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**IMPORTANT MEDICINE
SAFETY INFORMATION**

APPROVED
BY THE



Direct Healthcare Professional Communication

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Rucaparib (Rubraca[®]▼): interim data from Study CO-338-043 (ARIEL4) show a decrease in overall survival compared to standard of care

Dear Healthcare Professional,

Clovis Oncology Ireland Ltd, in agreement with the European Medicines Agency (EMA) and the Health Products Regulatory Authority (HPRA) would like to inform you of the following:

Summary

- A detrimental effect in terms of overall survival (OS) has been observed for rucaparib compared to the chemotherapy-containing control arm (19.6 months and 27.1 months respectively with a Hazard Ratio (HR) of 1.550 (95% CI: 1.085, 2.214), $p=0.0161$) following a planned interim analysis (IA) in the post-approval randomized controlled study CO-338-043 (ARIEL4).
- The European Medicines Agency (EMA) is performing a review of all available information to assess the impact of this information on the use of rucaparib as monotherapy for the 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.
- While the review is ongoing, physicians are recommended not to start monotherapy treatment with rucaparib in the above treatment indication.
- The recommendation above does not apply to the indication of 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.

- Safety data reported so far for rucaparib in the ARIEL4 study appear consistent with that reported in other clinical trials of rucaparib.

Background information

Rubraca received a conditional marketing authorisation (CMA) in May 2018 “*as 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*”. This indication was based on overall response rate results from a pooled population from two phase 2 single arm studies (Study CO-338-010 and Study CO-338-017).

The approval was subject to confirmation of rucaparib efficacy and safety in study CO-338-043 (ARIEL4), an ongoing phase 3, multicenter, randomized (2:1) study of rucaparib 600 mg BID (N=233) versus chemotherapy (N=116) in patients with relapsed, BRCA-mutant, high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer.

In the efficacy population in the ARIEL4 study, a difference in favour of rucaparib was observed for the primary endpoint of progression free survival by investigator (invPFS), with a reported median invPFS of 7.4 months for the rucaparib group compared to 5.7 months for the chemotherapy group (HR=0.639; p=0.0010).

However, an OS detriment was observed at the planned IA with 51% data maturity (final OS analysis planned at 70%) with a median OS of 19.6 months in the rucaparib group compared to 27.1 months in the chemotherapy group resulting in an OS HR of 1.550 (95% CI: 1.085, 2.214), p=0.0161. Patients included in the study were stratified at the time of randomization according to platinum sensitivity (platinum sensitive vs. partially platinum sensitive vs. platinum resistant). The HRs for OS in these subgroups were 1.12 (95% CI: 0.44-2.88), 1.15 (95% CI: 0.62-2.11) and 1.72 (95% CI: 1.13-2.64), respectively. Final OS data from the ARIEL4 study are not yet available.

The safety data reported for rucaparib in the ARIEL4 study appears to be in line with the known safety profile of the product.

The label of Rubraca was extended in January 2019 to include its use “*as 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*”. This approval was based on a PFS benefit reported in the ongoing randomized, double-blind, placebo-controlled phase 3 study CO-338-014 (ARIEL3). Final OS data from this study will be included in an ongoing review of the authorised use of Rubraca.

The EMA is assessing all available information, including additional OS data from the ARIEL3 study. An update of the OS data from the ARIEL4 study, which will be available soon, will also be part of the assessment. The outcome of this evaluation will be communicated as soon as available.

While the review is ongoing, physicians are recommended not to initiate treatment with rucaparib in the approved third line or more treatment setting, see above.

Call for reporting

Healthcare professionals and patients are encouraged to report any adverse events associated with the use of rucaparib in accordance with the national spontaneous reporting system via HPRAs Pharmacovigilance, website: www.hpra.ie, and to Clovis Oncology by visiting the following website where you will find a link to the reporting contact information for your country:

<https://www.clovisoncology.com/european-inquires-contact-info/>.

Company contact point

Giorgos Bakalos, Senior Vice President

Clovis Oncology UK Ltd

2nd floor, 77 Farringdon Road, London, EC1M 3JU

United Kingdom

www.clovisoncology.com

email: giorgos.bakalos@clovisoncology.com

phone: +353 16950030 (Clovis Medical Information)

Yours sincerely,



Giorgos Bakalos, MD, MSc, PhD

Senior Vice President, Medical Affairs