Direct Healthcare Professional Communication

<Date>

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 <National Competent Authority> 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 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 that 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 <include details (e.g. name, postal address, fax number, website address) on how to access the national spontaneous reporting system>, 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

<Contact point details for access to further information, including relevant website address(es), telephone number(s), and a postal address>

Yours sincerely,

[Names, titles, roles]

References *[as applicable; add below]*

Communication Plan for Direct Healthcare Professional Communication

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	Rubraca 200 mg, 250 mg, and 300 mg film-coated tablets (rucaparib)
Marketing authorisation holder(s)	Clovis Oncology Ireland Ltd.
Safety concern and purpose of the communication	Important information about Rubraca (rucaparib) being administered as monotherapy treatment for 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.
DHPC recipients	Gynaecological oncologists and nurse prescribers, plus Chief pharmacists as per country specific distribution channels, relevant oncology hospitals and oncology clinics, according to local regulations.
Member States where the DHPC will be distributed	All EEA member states where Rubraca is approved for the indication.

Timetable	Date
DHPC and communication plan (in English) agreed by CHMP	22 April 2022
Submission of translated DHPCs to the national competent authorities for review	28 April 2022
Agreement of translations by national competent authorities	3 May 2022
Dissemination of DHPC in all EEA member states where Rubraca is commercially available for any indication **(France, Germany, Italy, Netherlands, Spain)**	5 May 2022
Dissemination of DHPC to all other EEA member states where Rubraca is approved for any indication	10 May 2022