24 May 2018
EMA/272157/2018
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

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.

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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
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	A. Sancho-Lopez, G. Markey
Applicant	Clovis Oncology UK Limited
Application submission date	1 November 2016
Procedure start date	24 November 2016
Procedure number	EMA/H/C/004272
Invented name	Rubraca
Therapeutic indication	Rubraca is indicated 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. Further information on Rubraca can be found in the European public assessment report (EPAR) on the Agency's website ema.europa.eu/Find medicine/Human medicines/European public assessment reports.
CHMP opinion date	22 March 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	B. Bloechl-Daum, F. Naumann-Winter
Sponsor's report submission date	7 February 2017
COMP discussion and adoption of list of questions	30-31 October 2017
Oral explanation	14 March 2018
COMP opinion date	12 April 2018

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 marketing authorisation

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

Ovarian cancer (OC) is the seventh most commonly diagnosed cancer among women in the world. Epithelial OC is the most predominant pathologic subtype, with five major histotypes that differ in origination, pathogenesis, molecular alterations, risk factors, and prognosis. Genetic susceptibility is manifested by rare inherited mutations with high to moderate penetrance. Genome-wide association studies have additionally identified 29 common susceptibility alleles for OC, including 14 subtype-specific alleles. Several reproductive and hormonal factors may lower risk, including parity, oral contraceptive use, and lactation, while others such as older age at menopause and hormone replacement therapy confer increased risks. These associations differ by histotype, especially for mucinous OC, likely reflecting differences in aetiology.

Nearly all benign and malignant ovarian tumours originate from one of three cell types: epithelial cells, stromal cells, and germ cells. In developed countries, more than 90% of malignant ovarian tumours are epithelial in origin, 5%–6% of tumours constitute sex cord-stromal tumours (e.g., granulosa cell tumours, thecomas, etc.), and 2%–3% are germ cell tumours (e.g. teratomas, dysgerminomas, etc.).

About 90% of tumours are epithelial ovarian cancers that occur primarily in postmenopausal women. Germ cell tumours, which occur primarily in women in their early 20s, comprise 5% of tumours, and sex cord–stromal tumours, which secrete sex steroids and occur at any age (most commonly in a patient's 50s), comprise the remainder. Early diagnosis when tumours are small and still confined to the ovaries is the most important prognostic factor. Only about 45% of women with ovarian cancer survive for five years or longer from the date of diagnosis. The five-year survival rate is 92% for women with stage I epithelial ovarian cancers but only 17% to 28% for those with advanced-stage tumours (DOUBENI C et al, American Family Physician Volume 93, Number 11 June 1, 2016, pg 937-944).

Epithelial OC reflects a heterogeneous disease with histologic subtypes (histotypes) that differ in their cellular origin, pathogenesis, molecular alterations, gene expression, and prognosis. Malignant OC, also known as carcinomas, are comprised of five main histotypes: high-grade serous (HGSOC; 70%), endometrioid (ENOC; 10%), clear cell (CCOC; 10%), mucinous (MOC; 3%), and low-grade serous (LGSOC; <5%).

Rare high penetrant mutations in the BRCA1 and BRCA2 genes greatly increase lifetime risk and account for the majority of hereditary cases and 10%–15% of all cases (Reid et al, Cancer Biol Med 2017. doi: 10.20892).

The orphan condition is considered to include fallopian and primary peritoneal cancer.

The proposed therapeutic indication "*Rubraca is indicated 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"* falls within the scope of the designated orphan indication "*treatment of ovarian cancer*".

Intention to diagnose, prevent or treat

Based benefit/risk assessment of the CHMP the intention to treat the condition has been justified. The CHMP granted a conditional licence for this product.

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 10yrs 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 provided a prevalence calculation based on a bibliographical search. The publications used were focused primarily around the Globocan 2012 reporting of ovarian cancer and specifically by Ferlay et al 2013. There was no consultation of national registries or EUCAN or NORDCAN. The possibility of any change since the 2012 reporting was not discussed. In a recent publication from 2017

by Malvezzi et al it was noted that between 2002 and 2012 there had been a reduction in age-adjusted ovarian cancer mortality rates of 10%. The publication noted that the reduction was greater in young and middle-aged women than in the elderly and that this reduction was larger in the UK and Northern Europe. NORDCAN data between 2010 and 2014 showed a reduction in the age-adjusted incidence (Coburn S et al, Int. J. Cancer: 140, 2451–2460 (2017)). A similar drop in age-adjusted incidence was reported in Spain in 2015 (Galceran J et al, Clin Transl Oncol 2015). The sponsor initially proposed that the prevalence was 3 in 10,000. The COMP indicated that it was only interested in the crude data as an age-adjusted drop in mortality in younger women reasonably meant that there were more survivors of the best prognosis, and this could mean an increase in the prevalence. Following these considerations the sponsor submitted a revised prevalence calculation.

The COMP discussed the validity of the revised prevalence calculation. In their discussion the sponsor indicated that the age-standardised incidence of ovarian cancer is dropping in Europe. The sponsor discussed two main sources namely the Globocan report of 2012 and the Rarecare report of 2010. Prevalence reported in Orphanet and from the SEER database in the US and GLOBOCAN 2012 US was used as well. The strengths and limitations of the Globocan and Rarecare data were discussed. The Globocan data were considered more current as these were published in 2012 and the Rarecare data were published in 2003.

It was noted by the COMP that the Globocan 2012 data had to correct the estimates for fallopian and primary peritoneal cancers. The incidences and prevalence of this dataset span a period from 1990 to 2009 and, although not the most current, were considered more robust that those of Rarecare, especially with respect to full prevalence.

The COMP considered the use of Globocan rather than the Rarecare data, on the basis of wider coverage. The prevalence was revised upwards to 4.7/10,000 (initially 4.2 per 10,000) for the complete prevalence, using Globocan incidence multiplied by a duration of 5 years and correcting by a factor of 8.11% to account for fallopian and peritoneal cases. The latter comes in turn from SEER ratios. The COMP considered that a revised higher prevalence of 4.7 in 10,000 was probably closer to the current prevalence due to the limitations with the data collection period (between 1990 and 2009).

The sponsor's prevalence was then amended from 3 in 10,000 to 4.7 in 10,000 to include these assumptions by the COMP. By accepting this value the prevalence still falls within the limit of less than 5/10000. The COMP therefore recommended granting the Maintenance of the Orphan Designation.

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 produced a comprehensive listing of products authorised for use in this condition. Please refer to the following table.

Table 1.

Drug Name	Tradename(s)	EU-approved Indication	ESMO Guideline	Primary Endpoint
Drugs approved via the Centralized Procedure				
Doxorubicin	Caelyx®	Advanced ovarian cancer after failure of first-line platinum-based chemo (Caelyx); Advanced ovarian carcinoma (generic)	1st line as an alternative to paclitaxel, in combination with carboplatin 2nd line in platinum-resistant/refractory setting as single agent 2nd line in combination with carboplatin as an alternative to paclitaxel	OR
Topotecan	Hycamtin®, Potactasol®	Treatment of metastatic carcinoma of the ovary after failure of first-line or subsequent therapy	2nd line in platinum-resistant/refractory setting as single agent	RR, TTP, OS
Trabectedin	Yondelis®	Treatment of platinum-sensitive relapsed ovarian cancer in combination with PEGylated liposomal doxorubicin	2nd line in combination with PLD in partially platinum-sensitive population	PFS, OS
Targeted Therapies approved via the Centralized Procedure				
Bevacizumab	Avastin®	Front-line treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal in combination with carboplatin and paclitaxel In combination with carboplatin and gemcitabine for treatment of adult patients with first recurrence of platinum-sensitive epithelial ovarian, fallopian tube, or primary peritoneal cancer who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents. In combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin for the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents	1st line in patients with poor prognostic features in combination; continuous maintenance up to 1yr total treatment 2nd line in platinum-sensitive setting in combination; continuous maintenance until progression 2nd line in platinum-resistant setting in combination; continuous maintenance until progression	PFS

Olaparib	Lynparza®	Monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete response or partial response) to platinum-based chemotherapy	Patients with recurrent high-grade serous ovarian cancer and a germline or tumor BRCA mutation should be offered maintenance olaparib after a response to platinum-based chemotherapy	PFS
Niraparib	Zejula	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.	Not referenced in guideline	PFS
Approved drugs available as a generic product				
Drug Name		EU-approved Indication	ESMO Guideline	Primary Endpoint
Carboplatin	AT, BE, BG, CZ, CY, DE, DK, EE, ES, FI, FR, HU, IE, IS, IT, LT, LV, MT, NL, NO, PT, RO, SE, SK, UK	Advanced ovarian carcinoma of epithelial origin in 1st line therapy or in 2nd line therapy, after other treatments have failed	1st line; subsequent line, in combination	N/A
Cisplatin	AT, BE, BG, CY, CZ, DE, DK, EE, ES, FI, FR, EL, HU, IE, IT, LT, LU, LV, MT, NL, NO, PT, RO, SE, SK, UK	Single agent or combination for advanced or metastatic ovarian carcinoma	As an alternative to carboplatin where tolerability is an issue	N/A
Cyclo-phosphamide	AT, BG, CY, CZ, EE, ES, FR, DE, HU, IE, MT, PT, RO, SE, SK, UK	Single agent or combination for a wide range of neoplastic conditions including metastatic ovarian carcinoma	Not referenced in guideline	N/A
Epirubicin	AT, BE, BG, CY, CZ, DE, DK, EE, ES, FI, FR, EL, HU, IE, IS, IT, LT, LU, LV, LT, MT, NL, NO, PT, RO, SE, SK, UK	Wide range of neoplasms including advanced ovarian cancer	Not referenced in guideline	N/A

Gemcitabine	AT, BE, BG, CY, CZ, DE, DK, ES, FI, FR, EE, HU, IE, IS, IT, LV, LT, MT, NL, NO, PL, PT, RO, SE, SK, SI, UK	Locally advanced or metastatic epithelial ovarian carcinoma in combination with carboplatin in patients with relapsed disease following recurrence-free interval of >6 months after platinum-based, first-line therapy	2nd line in platinum-resistant/refractory setting as single agent 2nd line in platinum-sensitive setting in combination with carboplatin as an alternative to paclitaxel	N/A
Lomustine	CZ, DE, DK, ES, FI, NL, RO, SE, SK, UK	Wide range of neoplasms including second line treatment of ovarian cancer	Not referenced in guideline	N/A
Melphalan	CZ, DE, DK, EE, ES, FI, FR, IE, IS, LT, NL, NO, PT, RO, SE, SK, UK	Single agent or combination for advanced ovarian cancer	Not referenced in guideline	N/A
Methotrexate	AT, BE, BG, CY, CZ, DK, EE, ES, FI, FR, HU, IE, IS, LT, MT, NL, NO, PT, RO, SE, SK, UK	A number of neoplastic conditions including ovarian carcinoma	Not referenced in guideline	N/A
Paclitaxel	AT, BE, BG, CY, CZ, DE, DK, ES, EE, FI, FR, HU, IE, IS, LV, LT, MT, NL, NO, PL, PT, RO, SE, SK, SI, UK	First-line treatment of advanced carcinoma of the ovary in combination with cisplatin or carboplatin Second-line treatment of metastatic carcinoma of the ovary after failure of standard, platinum containing therapy	1st, 2nd line in combination 2nd line in platinum-resistant/refractory setting as single agent	N/A
Treosulfan	DE, DK, IE, NL, UK	For the treatment of all types of ovarian cancer, either supplementary to surgery or palliatively	Not referenced in guideline	N/A

PFS = progression-free survival
OS = overall survival
OR = overall response
TTP = time to progression
RR = response rate
N/A = not applicable

The sponsor has discussed the current ESMO guidelines which date from 2013 and also referenced in the ESMO addendum.

ESMO has updated the ovarian cancer treatment guideline regarding olaparib, a PARP inhibitor targeting BRCA positive ovarian cancer patients and recommending that "*Patients with recurrent high-grade serous ovarian cancer and a germline or tumour BRCA mutation should be offered maintenance olaparib after a response to platinum-based chemotherapy" (eUpdate – Ovarian Cancer Treatment Recommendations, Published: 21 September 2016. Authors: J.A. Ledermann1, C. Sessa2 & N. Colombo3 on behalf of the ESMO Guidelines Committee).*

There are several national review documents on how to manage patient with ovarian cancer produced by the Member States (NICE, SEOM Clinical Guideline in Ovarian cancer 2016(Spain)).

Significant benefit

The sponsor has proposed a product which mode of action is expected to be most efficacious in patients with ovarian cancer who have the BRCA mutation (either genomic or somatic deleterious mutations). Rucaparib works as a PARP inhibitor and therefore has the same mode of action as olaparib and niraparib (as mentioned above) but in contrast to these treatments which are authorised for maintenance treatment in patients in response from previous treatment, rucaparib has shown to induce responses in relapsed and progressive disease.

The final indication agreed with the CHMP in the setting of a conditional marketing approval was restricted to patients with platinum-sensitive disease unable to tolerate further platinum treatment.

The applicant was asked to discuss the potential overlap of the target population of with other products authorised and used in this setting, i.e. other chemotherapeutic agents in order to confirm significant benefit. After first line failure platinum sensitive patients and platinum resistant patients are identified. For platinum sensitive patients there are well-established first and second relapse line treatments (1st line platinum with a taxane or platinum with gemcitabine or PEGylated liposomal doxorubicin or carboplatin gemcitabine or paclitaxel with bevacizumab followed by bevacizumab maintenance or in the case of BRCA mutated olaparib maintenance; 2nd line platinum based combination or clinical trial).

The applicant used data from two individual open-label, single arm studies (Study 10 and ARIEL2). The data from the studies was pooled and the results were compared indirectly to what was considered as standard of care: either single agents normally reserved for platinum-resistant/refractory disease (paclitaxel, gemcitabine, topotecan or pegylated doxorubicin) or the combination treatment of trabectedin with pegylated doxorubicin. Of these regimen, the combination treatment of trabectedin and pegylated doxorubicin displays the highest efficacy, but is associated with substantial toxicity.

Even though the patients included into the pivotal studies of rucaparib were more heavily pretreated compared to published data on the standard of care (ORR < 35%, PFS 4-9 months), treatment with rucaparib was associated with higher ORR (65%) and longer PFS (10.9 months). These results compare favourably to published results with the standard of care in view of an expected decrease of response to treatment with later lines. In addition, the adverse reactions of rucaparib were generally mild/moderate and manageable with standard supportive care.

The Oncology SAG report acknowledged that there is a group of patients in whom platinum-containing regimes are contraindicated (e.g. allergy) as well as a group of patients who, having discussed preferred options, may refuse further platinum-containing treatment, including single agent carboplatin, due to expected toxicity. The SAG noted that the regimen considered to be associated with highest activity is the approved combination of trabectedin+PLD however this regimen was not often used due to the considerable toxicity. The SAG noted with all due caution in view of the uncertainties

associated with cross-trial comparison, that rucaparib is likely to have a more favourable toxicity profile compared to chemotherapy including trabectedin+liposomal doxorubicin.

The COMP was of the opinion that although the data was very limited from the Study10 and Ariel 2 a significant benefit could be accepted for this niche indication of patients with ovarian cancer, fallopian tube and primary peritoneal cancer who are unable to tolerate further platinum therapy and for whom the other approved PARP-inhibitors are not indicated. The COMP was however of the opinion that the argument of a major contribution to patient care (oral vs intravenous administration) alone was insufficient to support the confirmation of a significant benefit over all authorised treatments but it was contributing to the overall positive outcome [in view of considerably reducing the burden of the promising treatment.] The basis of significant benefit was mainly considered a clinically relevant advantage based on safety for oral rucaparib on the grounds that rucaparib offers similar efficacy in 3rd line treatment of platinum sensitive patients who were allergic or no longer wished to receive platinum compared to intravenously administered trabectedin + PEGylated doxorubicin which was considered more toxic than rucaparib. Rucaparib offers a different safety profile than trabectedin+PLD, with important reductions in haematologic AEs and other relevant side effects. More specifically, the adverse reactions CTCAE Grade 3 or higher for anaemia, neutropenia and thrombocytopenia were 23%, 9% and 5% for rucaparib, as compared to 19%, 72% and 23% for the T+PLD respectively (see SmPCs).

4. COMP position adopted on 12 April 2018

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product;
- the prevalence of ovarian cancer (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded in to be 4.7 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating in particular due to pain, weight loss, ascites and vaginal bleeding, and life-threatening with approximately half of the patients surviving less than five years;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, it has been shown on the basis of indirect comparison that orally administered Rubraca offers a clinically relevant advantage for pretreated patients with platinum-sensitive ovarian cancer carrying deleterious BRCA mutations and who cannot tolerate further platinum therapy. Alternatively, these patients would either be receiving other less efficacious monotherapy treatments or intravenous combination therapy using trabectedin and PEGylated doxorubicin which shows comparable efficacy, but with lower tolerability. The COMP concluded on the totality of data that the assumption that Rubraca may be of potential significant benefit to those affected by ovarian cancer as defined in the granted therapeutic indication still holds.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Rubraca, rucaparib, EU/3/12/1049 for treatment of ovarian cancer is not removed from the Community Register of Orphan Medicinal Products.