Lynparza

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
IA/0071	A.7 - Administrative change - Deletion of manufacturing sites	17/12/2024		Annex II and PL	
IB/0070	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	02/09/2024	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/2463	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2, 5.1 and 5.2 of the SmPC in order to include paediatric information based on final results from study D419EC00001 "Phase I/II, Open-Label, Multicenter Study to Evaluate the Safety, Tolerability, and Preliminary Efficacy of Durvalumab Monotherapy or Durvalumab in Combination with Tremelimumab in Pediatric Patients with Advanced Solid Tumors and Hematological Malignancies". In addition, the MAH took this opportunity to introduce editorial changes. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	27/06/2024	12/08/2024	SmPC, Annex II and PL	
PSUSA/10322 /202312	Periodic Safety Update EU Single assessment - olaparib	11/07/2024	n/a		PRAC Recommendation - maintenance
IB/0069	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	21/06/2024	n/a		
IB/0067	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	05/01/2024	n/a		
II/0061	Update of sections 4.8 and 5.1 of the SmPC in order to update the overall survival and safety information,	05/10/2023	25/01/2024	SmPC and	Section 4.8 of the SmPC was updated with revised frequency for adverse reactions that led to dose

	based on the final results from study D081SC00001 (PROpel), listed as a PAES in the Annex II; this is a randomised, double-blind, placebo-controlled, multicentre phase III study of olaparib plus abiraterone relative to placebo plus abiraterone as first-line therapy in men with metastatic castration resistant prostate cancer; the Annex II is updated in accordance. The RMP version 27.1 is approved. In addition, the MAH took the opportunity to revise 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			Annex II	interruption and/ or reduction of Olaparib combination treatments with bevacizumab and with abiraterone, based on a grouped terms analysis. In addition, frequency of the adverse drug reaction of grade 3 and above Dyspnoea was updated from uncommon to common. Section 5.1 of the SmPC was updated with final OS analysis, DCO 12 October 2022. Data maturity is 48%; median OS 42.1 (38.4, NC) months for olaparib/abiraterone, and 34.7 (31.0, 39.3) months for placebo/abiraterone, HR (95% CI) = 0.81 (0.67, 1.00), p=0.0544, in line with existing OS data
IAIN/0065	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/09/2023	25/01/2024	SmPC and PL	
II/0064	Update of sections 4.8 and 5.1 of the SmPC to update safety and efficacy results including a descriptive analysis of overall survival (OS) at seven years after the last patient was randomised in study D0818C0001 (SOLO1). This is a Phase III randomised, double blind, placebo controlled, multicentre study in which advanced ovarian cancer patients with BRCA mutations who had responded following first-line platinum-based chemotherapy were randomised 2:1 to receive either Olaparib (300 mg bd, tablet formulation) or placebo. The RMP version 28.1 is approved. In addition, the MAH took the opportunity to update section D of Annex II.	31/08/2023	25/01/2024	SmPC and Annex II	In study SOLO1, a descriptive analysis performed at seven years after the last patient was randomized demonstrated a clinically meaningful benefit in OS that numerically favoured the olaparib arm. The OS data were 38.1% mature (149 events/391 patients). Median OS was not reached in the olaparib arm and was 75.2 months in the placebo arm. The Hazard Ration (HR) (95% CI) was 0.55 (0.40-0.76). The risk of MDS/AML remains low in the first-line setting when olaparib maintenance treatment is given after one line of platinum chemotherapy for a duration of 2 years (1.5%) in SOLO1 study at 7 year follow up and 1.1% in PAOLA-1 study at 5 year follow up.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10322 /202212	Periodic Safety Update EU Single assessment - olaparib	06/07/2023	n/a		PRAC Recommendation - maintenance
IAIN/0063/G	This was an application for a group of variations. 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 A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release A.7 - Administrative change - Deletion of manufacturing sites	02/06/2023	25/01/2024	Annex II and PL	
IA/0062	B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter	23/05/2023	n/a		
II/0059	Submission of the final report from study AME02164. This is a Genetic Toxicity Evaluation using a Bacterial Reverse Mutation Test with Salmonella typhimurium LT2 Strains TA1535, TA1537, TA98 and TA100, and Escherichia coli WP2 Strain uvrA/pKM101. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	04/05/2023	n/a		

II/0057	Update of sections 4.8 and 5.1 of the SmPC in order to update the long-term safety data and the final OS analysis from PAOLA-1 study (D0817C00003). This is a Randomized, Double-Blind, Phase III Trial of Olaparib vs. Placebo in Patients with Advanced FIGO Stage IIIB – IV High Grade Serous or Endometrioid Ovarian, Fallopian Tube, or Peritoneal Cancer Treated with Standard First Line Treatment, Combining Platinum-Taxane Chemotherapy and Bevacizumab Concurrent with Chemotherapy and in Maintenance. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to make minor changes to the SmPC for clarity. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	30/03/2023	25/01/2024	SmPC	At the final analysis of overall survival (OS) (DCO 22 March 2022) in the homologous recombination deficiency (HRD) status positive patients (tBRCAm and/or GIS), there was a numerical improvement in OS with olaparib/bevacizumab arm vs placebo/bevacizumab arm: median time 75.2 months vs 57.3 months (HR 0.62; 95% CI: 0.45 to 0.85). The tBRCAm as randomised subgroup demonstrated a numerical reduction in the risk of death for olaparib/bevacizumab compared to placebo/bevacizumab (HR 0.63; 95% CI 0.41, 0.97). For more information, please refer to the Summary of Product Characteristics.
II/0058	Update of section 5.1 of the olaparib tablet SmPC based on results from study D0816C00020 (OPINION); this is a Phase IIIb single arm, multicentre study, investigating olaparib as a maintenance treatment in patients with platinum sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer following 2 or more lines of platinum-based chemotherapy and who did not have a known deleterious or suspected deleterious gBRCA mutation. The MAH also took the opportunity to make minor editorial corrections to the product information.	12/01/2023	25/01/2024	SmPC	At the time of the final OS analysis of study OPINION (DCO 17 Sept 2021), the OS data were 52.3% mature (146 events/279 patients). The median OS was 32.7 months (95% CI: 29.5, 35.3). For more information, please refer to the Summary of Product Characteristics.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0053	Extension of indication to include the use of Lynparza in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with metastatic castration-resistant prostate cancer in whom chemotherapy is not clinically indicated. Consequently, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC and Annex II are updated. The Package Leaflet is updated accordingly. The RMP version 26.1 has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	10/11/2022	16/12/2022	SmPC and PL	Please refer to Scientific Discussion 'Lynparza-EMEA/H/C/003726/II/0053'
IB/0056/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.7.a - Deletion of - a pharmaceutical form	01/09/2022	16/12/2022	SmPC, Labelling and PL	
II/0051/G	This was an application for a group of variations. C.I.6.a - Extension of indication to include the use of Lynparza tablets as monotherapy or in combination with endocrine therapy for the adjuvant treatment of adult patients with germline BRCA1/2-mutations who have HER2-negative, high risk early breast cancer	23/06/2022	02/08/2022	SmPC and PL	Please refer to Scientific Discussion 'Lynparza-H-C-3726-II-0051-G'

	previously treated with neoadjuvant or adjuvant chemotherapy. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 5.1 of the SmPC are updated. The SmPC of Lynparza capsule has been revised accordingly to reflect updated safety information. The Package Leaflet is updated in accordance. In addition, the list of local representatives in the PL has been revised. Version 23.3 of the RMP is approved. B.I.z – to reassess the control strategy for potentially mutagenic impurities in the active substance in view of the proposed extension of indication to an earlier line of cancer treatment. B.I.z - Quality change - Active substance - Other variation C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
PSUSA/10322 /202112	Periodic Safety Update EU Single assessment - olaparib	07/07/2022	n/a		PRAC Recommendation - maintenance
II/0055/G	This was an application for a group of variations. 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 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	30/06/2022	n/a		

	route of synthesis or manufacturing conditions 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.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.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 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				
IA/0052	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	22/11/2021	24/03/2022	SmPC	
II/0048	Update of section 5.1 of the olaparib tablet SmPC based on results from study D0816C00020	11/11/2021	24/03/2022	SmPC and	The primary endpoint was investigator-assessed PFS according to modified RECIST v1.1. Secondary endpoints

	(OPINION) listed as a PAES in the Annex II; this is a Phase IIIb single arm, multicentre study, investigating olaparib as a maintenance treatment in patients with platinum-sensitive relapsed ovarian, fallopian tube or primary peritoneal cancer following 2 or more lines of platinum based chemotherapy and who did not have a known deleterious or suspected deleterious gBRCA mutation; the Annex II is updated accordingly. The RMP version 22.1 has also been submitted. The SmPC is updated with the description of the OPINION study and the main result of the progression-free survival in non-gBRCAm patients with PSR ovarian cancer. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data			Annex II	included OS. Olaparib, when used as maintenance therapy, demonstrated clinical activity in patients with non-gBRCAm PSR ovarian cancer. At the time of primary PFS analysis, the OS data were 30% mature. The Median PFS was 9.2 months (95% CI; 7.6, 10.9).
II/0047	Update of sections 4.8 and 5.1 of the SmPC in order to update safety and efficacy information based on the final analysis of overall survival and safety update from study POLO, a Phase III, randomised, double-blind, placebo-controlled, multicentre study in gBRCAm patients with metastatic pancreatic adenocarcinoma whose disease had not progressed after receiving first-line platinum-based chemotherapy. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	02/09/2021	24/03/2022	SmPC	At final analysis of OS in study POLO (DCO 21 July 2020), the percentage of patients that were alive and in follow up was 28% in the olaparib arm and 18% in the placebo arm. Although OS did not demonstrate a statistically significant difference between treatment arms, the OS HR numerically favoured olaparib (HR: 0.83; 95% CI: 0.56 to 1.22; p=0.3487). The median OS was 19.0 months in the olaparib arm and 19.2 months in the placebo arm.

IA/0050/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	27/07/2021	n/a		
PSUSA/10322 /202012	Periodic Safety Update EU Single assessment - olaparib	08/07/2021	n/a		PRAC Recommendation - maintenance
II/0045	Update of section 5.1 of the SmPC of Lynparza capsules based on the final report from Study/D0816C00012 (ORZORA) listed as PAES in the Annex II of the Product Information. This is an Open Label, Single Arm, Multi-centre Study to Assess the Clinical Effectiveness and Safety of Lynparza (Olaparib) Capsules Maintenance Monotherapy in Platinum Sensitive Relapsed somatic or germline BRCA Mutated Ovarian Cancer Patients who are in Complete or Partial Response Following Platinum based Chemotherapy. The Annex II is updated accordingly. 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	06/05/2021	24/03/2022	SmPC and Annex II	The safety and efficacy of olaparib as a maintenance therapy in the treatment of patients with platinum sensitive relapsed (PSR) high grade serous ovarian, including fallopian tube or primary peritoneal cancer, who carry germline or somatic BRCA mutations and who are in complete or partial response following treatment with at least 2 prior lines of platinum-based chemotherapy were studied in a Phase IV open-label, single arm, multicentre study (ORZORA). The primary endpoints were to assess the real-world clinical effectiveness of olaparib maintenance monotherapy by investigator-assessed progression-free survival (PFS) according to modified Response Evaluation Criteria In Solid Tumours (RECIST) v1.1 in patients with BRCAm and sBRCAm ovarian cancer. Secondary end-points included overall survival (OS) in patients with BRCAm and sBRCAm ovarian cancer. One hundred and forty-five patients were enrolled in the BRCAm cohort (87 gBRCAm patients, 55 sBRCAm patients and 3 patients with germline or somatic

					mutation status undetermined). The study demonstrated that PFS in patients who were sBRCAm was consistent with that observed in BRCAm and gBRCAm patients. At the time of PFS analysis, the OS data were 30% mature.
II/0044	Update of sections 4.8 and 5.1 of the SmPC of Lynparza tablets based on updated efficacy and safety data from the Phase III PAOLA-1 study. In addition, the MAH took the opportunity to switch the order of the capsule and tablet formulations in Annex I of the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	06/05/2021	24/03/2022	SmPC	In study PAOLA-1, final analysis of PFS2 (DCO 22 March 2020, 53% maturity) in the overall population was statistically significant (HR 0.78, 95% CI 0.64-0.95, p=0.0125 with a median of 36.5 months for olaparib/ bevacizumab vs 32.6 months for placebo/bevacizumab). Overall survival data were immature in the overall population and biomarker subgroups. Sixty percent (60%) of patients in the olaparib/ bevacizumab arm and 74% in the placebo/bevacizumab arm received subsequent therapy and of these patients, 20% and 47% in the olaparib/bevacizumab and placebo/bevacizumab arms, respectively, received a PARP inhibitor.
II/0042	Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to add Myelodysplastic syndrome (MDS)/Acute myeloid leukaemia (AML) to the list of adverse drug reactions with the frequency uncommon, modify the existing warning on MDS/AML and update efficacy information based on final results from study SOLO-2 listed as a PAES in the Annex II; this is a phase III randomised, double blind, placebo controlled, multicentre study of olaparib maintenance monotherapy in platinum sensitive relapsed BRCA mutated ovarian cancer patients who are in complete or partial response following platinum based chemotherapy; the Package Leaflet and Annex II are updated accordingly. In addition, the MAH took the	11/02/2021	24/03/2022	SmPC, Annex II and PL	At the final analysis of OS (61% maturity) in SOLO2, the HR was 0.74 (95% CI 0.54-1.00; p=0.0537; median 51.7 months for olaparib vs 38.8 months for placebo) which did not reach statistical significance. The overall incidence of myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML) in patients treated in clinical trials with Lynparza monotherapy, including long term survival follow up, was <1.5%, with higher incidence in patients with BRCAm platinum-sensitive relapsed ovarian cancer who had received at least two prior lines of platinum chemotherapy and were followed up for 5 years (see SmPC section 4.8). The majority of events had a fatal outcome. The duration of therapy with olaparib in patients who developed MDS/AML varied from < 6 months to > 4 years.

	opportunity to make minor corrections to the SmPC. The RMP version 21.2 is approved. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				If MDS/AML is suspected, the patient should be referred to a haematologist for further investigations, including bone marrow analysis and blood sampling for cytogenetics. If, following investigation for prolonged haematological toxicity, MDS/AML is confirmed, Lynparza should be discontinued and the patient treated appropriately.
IB/0043/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.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	06/01/2021	n/a		
II/0036	Extension of indication to include the use of Lynparza tablets as monotherapy for the treatment of adult patients with metastatic castration-resistant prostate cancer and BRCA1/2-mutations (germline and/or somatic) who have progressed following prior therapy that included a new hormonal agent. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC are updated. The PL is updated accordingly. In addition, sections 4.2, 4.4 and 4.8 of the SmPC for Lynparza hard capsules are revised based on updated safety data analysis and minor changes are made to section 5.3. The RMP version 20.3 has also been accepted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or	17/09/2020	03/11/2020	SmPC and PL	Please refer to Scientific Discussion ‘Product Name-H-C-3726-II-36‘

	modification of an approved one				
II/0035	Extension of indication to include the use of Lynparza tablets in combination with bevacizumab for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy in combination with bevacizumab and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either a BRCA1/2 mutation and/or genomic instability. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC are updated. The PL is updated accordingly. In addition, sections 4.4 and 4.8 of the SmPC for Lynparza hard capsules are revised based on updated safety data analysis. Furthermore, the PI is brought in line with the latest QRD template version 10.1. The RMP version 20.3 is approved. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	17/09/2020	03/11/2020	SmPC, Annex II and PL	Please refer to Scientific Discussion 'Lynparza-H-C-003726-II-35'
PSUSA/10322 /201912	Periodic Safety Update EU Single assessment - olaparib	23/07/2020	24/09/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10322/201912.
IB/0041	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing	08/07/2020	n/a		

	authorisation, including the RMP - Other variation				
II/0033	Extension of Indication to support the use of Lynparza tablets (100mg and 150 mg) for the maintenance treatment of gBRCAm metastatic pancreatic cancer based on the results from the pivotal Phase 3 study, POLO; as a consequence, sections 4.1, 4.2, 4.8, 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to update section 4.8 for lynparza hard capsules (50 mg) to revise list of ADR based on the pooled safety data analysis. The RMP version 18.3 has also been submitted. Furthermore, the PI is brought in line with the latest guideline regarding the sodium content. The MAH also took the occasion to include some minor editorial changes in the PI. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	28/05/2020	03/07/2020	SmPC and PL	Please refer to Scientific Discussion 'Lynparza-H-C-003726-II-0033'
IB/0040/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	22/06/2020	n/a		

	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation				
IB/0039	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	22/04/2020	03/07/2020	Annex II	
IAIN/0037/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.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	28/01/2020	n/a		
R/0029	Renewal of the marketing authorisation.	25/07/2019	01/10/2019	SmPC and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Lynparza in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10322 /201812	Periodic Safety Update EU Single assessment - olaparib	11/07/2019	n/a		PRAC Recommendation - maintenance
II/0023	Extension of indication to include the use of Lynparza (tablet formulation) as monotherapy for the maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following	26/04/2019	12/06/2019	SmPC and PL	Please refer to the Scientific Discussion Lynparza-H-C-3726-II-23

	completion of first-line platinum-based chemotherapy. As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8 and 5.1 the SmPC of the tablet formulation have been updated. Sections 4.2, 4.4, 4.8 and 5.1 of the SmPC of the capsule formulation have also been modified to reflect information that is also relevant to the capsule formulation. The Package Leaflet has been updated accordingly. The RMP version 17.4 has also been accepted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0028	Update of section 5.2 of the SmPC in order to include information on the in vitro effect of olaparib on UGT enzymes based on results from in vitro assays. In addition, the MAH is proposing to change the due date for submission of the final CSR of the phase IV, open label, single arm study (D0816C00012/ORZORA) in patients with relapsed platinum sensitive ovarian cancer who are in response following platinum-based chemotherapy and who carry loss of function germline or somatic BRCA mutations, listed as a PAES in the Annex II. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	16/05/2019	01/10/2019	SmPC and Annex II	In vitro, olaparib produced little/no inhibition of UGT1A4, UGT1A9, and is not expected to be a clinically significant time dependent inhibitor of any of these CYP enzymes.

IB/0032	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	03/05/2019	01/10/2019	SmPC	
II/0020	Extension of indication to include the use of Lynparza tablets as monotherapy for the treatment of adult patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer; patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant or metastatic setting unless patients were not suitable for these treatments. Patient with hormone receptor (HR)-positive breast cancer should also have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy. As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.6, 4.8, 5.1 and 5.2 of the SmPC of Lynparza tablets have been updated. The SmPC of Lynparza capsule has been revised to reflect updated safety information and the Package Leaflet has been updated accordingly. Furthermore, RMP version 16.3 has also been accepted. Changes were also made to the PI to bring it in line with the SmPC guideline and excipients guideline which were reviewed by QRD and accepted by the CHMP. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	28/02/2019	08/04/2019	SmPC and PL	Please refer to the Scientific Discussion Lynparza-H-C-3726-II-20.
IAIN/0031	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP -	05/04/2019	12/06/2019	Annex II and	

	Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing			PL	
IAIN/0030/G	This was an application for a group of variations. 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 B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing	05/04/2019	12/06/2019	Annex II and PL	
IB/0026/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products 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 B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation	14/02/2019	n/a		
IB/0025/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The	21/11/2018	n/a		

	proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
IB/0024	B.I.e.5.b - Implementation of changes foreseen in an approved change management protocol - Requires further supportive data	25/10/2018	n/a		
II/0022	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	26/07/2018	08/04/2019	SmPC, Labelling and PL	The instructions on how to store Lynparza have been updated to recommend storage in a refrigerator (2°C – 8°C). If preferred, Lynparza capsules can be kept out of the refrigerator (below 30°C) for up to 3 months. After this period, any capsules that have not been used must be thrown away. Lynparza should not be frozen. The shelf-life has also been extended from 18 months to 2 years.
PSUSA/10322 /201712	Periodic Safety Update EU Single assessment - olaparib	12/07/2018	n/a		PRAC Recommendation - maintenance
IB/0021/G	This was an application for a group of variations. B.I.b.1.h - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition or replacement (excl. Biol. or immunol. substance) of a	16/05/2018	n/a		

	specification parameter as a result of a safety or quality issue B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation				
X/0016/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data Annex I_2.(a) Change of bioavailability Annex I_2.(b) Change of pharmacokinetics change in rate of release Annex I_2.(c) Change or addition of a new strength/potency Annex I_2.(d) Change or addition of a new pharmaceutical form	22/02/2018	08/05/2018	SmPC, Annex II, Labelling and PL	
PSUSA/10322 /201706	Periodic Safety Update EU Single assessment - olaparib	11/01/2018	n/a		PRAC Recommendation - maintenance
PSUSA/10322 /201612	Periodic Safety Update EU Single assessment - olaparib	20/07/2017	18/09/2017	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10322/201612.
IB/0017/G	This was an application for a group of variations. B.II.d.1.g - Change in the specification parameters and/or limits of the finished product - Addition or replacement (excluding biological or immunological product) of a specification parameter wit its corresponding test method as a result of a safety or	12/06/2017	18/09/2017	SmPC	

	quality issue B.II.f.1.a.1 - Stability of FP - Reduction of the shelf life of the finished product - As packaged for sale B.II.f.1.e - Stability of FP - Change to an approved stability protocol				
IB/0012	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	12/04/2017	n/a		
IB/0015	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	07/04/2017	n/a		
IB/0014	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	07/04/2017	n/a		
PSUSA/10322 /201606	Periodic Safety Update EU Single assessment - olaparib	12/01/2017	n/a		PRAC Recommendation - maintenance
IA/0011	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	12/12/2016	n/a		
II/0009/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	10/11/2016	12/12/2016	SmPC and PL	

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0008/G	This was an application for a group of variations. Update of section 4.2 and 5.2 of the SmPC with recommendations for patients with renal impairment based on the results of study D0816C00006 (MEA 006), that evaluated the influence of mild and moderate renal impairment on the pharmacokinetics of Olaparib. The Package Leaflet and RMP were updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update local representatives in the PL, to bring the PI in line with the latest QRD template version and introduce minor corrections in the PI. Furthermore, a grouping of two type IB variation is submitted to revise the study milestones dates for the category 3 study D0816C00005 and category 1 study D0816C00002 in the RMP. Annex II has been amended accordingly. The requested group of variations proposed amendments to the Summary of Product Characteristics, Annex II, Labelling, Package Leaflet and Annex A and to the Risk Management Plan (RMP) C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/09/2016	21/10/2016	SmPC, Annex II, Labelling and PL	The MAH provided a PK study conducted in patients with renal insufficiency (study D0816C00006). In patients with mild renal impairment (creatinine clearance 51 to 80 ml/min), AUC increased by 24% and Cmax by 15% compared with patients with normal renal function. No Lynparza dose adjustment is required for patients with mild renal impairment. In patients with moderate renal impairment (creatinine clearance 31 to 50 ml/min), AUC increased by 44% and Cmax by 26% compared with patients with normal renal function. Lynparza dose adjustment is recommended for patients with moderate renal impairment. These findings have been reflected in section 4.2 as follows: For patients with moderate renal impairment (creatinine clearance 31 to 50 ml/min) the recommended dose of Lynparza is 300 mg twice daily (equivalent to a total daily dose of 600 mg). Lynparza can be administered in patients with mild renal impairment (creatinine clearance 51 to 80 ml/min) with no dose adjustment. Lynparza is not recommended for use in patients with severe renal impairment or end-stage renal disease (creatinine clearance ≤ 30 ml/min) since there are no data in such patients.

	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				
PSUSA/10322 /201512	Periodic Safety Update EU Single assessment - olaparib	07/07/2016	n/a		PRAC Recommendation - maintenance
II/0001/G	This was an application for a group of variations. Update of sections 4.2, 4.4, 4.5, 4.6 and 5.2 of the SmPC in order to include further information related to pharmacokinetic interactions based on the in vivo interaction study D0816C00008, 3 in vitro interaction studies (ADME-AZS-Wave3-140714, ADME-AZS-Wave3-140725 and 140483) and data from previously submitted interaction studies. The provision of the final CSR for study D0816C00008 addresses the post-authorisation measure MEA 004. Further, the MAH provided the study report for in vitro study 8305083 as part of the application. In addition, the MAH took the opportunity to add the published ATC code in section 5.1 of the SmPC, and to implement minor editorial changes in the SmPC, labelling and Package Leaflet. A revised RMP version 9 was agreed during the procedure, which includes consequential changes related to data on interactions. Further, the MAH took the opportunity to update the due dates for the provision of the final study reports of the category 3	25/02/2016	31/03/2016	SmPC, Labelling and PL	Concomitant use of strong and moderate CYP3A inhibitors is not recommended and alternative agents should be considered. If a strong or moderate CYP3A inhibitor must be co-administered, the recommended olaparib dose reduction is to 150 mg taken twice daily (equivalent to a total daily dose of 300 mg) with a strong CYP3A inhibitor or 200 mg taken twice daily (equivalent to a total daily dose of 400 mg) with a moderate CYP3A inhibitor. Olaparib co administration with strong CYP3A inducers is not recommended. In the event that a patient already receiving olaparib requires treatment with a strong CYP3A inducer, the prescriber should be aware that the efficacy of olaparib may be substantially reduced. For further more detailed information, please consult section 4.5 of the SmPC.

	studies D0816C00005 and D0816C00006, and to add the new category 3 study D0816C00010. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
PSUSA/10322 /201506	Periodic Safety Update EU Single assessment - olaparib	14/01/2016	n/a		PRAC Recommendation - maintenance

IA/0006/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.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.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	11/01/2016	n/a		
IB/0004	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	16/12/2015	n/a		
IG/0633	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	09/12/2015	n/a		
IB/0003	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	17/11/2015	n/a		
