NOTIFICATION TO THE CHMP / EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 20 OF REGULATION (EC) 726/2004
E-mail: ReferralNotifications@ema.europa.eu

This notification is a referral under Article 20 of Regulation (EC) 726/2004 to the Committee for Human Medicinal Products (CHMP) made by the European Commission (EC):

Product(s) Name(s)	Rubraca
Active substance(s)	rucaparib camsylate
Pharmaceutical form(s)	All
Strength(s)	All
Route(s) of Administration	All
Marketing Authorisation Holder	Clovis Oncology Ireland Ltd.

Background

Rubraca contains rucaparib, an inhibitor of poly(ADP-ribose) polymerase (PARP) enzymes, including PARP-1, PARP-2, and PARP-3, which play a role in DNA repair. Rucaparib has been shown to have *in vitro* and *in vivo* anti-tumour activity in BRCA mutant cell lines through a mechanism known as synthetic lethality, whereby the loss of two DNA repair pathways is required for cell death.

It is a centrally authorised product currently authorised in two oncology indications:

1. Monotherapy for the maintenance treatment of adult patients with platinum sensitive relapsed high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy;

2. 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.

Rubraca was initially granted a conditional marketing authorisation (CMA) in 2018for the '3rd line or more treatment' indication (second indication above) based on overall response rate (ORR) data from a pooled population from two phase 2 single arm studies (Study CO 338 010 and Study CO 338 017). As a condition to the marketing authorisation, in order to further quantify the efficacy of Rubraca in terms of time-related endpoints in the approved indication, the marketing authorisation holder (MAH) was requested to submit the results from study CO-338-043 (ARIEL4), a phase 3, multicentre, open-label, randomised study evaluating the efficacy and safety of the active substance rucaparib versus chemotherapy for treatment of relapsed ovarian cancer.

The indication was extended in 2019 to the indication first mentioned above ("maintenance") based on progression-free survival (PFS) data from study CO-338-014 (ARIEL3) (variation EMEA/H/C/004272/II/0001). Limited interim overall survival (OS) data were available at the time of granting this extension of the indication but a detrimental effect on OS was considered unlikely. In order to further investigate the efficacy of rucaparib in the maintenance setting the MAH was requested to submit the results from the final OS analysis of the ARIEL3 study as an Annex II condition (post-authorisation efficacy study (PAES)) of the marketing authorisation.

Issues to be considered

A difference in favour of rucaparib was observed in the final analysis for the primary endpoint of progression free survival by investigator (invPFS) in study ARIEL4 comparing rucaparib 600 mg twice a day (N=233) versus chemotherapy (N=116). A median invPFS of 7.4 months was reported for the rucaparib group compared to 5.7 months for the chemotherapy group (HR=0.639; p=0.0010).

However, an interim analysis of OS performed at a 51% data maturity (final OS analysis currently planned at 69%, expected by end of April 2022), showed a detriment in OS [median OS was 19.6 months (95% CI: 16.8, 24.0) in the rucaparib group vs. 27.1 months (95% CI: 22.2, 38.1) in the chemotherapy group; HR=1.55 (95% CI: 1.085, 2.214), p=0.0161 (nominal)].

Based on the above, there is a concern that the efficacy of the product may not be confirmed in the approved '3rd line or more treatment' indication, potentially no longer outweighing the risks of rucaparib.

In light of the current emerging OS data, there is a need to review the findings in the context of all available data and assess their potential impact on the benefit/risk of Rubraca in the approved '3rd line or more treatment' indication.

In view of the above, the European Commission (EC) initiates a procedure under Article 20 of Regulation (EC) No 726/2004 and requests the Agency/CHMP to assess the above concerns and their impact on the benefit-risk balance of the centrally authorised medicinal product Rubraca (rucaparib) in the approved '3rd line or more treatment'.

The EC requests the Agency/CHMP to give its opinion by 31 October 2022 on whether the marketing authorisation for this product should be maintained or amended.

In addition, the EC requests the Agency/CHMP to give its opinion, as soon as possible, as to whether temporary measures are necessary to ensure the safe and effective use of this medicinal product.

Signed Date 22/04/2022
Olga Solomon
Head of Unit - Medicines: policy, authorisation and monitoring
Health and Food Safety Directorate General