Annex IV

Scientific conclusions

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On 27 August 2021 a type II variation for Rubraca (EMEA/H/C/004272/II/0029) was applied for to submit results from a phase 3, multicentre, open-label, randomised study evaluating the efficacy and safety of rucaparib versus chemotherapy for treatment of relapsed ovarian cancer (study CO-338-043 (ARIEL4)). This study is listed as the last specific obligation in the Annex II.

Although a difference in progression free survival (PFS) in favour of rucaparib was observed in the final analysis, an interim analysis of overall survival (OS) performed at a 51% data maturity, showed however a detriment in OS.

On 22 April 2022 pursuant to Article 20 of Regulation (EC) No 726/2004, the European Commission requested the CHMP to assess the impact of the above concerns on the benefit-risk balance of Rubraca in the approved "*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"* indication (hereinafter "3rd line or more treatment" indication, by opposition to the other approved in "maintenance" indication), and to issue an opinion on whether the marketing authorisation should be maintained or amended.

In addition, the European Commission requested the Agency to give its opinion, as to whether temporary measures were necessary to protect public health.

This opinion relates only to temporary measures recommended by the CHMP based on the preliminary data available at this time. These temporary measures are without prejudice to the outcome of the ongoing review under Article 20 of Regulation (EC) No 726/2004.

Overall summary of the scientific evaluation

While no changes to the safety profile were observed and 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, the findings on the interim analysis of OS performed at a 51% data maturity are of serious concern and may impact the benefit-risk balance of Rubraca.

Those OS findings are however not considered relevant for the "maintenance" indication because the negative impact on overall survival has so far only been observed in the "3rd line or more treatment" indication and the pathophysiological characteristics of these patients are markedly different compared to patients receiving "maintenance" treatment. In addition, while the "3rd line or more treatment" indication was based on a pooled population subgroup data from two phase 2 open label studies leading to a conditional approval and agreed specific obligations, the "maintenance" indication subsequently approved was based on data from a randomised, double-blind, placebo-controlled phase 3 study (ARIEL3) supporting this indication. During the initial assessment of the "maintenance" indication limited interim overall survival data were available, but a detrimental effect on OS was considered unlikely. More mature OS data in the maintenance setting have recently become available (top-line results from the final OS analysis of study ARIEL3 submitted on 12 April 2022), while the available OS data from ARIEL4 stem from an interim analysis with a 51% data maturity. Final OS data from the ARIEL4 study are not yet available.

In view of the findings reported in the ARIEL4 study (median OS 7.5 months shorter for the rucaparib arm, see details above) and until a thorough review of the data is finalised, as a precaution, the CHMP therefore considers 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.

The above temporary measure should be reflected in the product information of Rubraca and communicated to HCPs via a dedicated letter. The adequacy of these temporary measures will be reviewed as part of the ongoing procedure under Article 20 procedure of Directive 2001/83/EC.

For patients currently receiving treatment with Rubraca for the "3rd line or more treatment" indication, any treatment continuation or changes should be decided by patients and doctors in the clinical context of the individual situation, considering for instance the duration of treatment received, the perceived benefits and tolerability of treatment, and the benefit-risk balance given the available information.

Grounds for CHMP opinion

Whereas,

- The CHMP considered the procedure under Article 20 of Regulation (EC) No 726/2004, in particular regarding the need for temporary measures in accordance with Article 20(3) of Regulation (EC) No 726/2004 for Rubraca (rucaparib) and taking into account the grounds set out in Articles 116 of Directive 2001/83/EC.
- The CHMP reviewed data made available to the committee from study CO-338-043 (ARIEL4; comparing rucaparib to chemotherapy for treatment of relapsed ovarian cancer), including results from the interim analysis of overall survival (OS) performed at a 51% data maturity.
- The CHMP considers that the detriment in OS in the rucaparib group versus the group receiving chemotherapy observed in this interim analysis of OS, raised concerns on the benefit-risk balance of rucaparib in the "3rd line or more treatment" indication.
- Therefore, the CHMP temporarily recommends as a precaution, while the review is on-going and mature OS data become available, not to start new monotherapy treatment with rucaparib 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.

In view of the above, the Committee considers that the benefit-risk balance of Rubraca (rucaparib) remains favourable subject to the agreed temporary amendments to the product information. The Committee, as a consequence, recommends the variation to the terms of the marketing authorisation for Rubraca (rucaparib).

This opinion is without prejudice to the final conclusions of the ongoing procedure under Article 20 of Regulation (EC) No 726/2004.