package Leaflet	21/03/2002	22/05/2002	SmPC and PL	
I/0003	25_Change in test procedures of the medicinal product	13/12/2001	07/01/2002		
II/0001	Update of or change(s) to the pharmaceutical documentation	26/04/2001	23/05/2001		