Perjeta

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/0069	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	04/03/2024		Annex II	
II/0068/G	This was an application for a group of variations.	09/11/2023	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).

	B.II.h.1.a - Update to the Adventitious Agents Safety Evaluation information - Studies related to manufacturing steps investigated for the first time for one or more advantitious agents 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.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS B.I.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 A.z - Administrative change - Other variation 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				
IB/0067	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)	03/05/2023	n/a		

II/0066	To update sections 4.8 and 5.1 to reflect updated overall survival data and cardiac safety data, based on interim results from study BO25126 (APHINITY): A randomized multicenter, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer. In addition, the MAH took the opportunity to update the ATC code in the SmPC. Furthermore, the MAH has introduced editorial changes and updated the list of local representatives in the Package leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/04/2023		SmPC and PL	After a median follow-up of 101.2 months (8.4 years), at the third OS interim analysis, the number of deaths in patients randomised to the Perjeta arm in study APHINITY was 168 deaths [7.0%] compared with 202 deaths [8.4%] in the placebo arm; HR=0.83, 95% CI [0.68, 1.02]. In APHINITY, the incidence of symptomatic heart failure (NYHA class III or IV) with a LVEF decline of at least 10% points from baseline and to <50% was <1% (0.8% of Perjeta-treated patients vs 0.4% of placebo-treated patients). Of the patients who experienced symptomatic heart failure, 62.5% of Perjeta-treated patients and 66.7% of placebo-treated patients had recovered (defined as 2 consecutive LVEF measurements above 50%) at the data cutoff. The majority of the events were reported in anthracycline-treated patients. Asymptomatic or mildly symptomatic (NYHA class II) declines in LVEF of at least 10% points from baseline and to <50% were reported in 2.7% of Perjeta-treated patients and 2.9% of placebo-treated patients, of whom 84.4% of Perjeta-treated patients and 87.0% of placebo-treated patients had recovered at the data cutoff. For more information, please refer to the Summary of Product Characteristics.
IB/0065/G	This was an application for a group of variations. B.II.f.1.e - Stability of FP - Change to an approved stability protocol 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 B.I.a.4.c - Change to in-process tests or limits	27/09/2022	n/a		

	applied during the manufacture of the AS - Deletion of a non-significant in-process test 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 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 B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - 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.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting				

	material/intermediate/reagent - 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.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.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.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.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits 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.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter B.II.d.1.z - Change in the specification parameters and/or limits 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.1.z - Change in the specification parameters and/or limits of the finished product - Other variation 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.d.2.d - Change in test procedure for the finished				

	product - Other changes to a test procedure (including replacement or addition)				
II/0063	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	28/04/2022	n/a		
IG/1496	A.7 - Administrative change - Deletion of manufacturing sites	18/03/2022	n/a		
PSUSA/10125 /202106	Periodic Safety Update EU Single assessment - pertuzumab	13/01/2022	n/a		PRAC Recommendation - maintenance
IB/0062	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)	09/12/2021	07/06/2022	SmPC, Annex II and PL	
II/0060/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.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	16/09/2021	n/a		

	biol/immunol method 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.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) 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				
II/0059	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	02/09/2021	n/a		
WS/2093	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.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	02/09/2021	n/a		
N/0057	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/07/2021	07/06/2022	PL	

IB/0056	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/04/2021	07/06/2022	SmPC, Annex II and Labelling	
II/0054	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	09/04/2021	n/a		
II/0055	Submission of the final report from study BO25114 (JACOB). This is a double-blind, placebo-controlled, randomized, multicenter phase III study evaluating the efficacy and safety of pertuzumab in combination with trastuzumab and chemotherapy in patients with HER2-positive metastatic gastroesophageal junction and gastric cancer. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/01/2021	n/a		
PSUSA/10125 /202006	Periodic Safety Update EU Single assessment - pertuzumab	14/01/2021	n/a		PRAC Recommendation - maintenance
II/0053	Submission of the final report from study MO27775 (PERTAIN). This is a randomized, two-arm, open-label, multicenter Phase II trial assessing the efficacy and safety of pertuzumab given in combination with trastuzumab plus an aromatase inhibitor in first line patients with HER2-positive and hormone receptor-positive advanced (metastatic or locally advanced) breast cancer.	19/11/2020	n/a		

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IA/0052/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.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	04/09/2020	n/a		
II/0049/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.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	03/09/2020	n/a		
IB/0050	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing	09/07/2020	n/a		

	authorisation, including the RMP - Other variation				
II/0048	Update of section 4.8 of the SmPC in order to add safety information for elderly patients based on a safety review. Sections 4.2 and 4.4 of the SmPC and the Package leaflet have been updated accordingly. In addition, the MAH took the opportunity to make minor amendments to section 4.7 of the SmPC and to update the PL in accordance with the excipient guideline and in line with the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	17/04/2020	17/03/2021	SmPC and PL	The incidence of the following all grade adverse events was at least 5% higher in patients ≥ 65 years of age, compared to patients < 65 years of age: decreased appetite, anaemia, weight decreased, asthenia, dysgeusia, peripheral neuropathy, hypomagnesemia and diarrhoea. Limited data are available in patients > 75 years of age.
II/0047	Update of section 5.1 of the SmPC to include updated OS results based on the final report from study W020698 (CLEOPATRA), a phase III, randomized, double blind, placebo-controlled clinical trial to evaluate the efficacy and safety of pertuzumab + trastuzumab + docetaxel vs placebo + trastuzumab + docetaxel in previously untreated HER2-positive metastatic breast cancer. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	02/04/2020	17/03/2021	SmPC	A descriptive analysis of OS performed at the end of the study when 515 patients had died (280 in the placebo-treated group and 235 in the Perjeta-treated group) showed that the statistically significant OS benefit in favour of the Perjeta-treated group was maintained over time after a median follow-up of 99 months (HR 0.69, p < 0.0001 log-rank test; median time to death 40.8 months [placebo-treated group] versus 57.1 months [Perjeta-treated group]). Landmark survival estimates at 8 years were 37% in the Perjeta-treated group and 23% in the placebo-treated group.
PSUSA/10125 /201906	Periodic Safety Update EU Single assessment - pertuzumab	16/01/2020	n/a		PRAC Recommendation - maintenance

IA/0045/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.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	12/07/2019	n/a		
PSUSA/10125 /201806	Periodic Safety Update EU Single assessment - pertuzumab	31/01/2019	28/03/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10125/201806.
IB/0043	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	08/03/2019	n/a		
II/0041	Submission of the final report from the pregnancy registry (H4621g/GE28099; MotHER; listed as a category 3 study in the RMP). This is a an observational study of pregnancy and pregnancy outcomes in women with breast cancer treated with Herceptin (trastuzumab), Perjeta (pertuzumab) in combination with Herceptin, or Kadcyla (ado-trastuzumab emtansine) during pregnancy or within 7 months prior to conception. In addition, the MAH submitted updated RMP version 11, as part of this application.	17/01/2019	n/a		

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IA/0044	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)	11/01/2019	n/a		
II/0039	Update of section 4.8 of the SmPC and relevant section of the PL to include tumour lysis syndrome (TLS) as a rare adverse reaction. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	05/07/2018	28/03/2019	SmPC and PL	The assessment of the information available suggests that Tumor Lysis syndrome (TSL, a condition which may happen when cancer cells die quickly, causing changes in blood levels of minerals and metabolites shown in a blood test) could rarely occur in susceptible patients when treated with Perjeta; in particular, when additional risk factors such as renal impairment, dehydration, poor oral intake or older age are present. Symptoms may include kidney problems (weakness, shortness of breath, fatigue and confusion), heart problems (fluttering of the heart of a faster or slower heartbeat), seizures, vomiting or diarrhoea and tingling in the mouth, hands or feet.
II/0034	Extension of indication for Perjeta, in combination with trastuzumab and chemotherapy, for the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence. The submission is based on the primary analysis of efficacy and safety data from the pivotal Phase III study BIG-4-11/BO25126/TOC4939g (APHINITY). Sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated to reflect the study results. The Package Leaflet and RMP version 10.2	26/04/2018	31/05/2018	SmPC and PL	Please refer to the published Assessment Report Perjeta H-2547 -II-34-AR.

	have been updated accordingly. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IB/0038	B.I.e.5.b - Implementation of changes foreseen in an approved change management protocol - Requires further supportive data	08/05/2018	n/a		
II/0035	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/03/2018	30/04/2018	SmPC	An update of the posology is proposed based on an interim analysis of data from MetaPHER. This protocol-specified interim analysis was planned to evaluate the overall safety profile and tolerability of Herceptin SC in combination with Perjeta IV plus docetaxel in patients with HER2 positive advanced breast cancer (metastatic or locally recurrent). The presented data support inclusion of trastuzumab SC as an alternative to trastuzumab IV, and the safety profile of Herceptin SC+Perjeta IV+docetaxel based on the MetaPHER interim analysis seem consistent with the known safety profile of Herceptin IV+Perjeta IV+docetaxel. The proposed dosing recommendation in the Perjeta SmPC is as follows: When administered with pertuzumab the recommendation is to follow a 3-weekly schedule for trastuzumab administered as either: an IV infusion with an initial dose of trastuzumab 8 mg/kg body weight followed every 3 weeks thereafter by a maintenance dose of 6 mg/kg body weight or a fixed dose of trastuzumab injection (600 mg) every 3

					weeks irrespective of the patient's body weight. For additional information please refer to the SmPC.
IA/0037	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	13/04/2018	n/a		
T/0036	Transfer of Marketing Authorisation	20/02/2018	23/03/2018	SmPC, Labelling and PL	
PSUSA/10125 /201706	Periodic Safety Update EU Single assessment - pertuzumab	11/01/2018	n/a		PRAC Recommendation - maintenance
R/0031	Renewal of the marketing authorisation.	12/10/2017	08/12/2017	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 Perjeta in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0030	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	14/09/2017	n/a		
IB/0033	B.II.z - Quality change - Finished product - Other variation	25/08/2017	n/a		
II/0029	Update of sections 4.4, 4.8, 5.1 of the SmPC, annex II and relevant sections of the PL in order to update	20/07/2017	08/12/2017	SmPC and PL	The primary objective of BERENICE study was to evaluate the cardiac safety of two commonly used neoadjuvant

	information on cardiac safety and reflect the results from study BERENICE (WO29217) listed as a specific obligation in the Annex II.BERENICE is an ongoing Multicenter, Multinational, Phase II Study to Evaluate Perjeta in Combination with Herceptin and Standard Neoadjuvant Anthracycline-Based Chemotherapy in Patients with HER2- Positive, Locally Advanced, Inflammatory, or Early-Stage Breast Cancer. The MAH took the opportunity to introduce minor amendments in section 4.2. The RMP v.9 has also been updated to reflect the study results. 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				anthracycline/taxane based chemotherapy regimens when given in combination with neoadjuvant Perjeta and Herceptin. In the BERENICE trial, when Perjeta was administered in combination with trastuzumab and paclitaxel for four cycles following four cycles of two weekly doxorubicin and cyclophosphamide (dose dense AC), the most common ADRs (≥50%) were nausea, diarrhoea, fatigue and alopecia. The most common NCI-CTCAE (v.4) Grade 3-4 ADR (≥10%) was neutropenia. When Perjeta was administered in combination with trastuzumab and docetaxel for four cycles following four cycles of FEC the most common ADRs (≥50%) were nausea, diarrhea and alopecia. The most common NCI-CTCAE (v.4) Grade 3-4 ADRs (≥10%) were febrile neutropenia and diarrhoea. The overall safety profile seen in BERENICE is consistent with that observed in previous data in the neoadjuvant setting for NEOSPHERE and TRYPHAENA. In the neoadjuvant period of the BERENICE trial, the incidence of NYHA Class III/IV symptomatic LVD (congestive heart failure according to NCI-CTCAE v.4) was 1.5% in the group treated with dose dense doxorubin and cyclophosphamide (AC) followed by Perjeta plus trastuzumab and paclitaxel and none of the patients (0%) experienced symptomatic LVD in the group treated with FEC followed by Perjeta in combination with trastuzumab and docetaxel. The incidence of asymptomatic LVD (ejection fraction decrease according to NCI-CTCAE v.4) was 7% in the group treated with dose dense AC followed by Perjeta plus trastuzumab and paclitaxel and 3.5% in the group treated with FEC followed by Perjeta plus trastuzumab and docetaxel. Cardiac safety data from the

					BERENICE study were consistent with previous data in the neoadjuvant setting.
II/0028	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	23/02/2017	n/a		The primary objective of the study was to evaluate tolerability, particularly with respect to cardiac function, of the three treatment regimens during the neoadjuvant period of the study. The primary analyses (reported within variation II/0010) had shown that Perjeta and Herceptin were generally well tolerated, with low and similar rates of symptomatic LVSD, regardless of whether they were given sequentially after or concomitantly with anthracycline treatment, or concomitantly with carboplatin-based treatment. Overall, the final CSR has not identified any new safety concerns or unexpected findings regarding cardiac safety. No amendments to the Product Information were considered necessary.
PSUSA/10125 /201606	Periodic Safety Update EU Single assessment - pertuzumab	12/01/2017	n/a		PRAC Recommendation - maintenance
II/0026	Submission of study MO22324 (PHEREXA), a multicenter randomized Phase III study to compare the combination of trastuzumab and capecitabine, with or without pertuzumab, in patients with HER2-positive metastatic breast cancer that have progressed after one line of trastuzumabbased therapy in the metastatic setting. This submission fulfils the Annex II condition ANX 001 to the marketing authorisation. Annex II of the Marketing Authorisation has been updated to reflect the fulfilment of this condition. The	15/09/2016	27/10/2016	Annex II	The PHEREXA study was designed to compare the combination of Herceptin and Xeloda, with or without Perjeta, in patients with HER2-positive MBC who have progressed after one line of Herceptin-based therapy in the metastatic setting. The study did not meet its primary endpoint. The PFS analysis showed a modest treatment effect with an increase in median PFS of 2.1 months when the pertuzumab combination treatment was compared with trastuzumab and capecitabine only treatment. With an increase in median survival of 8.0 months, the interim analysis of the overall survival data indicates benefit in

	RMP is updated to reflect the completion of the study and the MAH has taken the opportunity to include in the RMP annexes a minor amendment of the BERENICE protocol. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				patients treated with pertuzumab, trastuzumab and capecitabine over patients treated with trastuzumab and capecitabine only. However, in light of the PFS result and statistical testing hierarchy, statistical significance cannot be concluded. Additional secondary endpoints (including ORR and CBR) were consistent with the primary efficacy endpoint and supportive of clinical benefit for the pertuzumab regimen. Overall, the safety profile of the pertuzumab regimen was consistent with the previous studies of pertuzumab. No new safety signals were observed in the PHEREXA trial. Although the magnitude of clinical benefit observed in this study for the test arm is modest, the safety profile is consistent with that seen for pertuzumab in other studies. Overall, the benefit-risk of Perjeta for the treatment in combination with Herceptin and Xeloda in a second line treatment setting remains positive. The magnitude of clinical benefit and the acceptable safety profile in the currently approved Perjeta breast cancer indications remains unchanged.
PSUSA/10125 /201512	Periodic Safety Update EU Single assessment - pertuzumab	07/07/2016	n/a		PRAC Recommendation - maintenance
IB/0025/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	30/06/2016	n/a		

	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				
N/0024	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	04/05/2016	27/10/2016	Labelling	
IG/0668/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	22/03/2016	n/a		
II/0021/G	This was an application for a group of variations. Submission of a revised RMP (version 6.0) in order to update the following information: the follow-up period of the PERUSE study is extended from 45 to 60 months. Consequently, the due date for study completion is amended to September 2020. Annex II of the Product Information is updated accordingly. Further to the outcome of the PSUSA/10125/201412 procedure and inclusion of diarrhoea management wording in the SmPC, RMP is updated to reflect this change. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing	25/02/2016	27/10/2016	Annex II	

	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				
PSUSA/10125 /201506	Periodic Safety Update EU Single assessment - pertuzumab	14/01/2016	n/a		PRAC Recommendation - maintenance
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/0020/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.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	25/11/2015	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				
IB/0018	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	22/10/2015	27/10/2016	Annex II	
PSUSA/10125 /201412	Periodic Safety Update EU Single assessment - pertuzumab	23/07/2015	18/09/2015	SmPC and PL	Please refer to Perjeta PSUSA/00010125/201412 EPAR: Scientific conclusions and grounds recommeding the variation to the terms of the marketing authorisation
II/0010	Extension of indication to include the use of pertuzumab in combination with trastuzumab and chemotherapy for the neoadjuvant treatment of adult patients with HER2-positive, locally advanced, inflammatory, or early stage breast cancer at high risk of recurrence. As a consequence, update of sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1, 5.2 of the SmPC. In addition, the MAH took the opportunity to make a correction in sections 2 and 6.6 of the SmPC regarding the dose contained in 1 ml of solution after dilution. The Package Leaflet is updated in accordance. The requested variation proposed amendments to the SmPC, Annex II, and Package Leaflet.	25/06/2015	28/07/2015	SmPC, Annex II and PL	Please refer to the scientific discussion Perjeta EMEA/H/C/002547/II/0010 for further information.

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
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/0012	Update of sections 4.2, 4.4, 4.8 and 5.1 of the SmPC further to the final results of Study CLEOPATRA. In addition, the applicant took the opportunity to correct values in section 5.1 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/03/2015	08/07/2015	SmPC	
PSUV/0011	Periodic Safety Update	09/01/2015	n/a		PRAC Recommendation - maintenance
IB/0014	B.II.b.z - Change in manufacture of the Finished Product - Other variation	22/12/2014	n/a		
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/0009	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of	24/07/2014	08/07/2015	Annex II	

	change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
PSUV/0008	Periodic Safety Update	10/07/2014	n/a		PRAC Recommendation - maintenance
II/0007	Update of section D of Annex II of the Product Information in order to amend the study protocol of MO22324 (PHEREXA) post-authorisation measure to reflect an updated statistical analysis and the deadline for fulfilment of this post-authorisation measure. 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	25/04/2014	30/06/2014	Annex II	The ongoing study MO22324 (PHEREXA) is one of the post-approval measures (Annex II obligation) for Perjeta and intends to confirm the efficacy of Perjeta in patient in mBC treated with trastuzumab. An amendment (amendment D) to the PHEREXA study protocol is proposed to reflect mainly an updated statistical analysis with the aim to increase the robustness of the overall survival (OS) analysis without compromising the maturity of the data.
PSUV/0006	Periodic Safety Update	09/01/2014	n/a		PRAC Recommendation - maintenance
IB/0005	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/09/2013	30/06/2014	SmPC and PL	
IB/0004	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	14/08/2013	n/a		

IB/0003	B.II.f.1.a.1 - Stability of FP - Reduction of the shelf life of the finished product - As packaged for sale	17/06/2013	30/06/2014	SmPC	
IG/0298	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/04/2013	n/a		
IA/0001	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	12/04/2013	n/a		