Phesgo

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
II/0027	Update of sections 4.2 and 4.4 of the SmPC in order to update administration instructions based on the final results from studies AL42478 and WP42873. AL42478 is an US expanded access, single-arm, multicentre study to provide at home subcutaneous administration of pertuzumab and trastuzumab fixed-	25/04/2025		SmPC and PL	4.2 Posology and method of administration Phesgo should only be initiated under the supervision of a physician experienced in the administration of anti-cancer agents. Phesgo should be administered by a healthcare professional prepared to manage anaphylaxis and in an environment where full resuscitation facilities are

[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).

	dose combination (PH FDC SC) for patients with HER2-positive breast cancer during the COVID-19 pandemic. WP42873 is a randomized, open-label, 2-arm, parallel group, single dose, multi-centre study in healthy male subjects to investigate the comparability of pharmacokinetics of the fixed-dose combination of pertuzumab and trastuzumab administered subcutaneously using a handheld syringe or using the on-body delivery system. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update section 2 and 4.4 of the SmPC, the Labelling and section 2 of the Package Leaflet in line with the Annex to the guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (EMA/CHMP/190743/2016) with regard to polysorbates, to bring the PI in line with version 10.4 of the QRD template and to update 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				immediately available. Once pertuzumab-based therapy has been safely established, the physician may determine the suitability of administration of Phesgo outside of the clinical setting (e.g. at home) by a healthcare professional (see section 4.4). 4.4 Special warnings and precautions for use […] Hypersensitivity reactions/anaphylaxis Patients should be observed closely for hypersensitivity reactions. Severe hypersensitivity reactions, including anaphylaxis and events with fatal outcomes, have been observed with pertuzumab in combination with trastuzumab and chemotherapy (see section 4.8). The majority of anaphylactic reactions occurred within the first 6 8 cycles of treatment when pertuzumab and trastuzumab were given in combination with chemotherapy. Medicinal products to treat such reactions, as well as emergency equipment, should be available for immediate use. For administration outside of the clinical setting, appropriate medications for the management of hypersensitivity reactions in line with local standard clinical practice (depending on severity and type of reaction e.g. epinephrine, beta-agonists, antihistamines and corticosteroids) should be available for immediate use. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10906 /202406	Periodic Safety Update EU Single assessment - pertuzumab / trastuzumab	16/01/2025	n/a		PRAC Recommendation - maintenance
II/0025/G	This was an application for a group of variations.	05/09/2024		Annex II	

	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 A.7 - Administrative change - Deletion of manufacturing sites 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.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.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.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.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch				

	control/testing takes place and any of the test method at the site is a biol/immunol method B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.a.2.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				
II/0023/G	This was an application for a group of variations. Update of sections 4.8 and 11 of the SmPC in order to update the dosimetry methodology, based on results obtained with a new generation software and in accordance with the recommendations of ICRP 103, in order to fulfil a recommendation (REC). 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	25/07/2024		SmPC, Annex II and PL	Results from the final analysis of invasive disease free survival (iDFS) and overall survival (OS) of the DEDERICA study, an open-label, multicentre, randomized study conducted in 500 patients with HER2-positive early breast cancer that was operable or locally advanced (including inflammatory) with a tumour size > 2 cm or node-positive in the neoadjuvant and adjuvant settings, with clinical cut-off date of 2 June 2023 and a median follow up of 51 months were submitted with this application. Results were similar in the two treatment groups with respect to iDFS. The majority of patients in both groups (90.4% and 88.9% in the P+H IV and PH FDC SC arm, respectively) remained event-free until the end of the study. The hazard ratio was 1 with a 95% CI between 0.68 and 2.11. Results were

	A.6 - Administrative change - Change in ATC Code/ATC Vet Code				similar in the two treatment groups with respect to OS with a hazard ratio of 1.26 and a 95% CI ranging between 0.58 and 2.72. In the pivotal trial FEDERICA, SAEs were equally distributed between the Phesgo treatment arm and the intravenous pertuzumab in combination with trastuzumab treatment arm. The following adverse drug reactions were reported with a higher frequency (≥ 5 %) with Phesgo compared to intravenous pertuzumab in combination with trastuzumab: alopecia 79 % vs 73 %, myalgia 27.0 % vs 20.6 %, and dyspnea 12.1 % vs 6 %. For more information, please refer to the Summary of Product Characteristics.
IA/0024/G	This was an application for a group of variations. 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.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		
PSUSA/10906 /202306	Periodic Safety Update EU Single assessment - pertuzumab / trastuzumab	11/01/2024	n/a		PRAC Recommendation - maintenance
II/0021	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	09/11/2023	n/a		
II/0020/G	This was an application for a group of variations.	26/10/2023	n/a		

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

	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 or addition) for the AS or a starting material/intermediate				
PSUSA/10906 /202212	Periodic Safety Update EU Single assessment - pertuzumab / trastuzumab	06/07/2023	n/a		PRAC Recommendation - maintenance
IB/0019/G	This was an application for a group of variations. B.II.c.2.z - Change in test procedure for an excipient - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	26/06/2023	n/a		
N/0018	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		
PSUSA/10906 /202206	Periodic Safety Update EU Single assessment - pertuzumab / trastuzumab	12/01/2023	n/a		PRAC Recommendation - maintenance

IA/0016	B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure	09/12/2022	n/a		
II/0012/G	This was an application for a group of variations. 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 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	06/10/2022	n/a		
IB/0013	B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)	13/07/2022	n/a		
PSUSA/10906 /202112	Periodic Safety Update EU Single assessment - pertuzumab / trastuzumab	07/07/2022	n/a		PRAC Recommendation - maintenance
IA/0010/G	This was an application for a group of variations. B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.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.c - Change in the specification parameters	08/02/2022	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method				
PSUSA/10906 /202106	Periodic Safety Update EU Single assessment - pertuzumab / trastuzumab	13/01/2022	n/a		PRAC Recommendation - maintenance
II/0004	Update in Section 4.8, Undesirable Effects, to present the pooled data from Perjeta and Phesgo studies. In addition to this, the MAH has taken the opportunity to introduce minor updates in the SmPC and the Package leaflet: • Update in Section 9 of the SmPC to reflect the date of first authorisation • Editorial update in Section 4 of the the Package leaflet to add a space • Update in Section 6 of the the Package leaflet to adapt to the revised QRD Template v10.2 C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/01/2022	27/07/2022	SmPC and PL	
WS/2131	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	25/11/2021	n/a		

II/0007	Update of the immunogenicity information in the section 4.8 of the SmPC based on the analysis of the Federica study (Phase III clinical trial in patients with HER2 overexpressing early breast cancer). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/09/2021	27/07/2022	SmPC	In the FEDERICA study, the incidence of treatment-emergent anti-pertuzumab and anti-trastuzumab antibodies was 6.1 % (15/245) and 0.4 % (1/245), respectively, in patients treated with intravenous pertuzumab and trastuzumab. Among patients that tested positive to anti-pertuzumab antibodies, neutralizing anti-pertuzumab antibodies were detected in two patients. The incidence of anti-pertuzumab and anti-trastuzumab antibodies detected at any time point (including baseline) was 10.3 % (26/252) and 1.2 % (3/252), respectively, in patients treated with intravenous pertuzumab and trastuzumab. Among these patients, neutralizing anti-pertuzumab antibodies were detected in three patients. The incidence of treatment-emergent anti-pertuzumab, anti-trastuzumab, and anti-vorhyaluronidase alfa antibodies was 8.3 % (20/241), 1.7 % (4/241), and 3.8 % (9/238), respectively, in patients treated with Phesgo. Among these patients, neutralizing anti-pertuzumab antibodies were detected in two patients, and neutralizing anti-trastuzumab antibodies were detected in one patient. The incidence of anti-pertuzumab, anti-trastuzumab, and anti-vorhyaluronidase alfa antibodies detected at any time point (including baseline) was 12.1 % (30/248), 3.2 % (8/248), and 9 % (22/245), respectively, in patients treated with Phesgo. Among these patients, neutralizing anti-pertuzumab antibodies were detected in three patients, neutralizing anti-trastuzumab antibodies were detected in one patient, and neutralizing anti-vorhyaluronidase alfa antibodies were detected in one patient. For more information, please refer to the Summary of

					Product Characteristics.
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		
PSUSA/10906 /202012	Periodic Safety Update EU Single assessment - pertuzumab / trastuzumab	08/07/2021	n/a		PRAC Recommendation - maintenance
II/0002	Update of sections 4.2, and 4.8, and 5.1 of the SmPC in order to support the safety of switching from intravenous to subcutaneous route of administration or vice versa, based on results from study MO40628; this is a Phase II, randomised, open-label, cross-over study to assess preference for intravenous or subcutaneous route of administration in patients with HER2-positive early breast cancer. Minor editorial changes have been introduced in the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/06/2021	27/07/2022	SmPC	SmPC new text This variation introduced information on switching from intravenous pertuzumab and trastuzumab to Phesgo. Study MO40628 investigated the safety of switching between intravenous pertuzumab and trastuzumab and Phesgo subcutaneous and vice versa with a primary objective to evaluate patient preference for either the intravenous or the subcutaneous route of administration: 85 % of patients preferred the subcutaneous route, whereas 13.8 % preferred the IV administration, and 1.2 % had no preference. A total of 160 patients were included in this 2-arm, cross-over study: 80 patients were randomized to Arm A (3 cycles of intravenous pertuzumab and trastuzumab followed by 3 cycles of Phesgo) and 80 patients were randomized to Arm B (3 cycles of Phesgo followed by 3 cycles intravenous pertuzumab and

					trastuzumab). At primary analysis, the median exposure to adjuvant pertuzumab and trastuzumab (both IV and SC administration) was 11 cycles (range: 6 to 15). Among the patients in Arm A, the incidence of AEs during Cycles 1-3 (intravenous treatment) was 77.5 % (62/80 patients) compared to Cycles 4-6 (subcutaneous treatment) which was 72.5 % (58/80 patients). Among the patients in Arm B, the incidence of AEs during Cycles 1-3 (subcutaneous treatment) was 77.5 % (62/80 patients) compared to Cycles 4-6 (intravenous treatment) which was 63.8 % (51/80 patients), mainly due to higher incidence of local injection site reactions (all grade 1 or 2) during Phesgo administration. Pre-switching rates (Cycles 1-3) for serious adverse events, grade 3 adverse events and treatment discontinuations due to adverse events were low (<106 %) and similar to post-switching rates (Cycles 4-6). No grade 4 or grade 5 adverse events were reported. For more information, please refer to the Summary of Product Characteristics.
IB/0005	B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation	14/06/2021	n/a		