22 April 2022
EMA/250815/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report on temporary measures

Procedure under Article 20 of Regulation (EC) No 726/2004

Invented name: Rubraca

INN: rucaparib

Procedure number: EMEA/H/A-20/1518/C/4272/0033

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Information on the procedure

On 27 August 2021, a type II variation application for Rubraca (EMEA/H/C/004272/II/0029) was submitted 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.

During the assessment of the type II variation application, 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.

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 the CHMP to assess the impact of the above concerns on the benefit-risk balance in the approved "3rd line or more treatment" indication, i.e.

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,

and to issue a recommendation on whether the relevant 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.

The current report 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.

2. Scientific discussion

2.1. Introduction

Rubraca contains rucaparib, an inhibitor of poly(ADP-ribose) polymerase (PARP) enzymes, including PARP-1, PARP-2, and PARP-3, which play a role in DNA repair. Rucaparib has been shown to have *in vitro* and *in vivo* anti-tumour activity in BRCA1 and BRCA2 mutant cell lines through a mechanism known as synthetic lethality, whereby the loss of two DNA repair pathways is required for cell death.

It is a centrally authorised product currently authorised in two oncology indications:

1. *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*. Hereinafter "maintenance" indication.

2. *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*. Hereinafter "3rd line or more treatment" indication.

Rubraca was first granted a conditional marketing authorisation (CMA) in 2018 in the "3rd line or more treatment" indication (2. above) based on overall response rate (ORR) data from a pooled population from two Phase 2 single arm studies (Study CO 338 010 and Study CO 338 017).

This initial CMA was granted subject to the specific obligation (SOB) 001: *"In order to further confirm the safety and efficacy of rucaparib in the treatment of platinum sensitive, relapsed or progressive, BRCA mutated (germ line and/ or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, the MAH should submit the results of study CO 338-043 (ARIEL 4), a phase 3, multicentre, open label, randomised study evaluating the efficacy and safety of rucaparib versus chemotherapy for treatment of relapsed ovarian cancer"*, with due date Q2 2023, as included in Annex II.

In 2019 the indication was extended to add the first indication mentioned above (1. above, "maintenance") in 2019 based on progression-free survival (PFS) data from study CO-338-014 (ARIEL3, a phase 3 double-blind efficacy study of oral rucaparib in patients with platinum-sensitive, high-grade serous or endometrioid EOC, FTC, or PPC who receive either rucaparib or placebo as maintenance therapy following a response to platinum-based chemotherapy) (variation EMEA/H/C/004272/II/0001). Limited interim overall survival data were available at the time of granting this extension of the indication, but a detrimental effect on OS was considered unlikely at the time. In order to further investigate the efficacy of rucaparib in the maintenance setting the MAH was requested to submit the results from the final OS analysis of the ARIEL3 study as an annex II condition (PAES). 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), that do not indicate so far such negative impact on OS in this setting. Of note, pathophysiological characteristics of patients treated under the "3rd line or more treatment" indication are markedly different compared to those treated under the "maintenance" indication.

2.2. Clinical data

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 comparing rucaparib 600 mg BID (N=233) versus chemotherapy (N=116). A median invPFS of 7.4 months was reported for the rucaparib group compared to 5.7 months for the chemotherapy group (HR=0.639; p=0.0010).

However, an interim analysis of OS performed at a 51% data maturity (final OS analysis currently planned at 69%, expected by end of April 2022), showed a detriment in OS [median OS was 19.6 months (95% CI: 16.8, 24.0) in the rucaparib group vs. 27.1 months (95% CI: 22.2, 38.1) in the chemotherapy group; HR=1.55 (95% CI: 1.085, 2.214), p=0.0161 (nominal)].

Patients included in the study were stratified at the time of randomisation 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.

Based on the above, there is a concern that the efficacy of the product may not be confirmed in the "3rd line or more treatment" indication, potentially no longer outweighing the risks of rucaparib in that indication.

3. Benefit-risk balance

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), the findings on the interim analysis of OS performed at a 51% data maturity in study ARIEL4 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.

4. Risk management

4.1. Risk minimisation activities

4.1.1. Amendments to the product information

The CHMP considered that the following restriction should be introduced in Annex II D as a temporary measure while the review is ongoing:

- **Temporary measure**

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.

4.1.2. Direct Healthcare Professional Communication/Communication plan

The CHMP adopted the wording of a direct healthcare professional communication (DHPC) to communicate the temporary restriction described above to healthcare professionals. The CHMP also agreed on a communication plan.

5. Grounds for 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 recommendation is without prejudice to the final conclusions of the ongoing procedure under Article 20 of Regulation (EC) No 726/2004.