17 January 2019
EMA/22653/2019
Committee for Orphan Medicinal Products

Withdrawal Assessment Report - Orphan Maintenance

Rubraca (rucaparib)
Treatment of ovarian cancer
EU/3/12/1049 (EMA/OD/085/12)
Sponsor: Clovis Oncology UK Limited

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Product and administrative information

Product	
Active substance	Rucaparib
International Non-Proprietary Name	Rucaparib
Orphan indication	Treatment of ovarian cancer
Pharmaceutical form	Film-coated tablet
Route of administration	Oral use
Pharmaco-therapeutic group (ATC Code)	L01XX55
Sponsor's details:	Clovis Oncology UK Limited Sheraton House Castle Park Cambridge CB3 0AX United Kingdom
Orphan medicinal product designation procedural history	
Sponsor/applicant	Clovis Oncology UK Limited
COMP opinion date	5 September 2012
EC decision date	10 October 2012
EC registration number	EU/3/12/1049
Type II variation procedural history	
Rapporteur / co-Rapporteur	J. C. Jiménez, G. Markey
Applicant	Clovis Oncology UK Limited
Application submission date	1 June 2018
Procedure start date	23 June 2018
Procedure number	EMA/H/C/004272/II/0001
Invented name	Rubraca
Therapeutic indication	Extension of indication to include new indication for Rubraca 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 Further information on Rubraca can be found in the European public assessment report (EPAR) on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/rubraca
CHMP opinion date	13 December 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	B. Bloechl-Daum, F. Naumann-Winter
Sponsor's report submission date	18 June 2018
COMP discussion and adoption of list of questions	11-13 September 2018
Sponsor's withdrawal request	27 November 2018

Following receipt of the COMP list of questions, the sponsor formally requested the withdrawal of the orphan designation on 27 November 2018, prior to the oral hearing.

2. Grounds for the COMP opinion at the designation stage

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2012 was based on the following grounds:

- ovarian cancer (hereinafter referred to as "the condition") was estimated to be affecting not more than 2.1 in 10,000 persons in the European Union, at the time the application was made; this was based on data derived from Globocan and Eurocare; this is not more than 5 in 10,000 persons as established in Article 3(1) (a) of Regulation (EC) 141/2000;
- the sponsor has provided satisfactory argumentation to establish that the condition is chronically debilitating, in particular due to abdominal pain or discomfort, an abdominal mass, bloating, back pain, urinary urgency, constipation, tiredness and a range of other non-specific symptoms, as well as more specific symptoms such as pelvic pain, abnormal vaginal bleeding or involuntary weight loss. There can be a build-up of fluid (ascites) in the abdominal cavity. The life threatening nature of the condition is associated with the fact that most patients with ovarian cancer have widespread disease at presentation. This may be partly explained by the relatively early spread of high grade papillary serous cancers to the rest of the peritoneal cavity. Five year survival in Europe has been estimated to be 40%;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that rucaparib may be of significant benefit to those affected by the condition. This appears justified in particular with regards to a potential clinically relevant advantage based on preliminary clinical data where patients with the BRCA mutation as well as patients who are platinum resistant have shown clinical response.

3. Review of criteria for orphan designation at the time of type II variation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

The sponsor is proposing that ovarian cancer is a distinct medical entity that is an orphan condition. The COMP has previously seen a submission for the same condition from the sponsor earlier in 2018 and has accepted the condition as still valid.

The approved therapeutic indication "Rubraca is indicated as monotherapy for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy" falls within the scope of the designated orphan indication "treatment of ovarian cancer".

Intention to diagnose, prevent or treat

Based on the CHMP assessment the intention to treat the condition has been justified, see EPAR.

Chronically debilitating and/or life-threatening nature

The five-year net (relative) survival for all stages of ovarian cancer is 46%; the one-year net survival is 72% and the ten-year net survival is 35% (Statistics and outlook for ovarian cancer". www.cancerresearchuk.org. Archived from the original on 2015-05-18). In a recent publication by E.A. Eisenhauer (2017) it was noted that Malvezzi et al reported in 2016 that there was an overall decline in mortality rates with an EU mortality rate of 5.2 per 100,000 in 2012. The authors attribute the majority of the decline in mortality to changes in incidence rates through oral contraceptive use and, beginning about 10 years ago, declines in menopausal hormone use.

The improvement in the 5 year net survival rate in 2015 was modest at 46% versus the 30-40% noted in 2010 and ovarian cancer is in 2018 still a life-threatening disease.

Number of people affected or at risk

The sponsor has done an extensive prevalence calculation based on literature and databases. No dedicated literature or registry provided current prevalence data for the EU. They establish that the prevalence is within a range of 4.6 to 5.4 in 10,000 depending on a range of assumptions with respect to current incidence, survival and cure rate. The results underscore the difficulty of estimating current prevalence. However, even assuming plausible values (e.g. 1.5% decrease in incidence per year from the most recent publication of incidence in 2012, 5-year survival rates of 39% for the EU overall and 5% cure rate) the prevalence was concluded to be 4.9 per 10,000. The COMP accepted these assumptions and the final figure provided by the sponsor for this point in time but highlighted the necessity to closely follow the prevalence of ovarian cancer in the future.

Article 3(1)(b) of Regulation (EC) No 141/2000

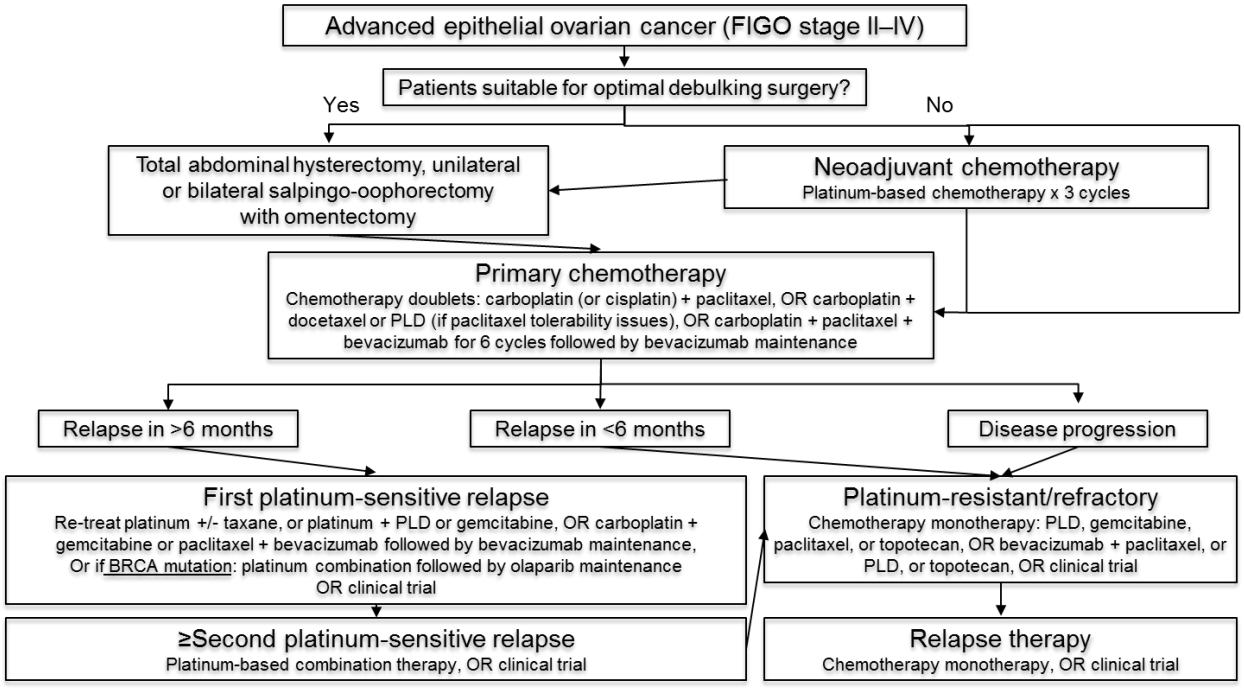
Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The sponsor has submitted a list of the currently approved medicines for use in the treatment of ovarian cancer in Europe: Rucaparib, olaparib, niraparib, bevacizumab, doxorubicin, topotecan, trabectedin, carboplatin, cisplatin, cyclo-phosphamide, epirubicin, gemcitabine, lomustine, melphalan, methotrexate, paclitaxel and treosulfan.

The sponsor has highlighted the different Guidelines published in Europe. ESMO has issued clinical practice guidelines for the diagnosis, treatment and follow-up of patients with newly diagnosed and relapsed epithelial ovarian carcinoma in 2010 (Colombo, Peiretti et al. 2010) with updates in 2013 (Ledermann, Raja et al. 2013) and 2016 (Ledermann, Sessa et al. 2016). These guidelines provide recommendations for the diagnosis, staging and risk assessment, and treatment (both primary and recurrent) of ovarian cancer, along with subsequent follow-up of patients.

The sponsor has provided the currently accepted treatment algorithm for ovarian cancer.



PLD, pegylated liposomal doxorubicin

The treatment algorithm highlights the current core treatments used in the management of the different stages of ovarian cancer. Although there are many medicines for use in this condition the treatment algorithm highlights the importance of platinum based treatments as well as paclitaxel and bevacizumab. PARP inhibitors are recommended for use in maintenance treatment in patients with first platinum-sensitive relapse with a BRCA mutation. The publication of the guidelines preceded the marketing authorisation of niraparib.

Significant benefit

The sponsor is proposing that rucaparib will offer significant benefit when used as maintenance treatment. Rucaparib is a PARP inhibitor with the same mode of action as olaparib and niraparib. The indications for these two products offer some substantial overlap with the wording proposed for Rucaparib: "*Rubraca is indicated as monotherapy for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy*".

Olaparib: *Lynparza is indicated 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.*

Niraparib: *Zejula is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.*

The sponsor did an indirect comparison between data generated with their product and olaparib and niraparib to establish the basis of significant benefit as they have not conducted a direct comparison study to either product.

The sponsor compares their pivotal Phase 3 study CO-338-014, for rucaparib to niraparib which was investigated in a single global Phase 3, randomized, double-blind trial of maintenance treatment with

niraparib versus placebo in patients with platinum-sensitive ovarian cancer who had received at least 2 platinum-based regimens and were in response to their last platinum-based chemotherapy (NOVA). An indirect comparison to olaparib was also submitted using two randomized, double-blind studies of maintenance treatment with olaparib versus placebo in gBRCA1/2 patients with platinum-sensitive serous ovarian cancer who had received at least 2 platinum-based regimens and were in response to their last platinum-based chemotherapy (Phase 2:Study 19 and Phase 3:SOLO2).

The sponsor highlights that: "*The efficacy outcomes in the placebo control groups have remained consistent and highly reproducible across the studies.*"

The sponsor also notes that: "*The efficacy of rucaparib in terms of PFS shows benefit over the currently approved PARP inhibitors olaparib and niraparib across all ovarian cancer patients. In particular patients with residual disease not included in olaparib and niraparib studies.*"

The sponsor claims that the efficacy seen in the more severe patient population included in their study would indicate that their product would cover patients with residual disease where olaparib and niraparib have no established benefit because of the characteristics of the inclusion criteria of their respective trials used to support the marketing authorization, where these patients were not included. However this argument is not convincingly supported by data and should be further discussed by the sponsor.

Since all PARPi are authorised for patients in complete or partial response without further specification of the residual disease, the sponsor is asked to further elaborate on the benefits of rucaparib as compared to niraparib and olaparib.

4. COMP list of issues

Significant benefit:

The sponsor is invited to further elaborate using clinical data, the proposed clinically relevant advantage of rucaparib in the therapeutic maintenance treatment of ovarian cancer patients in comparison to the two other PARP inhibitors olaparib and niraparib which have a very similar approved therapeutic indication as well as bevacizumab.