EMA/26688/2021

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
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	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

[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).

	pharmacokinetics, safety and tolerability of rucaparib 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. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				hepatic impairment and the patients with normal hepatic 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. Submission of the final reports from four non-clinical studies (Report 181000, OPT-2018-074, 8388100 and CLO-P8799). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission	03/12/2020	n/a		

	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. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/11/2020		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. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.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 /201912	Periodic Safety Update EU Single assessment - rucaparib	09/07/2020	n/a		PRAC Recommendation - maintenance

II/0019/G	This was an application for a group of variations. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority 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. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits 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 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 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 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. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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		
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 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. 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. 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.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	26/09/2018	n/a		

	size 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 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				