Annex IV

Scientific conclusions

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Rubraca (rucaparib) is authorised since 2018 and is indicated:

- as monotherapy for the treatment of adult patients with platinum sensitive, relapsed or progressive, breast cancer gene (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 ("3rd line or more treatment" or "treatment" indication);
- 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 ("maintenance" indication).

Rubraca was first granted a conditional marketing authorisation (CMA) in the "treatment" indication based on overall response rate (ORR) data from a pooled population from two phase 2 single arm studies, namely study CO-338-010 and study CO-338-017. This CMA 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 versus chemotherapy 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. This study is listed as a specific obligation in Annex II of the product information of Rubraca.

On 27 August 2021 a type II variation application (EMEA/H/C/004272/II/0029) was submitted to EMA to evaluate results from study CO-338-043 (ARIEL4). During the assessment of this procedure, although a difference in progression free survival (PFS) as assessed by the investigator (invPFS) was observed in favour of rucaparib in the final analysis, an interim analysis of overall survival (OS) performed at a 51% data maturity showed nevertheless a detriment in OS in patients treated with rucaparib compared to patients receiving chemotherapy.

In view of the above, on 22 April 2022, the European Commission (EC) triggered a referral under Article 20 of Regulation (EC) No 726/2004, and requested CHMP to assess the impact of the above concerns on the benefit-risk balance in the approved "third line or more treatment" indication and to issue a recommendation on whether the relevant marketing authorisation(s) should be maintained or amended. In addition, the EC requested the EMA to give its opinion, as to whether temporary measures were necessary to protect public health. Of note, the "maintenance" indication is not included in this review as its approval was based on data from a randomised, double-blind, placebo-controlled phase 3 study (ARIEL3). During the initial assessment of the "maintenance" indication limited interim OS data were available, but a detrimental effect on OS was considered unlikely. More mature OS data in the maintenance setting have recently become available and do not raise concern on a potential detrimental effect on OS.

At the April 2022 CHMP plenary meeting, based on the available data, the Committee agreed as a temporary measure that no new treatment with Rubraca should be initiated in 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. CHMP also agreed on a direct healthcare professional communication (DHPC) to communicate this temporary restriction to healthcare professionals, together with a communication plan.

In the framework of the referral procedure, CHMP considered all available data submitted by the MAH including new data using a final analysis of OS data with a cut-off date of 10 April 2022 at 70% maturity, second event of progression free survival (PFS2) together with safety data.

Overall summary of the scientific evaluation

Favourable effects

In study ARIEL4, a statistically significant gain in invPFS, the primary endpoint, was reported in the rucaparib treatment group compared with chemotherapy with a reported median invPFS of 7.4 months for the rucaparib group compared to 5.7 months for the chemotherapy group (hazard ration (HR) 0.665 [95% CI, 0.516-0.858]; p=0.0017). Results for secondary endpoints such as overall response rate (ORR) and duration of response (DOR) were also numerically higher for rucaparib but failed to be statistically significant.

Unfavourable effects

In the intent-to-treat (ITT) population, 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 observed detrimental effect on OS is driven by results in the platinum resistant subgroup in which the worst results were observed (HR 1.51; [95% CI: 1.05, 2.17]; p=0.0251) representing 51% of the patient population. The HR for OS in the other subgroups of fully platinum sensitive and partially platinum sensitive were 1.24 [95% CI: 0.62, 2.50] (p=0.5405) and 0.97 [95% CI: 0.58, 1.62] (p=0.9129), respectively, which are not considered reassuring.

For progression-free survival on a subsequent line of treatment (PFS2) in all populations, no difference was observed between the rucaparib and chemotherapy arms.

In terms of safety, rucaparib treatment was associated with more severe adverse events (SAEs) compared to chemotherapy, such as Grade 3 or higher adverse events (AEs), serious AEs, AEs leading to death, and AEs leading to study drug interruptions or study drug dose reduction compared to the chemotherapy control arm.

The most common AEs in the rucaparib group were combined anaemia/haemoglobin decreased, nausea, combined asthenia/fatigue/lethargy, combined alanine aminotransferase (ALT)/aspartate aminotransferase (AST) increased, and vomiting. The most common Grade 3 or higher treatment-emergent adverse events (TEAEs) in the rucaparib group were combined anaemia/haemoglobin decreased and combined neutropaenia/decreased absolute neutrophil count. SAEs in the rucaparib group were mostly caused by myelosuppression from anaemia/decreased haemoglobin. Intestinal obstruction and death were observed at a higher frequency in the rucaparib group compared to the chemotherapy group and were most often leading to study drug discontinuation with rucaparib treatment. Several concerns were also related to the timing of deaths due to progression, AEs or other causes, which could not be alleviated by the MAH during the procedure.

Benefit-risk assessment and discussion

Results from study ARIEL4 were expected to confirm the efficacy (and safety) of rucaparib evidenced in a pooled analyses from two single arm trials (Study CO 338 010 and Study CO 338 017) that supported the initial conditional authorisation of Rubraca (rucaparib) in the "treatment" indication.

Despite a statistically significant gain in terms of invPFS reported in the study, a detrimental effect of rucaparib on OS compared with the chemotherapy control was observed within the interim and final data analyses of the study.

The subgroup of platinum sensitive patients of the study, particularly those partially sensitive, represented the most relevant population to confirm the benefit-risk balance of rucaparib in the approved "treatment" indication. However, and albeit the limitations to extract from the study definitive conclusions from subgroups' data in the platinum sensitive populations, results on OS were not considered reassuring as explained in above.

The MAH claimed the findings were the result of the crossover of patients from the control arm to rucaparib following disease progression, which was allowed for all patients irrespective of their platinum-sensitivity status. In this context, the MAH provided results from several sensitivity analyses. However, despite non-negative OS results were observed in some of these analyses, concerns remain in terms of the methods used in said analyses, which relied on strong assumptions and which did not allow to rule out a detrimental effect on OS.

Further, convincing evidence to support that the detrimental effect on OS could be specifically considered related to platinum resistant disease is not available. Hence, it is not possible to exclude a detrimental effect in other subgroups including platinum sensitive patients.

The detriment in OS could also not be fully explained as PFS2 curves overlap and timing of deaths, either due to underlying disease, adverse events, or other causes is unknown.

Moreover, the subgroup of study patients with platinum-sensitive disease included in the study was not identical to the approved "treatment" indication (platinum-sensitive patients who are unable to tolerate further platinum-based therapy) since part of the patients in the study received platinum therapy either as control or subsequent therapy. This hampered interpretation of the OS results of the study by subsequent platinum therapy in all platinum-sensitivity subgroups. Importantly, additional data provided during the procedure did not alleviate the concern that the OS detriment may also be applicable for the "treatment" indication as approved for Rubraca.

Regarding safety aspects, uncertainties remain in connection with the timing of deaths due to progression, AEs or other causes. It is thus unclear how far AEs or related aspects (e.g. discontinuations, treatment interruptions) contributed to the observed OS detriment.

All in all, it remains unclear whether the OS detriment is caused by a safety issue, a lack of efficacy or a combination of both. Thus, major concerns remain regarding a potential detrimental effect of rucaparib on OS compared to chemotherapy in the specific patient population covered by the "treatment" indication. Therefore, the benefit-risk balance of Rubraca in that indication can no longer be considered favourable.

As a result, CHMP is of the view that the indication of Rubraca should be restricted to the maintenance treatment as monotherapy for 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 and that the product information should be amended accordingly.

CHMP opinion

Whereas,

- CHMP considered the procedure under Article 20 of Regulation (EC) No 726/2004 for Rubraca (rucaparib).

- CHMP reviewed all data made available by the MAH to the Committee from study CO-338-043 (ARIEL4; comparing rucaparib to chemotherapy for treatment of relapsed ovarian cancer) including results from the final analysis of overall survival (OS).
- CHMP considered that it is possible that the OS detriment in the rucaparib group versus the group receiving chemotherapy observed in study ARIEL4 is relevant for the 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 ("treatment" indication).
- It remains unclear whether the OS detriment is caused by a lack of efficacy, a safety issue or a combination of both.
- Since the treatment indication was subject to confirmation of rucaparib efficacy and safety in study CO-338-043 (ARIEL4) and no other available data could alleviate these concerns, CHMP concluded that the benefit of Rubraca (rucaparib) in this indication does not outweigh its risks.
- In view of the above, the Committee concluded that the benefit-risk balance of Rubraca (rucaparib) in the treatment indication is negative. Therefore, this product should only be used 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.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisation for Rubraca (rucaparib), subject to changes to the product information.