# Rubraca

## 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 |
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| IAIN/0044 | C.I.12 - Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring | 02/04/2024 | | SmPC and PL | |

[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).

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| IB/0042/G | This was an application for a group of variations.<br><br>B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data<br>B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data) | 14/02/2024 | | SmPC | |
| II/0036 | Extension of indication to include 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 for RUBRACA, based on interim results from study CO-338-087 (ATHENA); this is a Phase III, randomised, double-blind, dual placebo controlled study of rucaparib as monotherapy and in combination with nivolumab in patients with newly diagnosed EOC, FTC, or PPC who have responded to their first-line treatment (surgery and platinum-based chemotherapy). As a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance, in addition, the list of local representatives has been updated. Version 8.1 of the RMP has also been approved.<br>The variation leads to amendments to the Summary of Product Characteristics, Annex II and Package | 12/10/2023 | 15/11/2023 | SmPC and PL | Please refer to Scientific Discussion 'Rubraca-H-C-004272-II-0036' |

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| | Leaflet and to the Risk Management Plan (RMP).<br><br>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | | | | |
| IAIN/0041 | A.1 - Administrative change - Change in the name and/or address of the MAH | 10/10/2023 | 15/11/2023 | SmPC, Labelling and PL | |
| PSUSA/10694 /202212 | Periodic Safety Update EU Single assessment - rucaparib | 06/07/2023 | n/a | | PRAC Recommendation - maintenance |
| T/0040 | Transfer of Marketing Authorisation | 26/05/2023 | 08/06/2023 | SmPC, Labelling and PL | |
| II/0037 | Update of sections 4.4 and 5.1 of the SmPC in order to update the efficacy and safety information based on the final results from study CO-338-014 (ARIEL 3) listed as a category 1 PAES in the Annex II; this is a phase 3, multicenter, randomized, double-blind, placebo-controlled study of rucaparib as switch maintenance following platinum-based chemotherapy in patients with platinum-sensitive, high grade serous or endometrioid epithelial ovarian, primary peritoneal or fallopian tube cancer. Annex II and the RMP version 7.1 are updated accordingly. In addition, the MAH took the opportunity to introduce minor editorial changes to the PI.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to | 25/05/2023 | 15/11/2023 | SmPC and Annex II | In study ARIEL 3, at the final OS analysis (70% maturity) the Hazard Ratio (HR) was 1.00 (95% CI: 0.81, 1.22; median 36 months for rucaparib vs 43.2 months for placebo) for the ITT population. For the HRD and tBRCA subgroups the reported HRs were 1.01 (95% CI: 0.77, 1.32; median 40.5 months for rucaparib vs 47.8 months for placebo) and 0.83 (95% CI: 0.58, 1.19; median 45.9 months for rucaparib vs 47.8 months for placebo), respectively. In an exploratory subgroup analysis of patients without a tBRCA mutation (non-nested, non-tBRCA subpopulations [LOH+, LOH-, LOH unknown]), the HR for OS was 1.084 (95% CI: 0.841, 1.396; median 32.2 months for rucaparib vs 38.3 months for placebo). The median survival follow-up for all patients was 77 months (6.4 years) with a range of 2 days to 93 months (7.6 years). |

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| | new quality, preclinical, clinical or pharmacovigilance data | | | | At the time of the final analysis, 89% of patients in the placebo arm had received at least one subsequent treatment, of whom 46% received a PARP inhibitor. In the rucaparib arm, 78% of patients had received at least one subsequent treatment.<br>For more information, please refer to the Summary of Product Characteristics. |
| PSUSA/10694 /202206 | Periodic Safety Update EU Single assessment - rucaparib | 12/01/2023 | n/a | | PRAC Recommendation - maintenance |
| IAIN/0038 | A.1 - Administrative change - Change in the name and/or address of the MAH | 07/12/2022 | 08/06/2023 | SmPC, Labelling and PL | |
| II/0029 | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 15/09/2022 | 09/11/2022 | SmPC, Annex II and PL | |
| A20/0033 | Pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested on 22 April 2022 the opinion of the European Medicines Agency to assess the impact of the results from a phase 3 study listed as a specific obligation relating to the following indication of Rubraca: 'monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, BRCA mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum based chemotherapy, and who are unable to tolerate further platinum based chemotherapy'. | 21/07/2022 | 21/09/2022 | SmPC, Annex II and PL | Please refer to the assessment report: Rubraca EMEA/H/A-20/1518/C/4272/0033 |

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| | These are results from study CO-338-043 (ARIEL4): a phase 3, multicentre, open-label, randomised study evaluating the efficacy and safety of rucaparib versus chemotherapy for treatment of relapsed ovarian' showing a detrimental effect of rucaparib on overall survival (OS) compared with the chemotherapy control.<br>The CHMP was requested to assess the impact thereof on the benefit-risk balance of Rubraca in this indication and to give its opinion whether the marketing authorisation of this product should be maintained or varied. | | | | |
| IB/0034/G | This was an application for a group of variations.<br><br>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<br>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<br>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 | 19/07/2022 | n/a | | |

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| | corresponding test method<br>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<br>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS | | | | |
| PSUSA/10694 /202112 | Periodic Safety Update EU Single assessment - rucaparib | 07/07/2022 | n/a | | PRAC Recommendation - maintenance |
| IA/0032/G | This was an application for a group of variations.<br><br>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<br>B.II.f.1.e - Stability of FP - Change to an approved stability protocol | 22/03/2022 | n/a | | |
| R/0030 | Renewal of the marketing authorisation. | 27/01/2022 | 04/03/2022 | | The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Rubraca, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion. |

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| PSUSA/10694 /202012 | Periodic Safety Update EU Single assessment - rucaparib | 22/07/2021 | 16/09/2021 | SmPC and PL | Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10694/202012. |
| IB/0028 | B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data | 18/05/2021 | n/a | | |
| R/0025 | Renewal of the marketing authorisation. | 28/01/2021 | 04/03/2021 | | The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Rubraca, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion. |
| IA/0026 | A.6 - Administrative change - Change in ATC Code/ATC Vet Code | 16/02/2021 | 16/09/2021 | SmPC and PL | |
| PSUSA/10694 /202006 | Periodic Safety Update EU Single assessment - rucaparib | 14/01/2021 | n/a | | PRAC Recommendation - maintenance |
| II/0020 | Update of sections 4.2 and 5.2 of the SmPC in order to update the information on the use of rucaparib in patients with hepatic impairment based on final results from Part I of Study CO-338-078 listed as a category 3 study in the RMP; this is a phase 1, open-label, parallel group study to determine the pharmacokinetics, safety and tolerability of rucaparib | 12/11/2020 | 17/12/2020 | SmPC, Annex II, Labelling and PL | The Applicant has conducted a Phase 1, open-label, parallel-group, PK, safety, and tolerability study in patients with advanced solid tumour and either normal hepatic function or moderate hepatic impairment. Pharmacokinetic exposure parameters of rucaparib and M324 metabolite were compared between the patients with moderate hepatic impairment and the patients with normal hepatic |

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| | in patients with an advanced solid tumour and either moderate hepatic impairment or normal hepatic function; the Package Leaflet is updated accordingly. The RMP version 4.2 has also been submitted. In addition, the MAH took the opportunity to make minor corrections in the SmPC, to update the list of local representatives in the Package Leaflet, and to bring the PI in line with the latest QRD template version 10.1 and excipient guideline.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | function. The number of total patients recruited was 16, 8 patients per group. The statistical comparison of the exposure parameters demonstrated the lack of impact on Cmax due to the hepatic function, but a clinically relevant increase in AUC of rucaparib and its main metabolite (M324) in patients with moderate hepatic impairment compared to patients with normal hepatic function. The SmPC has been amended to include a cautionary statement in patients with moderate hepatic impairment. |
| II/0024/G | This was an application for a group of variations.<br><br>Submission of the final reports from four non-clinical studies (Report 181000, OPT-2018-074, 8388100 and CLO-P8799).<br><br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority<br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority<br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority<br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission | 03/12/2020 | n/a | | |

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| | of studies to the competent authority | | | | |
| II/0023 | Update of sections 4.5, 4.6 and 5.2 of the SmPC to add drug-drug interaction (DDI) information with rosuvastatin and oral contraceptives based on the results of Study CO-338-095 listed as a category 3 study in the RMP; Study CO-338-095 is a phase 1, open-label, DDI study to determine the effect of rucaparib on the pharmacokinetics of oral rosuvastatin (Arm A) and oral contraceptives (ethinylestradiol and levonorgestrel - Arm B) in patients with advanced solid tumours. The RMP version 6.0 has also been submitted.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 26/11/2020 | 04/03/2021 | SmPC | Results of a Phase I, open-label, 2-arm study to investigate the drug-drug interaction (DDI) between rucaparib and oral rosuvastatin (Arm A) and between rucaparib and oral ethinylestradiol and levonorgestrel (Arm B) have been submitted. The evaluation of the impact of concomitant administration of rucaparib in patients receiving BCRP substrates or oral contraceptives suggested a weak effect of rucaparib in increasing the exposure of BCRP substrates and oral contraceptives by less than 1.5-fold. The SmPC has been updated to include the increase in exposure. No dose modification is recommended given the minor increase in the exposure. The safety profile of rucaparib was consistent with its already known safety profile. |
| IB/0021/G | This was an application for a group of variations.<br><br>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS<br>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS<br>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 | 27/07/2020 | n/a | | |
| PSUSA/10694 | Periodic Safety Update EU Single assessment - | 09/07/2020 | n/a | | PRAC Recommendation - maintenance |

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| /201912 | rucaparib | | | | |
| II/0019/G | This was an application for a group of variations.<br><br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority<br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority | 28/05/2020 | n/a | | |
| IB/0017/G | This was an application for a group of variations.<br><br>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS<br>B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits<br>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 specification parameter as a result of a safety or quality issue<br>B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure | 22/04/2020 | n/a | | |
| R/0016 | Renewal of the marketing authorisation. | 27/02/2020 | 17/04/2020 | | The CHMP, having reviewed the available information on |

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| | | | | | the status of the fulfilment of Specific Obligations and having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Rubraca, subject to the Specific Obligations and Conditions as laid down in Annex II to the Opinion. |
| PSUSA/10694 /201906 | Periodic Safety Update EU Single assessment - rucaparib | 16/01/2020 | n/a | | PRAC Recommendation - maintenance |
| IB/0014 | C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | 04/09/2019 | n/a | | |
| IB/0013 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 14/06/2019 | n/a | | |
| IB/0012 | B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data) | 12/04/2019 | 27/01/2020 | SmPC | |
| II/0009 | C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority | 11/04/2019 | n/a | | |
| PSUSA/10694 /201809 | Periodic Safety Update EU Single assessment - rucaparib | 11/04/2019 | n/a | | PRAC Recommendation - maintenance |
| R/0008 | Renewal of the marketing authorisation. | 31/01/2019 | 13/03/2019 | | The CHMP, having reviewed the available information on the status of the fulfilment of Specific Obligations and |

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| | | | | | having confirmed the positive benefit risk balance, is of the opinion that the quality, safety and efficacy of this medicinal product continue to be adequately and sufficiently demonstrated and therefore recommends the renewal of the conditional MA for Rubraca, subject to the Specific Obligations and Conditions as laid down in Annex II to the opinion. |
| IAIN/0010/G | This was an application for a group of variations.<br><br>B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site<br>B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing | 11/02/2019 | 27/01/2020 | Annex II and PL | |
| IB/0006 | B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data | 31/01/2019 | n/a | | |
| II/0001 | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | 13/12/2018 | 23/01/2019 | SmPC, Annex II and PL | Please refer to Scientific Discussion 'Rubraca-H-C-004272-II-001' |
| II/0002 | C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority | 13/12/2018 | n/a | | |

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| T/0005 | Transfer of Marketing Authorisation | 14/11/2018 | 07/12/2018 | SmPC, Labelling and PL | |
| II/0003 | To update section 5.2 of the SmPC based on final results from Part 1 of study CO-338-45; this is a Phase 1, single-dose study of the disposition of [14C]-radiolabelled rucaparib in patients with advanced solid tumours<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 15/11/2018 | 23/01/2019 | SmPC | Following administration of a single oral dose of [14C]-rucaparib to patients with solid tumours, unchanged rucaparib accounted for 64.0% of the radioactivity in plasma. Oxidation, N-demethylation, N-methylation, glucuronidation, and N-formylation were the major metabolic pathways for rucaparib. The most abundant metabolite was M324, an oxidative deamination product of rucaparib, accounting for 18.6% of the radioactivity in plasma. In vitro, M324 was at least 30 fold less potent than rucaparib against PARP-1, PARP-2, and PARP-3. Other minor metabolites accounted for 13.8% of the radioactivity in plasma.<br>The overall mean recovery of radioactivity was 89.3%, with a mean recovery of 71.9% in faeces and 17.4% in urine by 288 hours post dose. Rucaparib accounted for 44.9% and 94.9% of radioactivity in urine and faeces, respectively; while M324 accounted for 50.0% and 5.1% of radioactivity in urine and faeces, respectively. Ninety percent of the observed faecal recovery was achieved within 168 hours post-dose. The mean half-life (t1/2) of rucaparib was 25.9 hours. |
| IB/0004/G | This was an application for a group of variations.<br><br>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 | 26/09/2018 | n/a | | |

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| | 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<br>B.I.a.3.d - Change in batch size (including batch size ranges) of AS or intermediate - More than 10-fold increase compared to the originally approved batch size<br>B.I.a.3.d - Change in batch size (including batch size ranges) of AS or intermediate - More than 10-fold increase compared to the originally approved batch size | | | | |