Direct Healthcare Professional Communication

<Date>

Rubraca▼ (rucaparib): restriction of indication

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

- Rubraca should no longer be used 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.
- A detrimental effect of rucaparib on overall survival (OS) compared with the chemotherapy control, has been observed within the final analysis of data from the phase 3 study CO-338-043 (ARIEL4) for treatment of patients with advanced, recurrent ovarian cancer (HR = 1.31 [95% CI: 1.00, 1.73]).
- Ongoing treatment in this setting should be reconsidered and patients be informed of the latest data and recommendations.
- Rubraca remains authorised 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.

Background information

Based on overall response rate (ORR) results from a pooled population from two phase 2 single-arm studies (CO-338-010 and CO-338-017), rucaparib received a conditional marketing authorisation (CMA) in May 2018 for the following indication: "*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 conditional authorisation was subject to confirmation of rucaparib efficacy and safety in study CO-338-043 (ARIEL4); a phase 3, multicentre, open-label, 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, who received two or more prior lines of chemotherapy. The patients included in the study were stratified at the time of randomization according to platinum sensitivity (fully platinum sensitive *vs* partially platinum sensitive *vs* platinum resistant). In addition, patients initially randomized to chemotherapy had the option to cross-over to rucaparib treatment following disease progression; at the final OS analysis, 69% of patients (n=80/116) in the control arm had received subsequent treatment with rucaparib.

In the intent-to-treat (ITT) population of 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 0.665 [95% CI, 0.516-0.858]; p=0.0017). However, at the final analysis of the secondary endpoint of OS, a detrimental effect was observed for patients randomized to rucaparib. Median OS was 19.4 months in the rucaparib group compared with 25.4 months in the chemotherapy group, resulting in a HR of 1.31 [95% CI: 1.00, 1.73] (p=0.0507). The HRs for OS in the subgroups of fully platinum sensitive, partially platinum sensitive and platinum resistant were 1.24 [95% CI: 0.62, 2.50] (p=0.5405), 0.97 [95% CI: 0.58, 1.62] (p=0.9129), and 1.51 [95% CI: 1.05, 2.17] (p=0.0251) respectively.

It is acknowledged that in the context of the approved treatment indication, the subgroup of platinum sensitive patients (particularly those partially sensitive) represents the most relevant population. Although no statistically significant differences were observed in OS (HR = 1.07 [95% CI: 0.71, 1.62]; p=0.5405) in this subgroup of (combined) platinum sensitive patients, results were not considered reassuring.

In view of the above data, the benefit/risk of rucaparib can no longer be considered favourable in the third line treatment indication.

Rucaparib remains authorised 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.

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]*

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	Rubraca (rucaparib) 200 mg, 250 mg, and 300 mg film-coated tablets
Marketing authorisation holder(s)	Clovis Oncology Ireland Ltd.
Safety concern and purpose of the communication	To alert healthcare professionals that the third-line treatment indication for Rubraca (rucaparib) (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) is being withdrawn following the observation of a detrimental effect of rucaparib on overall survival (OS) compared with the chemotherapy control within the final analysis of data from phase 3 study CO-338-043 (ARIEL4).
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, as agreed with Competent Authorities at the time of the previous DHPC dated April 2022.
Member States where the DHPC will be distributed	All EEA member states where Rubraca is authorised.

Timetable	Date
DHPC and communication plan (in English) agreed by CHMP	21 July 2022
Submission of translated DHPCs to the national competent authorities for review	27 July 2022
Agreement of translations by national competent authorities	2 August 2022
Dissemination of DHPC in all EEA member states where Rubraca is commercially available **(France, Germany, Italy, Netherlands, Spain)**	8 August 2022
Dissemination of DHPC to all other EEA member states	12 August 2022