16 March 2018
EMA/214775/2018
Committee for Orphan Medicinal Products

Withdrawal Assessment Report – Orphan Maintenance

Lynparza (olaparib)
Treatment of ovarian cancer
EU/3/07/501 (EMA/OD/063/07)
Sponsor: AstraZeneca AB

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	Olaparib
International Non-Proprietary Name	Olaparib
Orphan indication	Treatment of ovarian cancer
Pharmaceutical form	Capsule, hard
Route of administration	Oral use
Pharmaco-therapeutic group (ATC Code)	L01X
Sponsor's details:	AstraZeneca AB SE-151 85 Södertälje Sweden
Orphan medicinal product designation procedural history	
Sponsor/applicant	AstraZeneca AB
COMP opinion date	10 October 2007
EC decision date	06 December 2007
EC registration number	EU/3/07/501
Post-designation procedural history	
COMP opinion on review of designation at initial MA authorisation	13 November 2014
Type II variation procedural history	
Rapporteur / co-Rapporteur	Alexandre Moreau, Bart Van der Schueren
Applicant	AstraZeneca AB
Application submission date	6 April 2017
Procedure start date	18 May 2017
Procedure number	EMEA/H/C/003726/X/0016/G
Invented name	Olaparib
Therapeutic indication	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. Further information on Lynparza 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 February 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	F Naumann-Winter - B Bloechl-Daum –K. Kopečková
Sponsor's reports submission date	23 October 2017 – 20 November 2017
COMP discussion and adoption of list of questions	5-7 December 2017
Oral explanation	13 March 2018

Following communication of the outcome of the discussion, the sponsor formally requested the withdrawal of the orphan designation on 15 March 2018, prior to final opinion.

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 2007 was based on the following grounds:

- ovarian cancer (hereinafter referred to as "the condition") was estimated to be affecting approximately 2.9 in 10,000 persons in the Community, at the time the application was made;
- the condition is life threatening due to poor long term survival;
- although satisfactory methods of treatment of the condition have been authorised in the Community, justifications have been provided that olaparib may be of significant benefit to those affected by the condition.

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 orphan condition affects predominantly older postmenopausal women. About 90% of primary malignant ovarian tumours are epithelial and WHO classification of ovarian tumours recognizes the following histotypes: serous, mucinous, endometrioid, clear cell, Brenner (transitional cell), mixed epithelial, undifferentiated, and unclassified. In the last few years a dualistic model for the pathogenesis of this disease has emerged which divides epithelial tumours into type 1 and type 2 ovarian carcinomas.

Type 1 cancers tend to be low-grade and indolent tumours and include low-grade serous, endometrioid, mucinous, clear-cell and malignant Brenner tumours; they are relatively genetically stable and are characterised by mutations of KRAS, BRAF, ERBB2, PTEN, PIK3CA and ARID1A.

Type 2 tumours are high-grade, aggressive tumours comprising high-grade serous, high-grade endometrioid, malignant mixed mesodermal tumours and undifferentiated tumours, frequently associated with TP53 mutations, and BRCA1/2 mutation due to a combination of germline and somatic mutations.

It is important to note that the majority of high-grade serous ovarian and peritoneal tumours originate in the fimbria of the fallopian tube (Lederman et al 2013, Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up, Annals of Oncology 24 (S6): vi24–vi32, 2013)". For the COMP the inclusion of fallopian and primary peritoneal cancer is included in the "ovarian cancer" orphan indication, on the basis of common tissue origin, molecular pathology, clinical characteristics and natural history leading to the same staging and treatment. This inclusion should be reflected in the prevalence calculations as well.

The already approved indication is:

Lynparza is indicated as 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

is the extension pertains to the following therapeutic indication:

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.This falls within the scope of the designated orphan indication “treatment of ovarian cancer.

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP

Chronically debilitating and/or life-threatening nature

The sponsor discusses 5 year survival data from the US SEER database, plotted against the stage of the disease. The majority of patients diagnosed with locally advanced or metastatic disease die from their disease, with 5-year survival rates of 29% for advanced stages.

It can be acknowledged that 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.

Number of people affected or at risk

As an overall comment, the inclusion of fallopian and primary peritoneal cases is not explicit in the sponsor’s calculations.

The applicant reports both 5 year partial prevalence (proposed 2.05 per 10,000) as well as estimates of complete prevalence of ovarian cancer (proposed 4.35 per 10,000) for 2017 in Europe. This report will only focus on the full point prevalence as the relevant index. This is because late recurrences (much more than 5 years) are indeed possible, and such cases are documented and described in literature (e.g. Izycka et al, Eur J Gynaecol Oncol. 2015;36(3):351-3). Cancer research UK also cites that approximately 35% of patients survive ten years or more (2010-2011 data).

The proposed 4.35 complete prevalence was estimated by the formula P=I x D [COMP/436/01]. Incidence was derived from Globocan 2012. For 2017 estimates, median survival of 5 years served as a surrogate for the disease duration. This estimate for duration was proposed by the applicant on the basis of a median survival, sourced from Cancer research UK cumulative survival data. The applicant therefore believes that the statutory threshold of 5/10,000 in the EU is respected.

There are however several reasons to consider otherwise:

- Regarding the duration of the condition, the survival data that the applicant uses are 2010-2011 data (from the Cancer research UK 2014 source). As such, any recent changes in survival, because of diagnostic earlier detection and/or treatment advancements, are not taken into consideration.
- Regarding the definition of the condition itelf, it is unclear if the applicant includes primary pertineal and fallopian in its considerations.

- The applicant acknowledges that in the RARECARE report (Rarecare 2017) a combined complete prevalence for subsets of epithelial rare tumours of ovary and fallopian tube (which includes adenocarcinoma with variants of ovary, mucinous adenocarcinoma of ovary, clear cell adenocarcinoma of ovary, adenocarcinoma with variants of fallopian tube) challenges the statutory threshold and cites a figure of 5.32 per 10,000. The Rarecare website accessed on Nov 29, yields a 5.9 per 10,000 including ovarian and fallopian cancer. The sponsor notes that the source data used by RARECARE does not come from all EU countries. In addition, that not all countries use national regisitries, and instead have estimated incidence and prevalence on regional databases that do not include all patients in a given country. These reasons may be further elaborated in a list of issues.
- There is substantial uncertainty regarding the epidemiology of the condition in the literature (J Natl Cancer Inst. 2017 Oct 1;109(10) which argues that "with most studies capturing exposure information from 10 or more years ago, evaluation of how changing patterns of exposures, such as new oral contraceptive formulations and increased intrauterine device use, might influence ovarian cancer risk and survival is difficult". The use of updated data is relevant in that regard. A newer epidemiological report that was published from Rarecare in November 2017 could also have been commented on. (Rare ovarian tumours: Epidemiology, treatment challenges in and outside a network setting,Ray-Coquard et al, EJSO November 2017).

The sponsor was invited to elaborate on a) the inclusion of fallopian and primary peritoneal b) the reliance of the 2017 estimate on older data and justify the exclusion of Rarecare considerations.

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

Several medicinal products are authorised in the EU for the treatment of ovarian cancer such as bevacizumab, carboplatin, cisplatin, cyclophosphamide, docetaxel, doxorubicin, epirubicin, 5FU, irinotecan, mephalan, methotrexate, mitoxantrone, paclitaxel, treosulphan, pazopanib, trabectedin, olaparib, niraparib.

The last addition of niraparib refers to the following indication: 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. Therefore a very similar indication to the one proposed for Lynparza.

European Guidelines have been published by ESMO (Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up Lederman et al 2013, Annals of Oncology 24 (S6): vi24–vi32, 2013).

As per these guidelines, the role of surgery is important for both early and advanced disease. In early stage primary treatment the role of surgery is also important for staging, while for advanced disease complete cytoreduction of all macroscopic visible disease, after a maximal surgical effort, has been shown to be associated with a significantly increased survival. However, the value of surgical cytoreduction in relapsed epithelial ovarian cancer remains controversial and is not regarded as standard of care. Adjuvant carboplatin single-agent chemotherapy is considered for patients with intermediate and high-risk stage I disease.

Chemotherapy is recommended for all patients with FIGO stage II–IV disease post-surgery. Standard chemotherapy consists of a combination of paclitaxel and carboplatin every 3 weeks. With regards to treatment of recurrent disease, patients experiencing a durable response to platinum induction have a high probability to respond again to platinum compounds, but salvage chemotherapy in platinum refractory patients' results in low response rates.

Significant benefit

The sponsor provides a discussion versus niraparib, which has a similar indication in maintenance of platinum sensitive relapsed (PSR) patients. No other product has a label as monotherapy maintenance treatment in that population, and as such a discussion versus niraparib would be most relevant. An indirect comparison of the results from study 19 and SOLO2 versus the pivotal study for niraparib (NOVA) is performed by the sponsor and the data are juxtaposed and critically discussed.

The argument of SB is double: a claim for improved efficacy and a claim of improved safety.

On the first point, the sponsor argues that the magnitude of benefit observed with olaparib in PSR ovarian cancer patients was similar to or better than that demonstrated with either bevacizumab or niraparib (olaparib HR 0.35 vs HR 0.48 for bevacizumab vs HR 0.42 for niraparib [FDA pooled analysis]). It is also stressed that the final OS data from Study 19 with >6 year follow up and at 79% maturity demonstrated a notable numerical benefit for patients treated with olaparib, which while not statistically significant (due to multiple testing of OS and testing within a subgroup of the full analysis set) was numerically superior in magnitude to OS data from approved agents (which also had less mature OS data and/or were also not statistically significant).

Table 1. PFS and OS data of the two pivotal studies (adopted from the sponsor's application)

	Study 19		NOVA trial (combined)	
	Olaparib capsule	**Placebo**	**Niraparib**	**Placebo**
Number of Patients	136	129	372	181
PFS (primary assessment method)	(investigator) DCO 30 June 2010		(BICR –FDA pooled analysis)	
Median PFS (months)	8.4	4.8	11.3	4.7
Difference in mPFS (months)	3.6		6.6	
HR (95% CI)	0.35 (0.25-0.49)		0.42 (0.34-0.53)	
P-value (2-sided)	p<0.00001		p=Not reported	
Overall Survival				
Median OS (months)	29.8	27.8	NR	NR
HR (95% CI)	0.73 (0.55-0.95)		0.73 (0.48-1.11)	
Nominal P-value (2-sided)	p=0.021		p=Not reported	

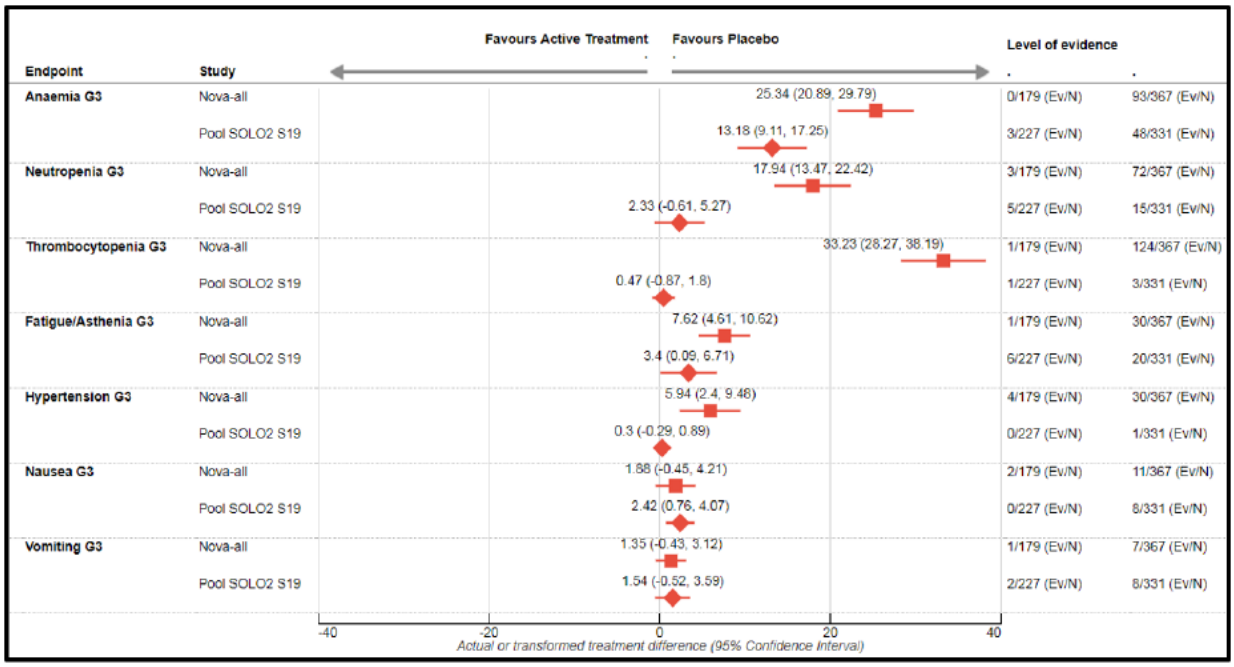
Those arguments of the sponsor have however to be considered with caution. Indeed, the PFS comparison versus niraparib, shows similar and comparable outcomes regarding HR, notwithstanding that the comparability of the two studies has not been commented upon. The existence of long term data for Study19 versus the non-existence of mature OS data for NOVA does not produce any relevant arguments either, but rather confirms that comparison and hence justification of significant benefit is not possible. The HR of death are similar for the two studies.

A second significant benefit argument is put forward on the basis of improved safety versus niraparib.It was argued that Study 19 and SOLO2 were broadly similar in terms of design and patient population, both to each other, and to that of the overall safety analysis population included in the NOVA study conducted with niraparib. Data from these two olaparib studies have been pooled and an indirect comparison of olaparib and niraparib was performed.

Olaparib was favoured for haematological toxicity (anemia, neutropenia, thrombocytopenia and leukopenia), rash, dyspnea, nasopharyngitis, stomatitis, constipation, dry mouth, AST and ALT elevation, myalgia, anxiety, insomnia, palpitations and hypertension. Many of these are toxicities that require management with intervention or dose modifications. Niraparib was favoured for dysgeusia, fatigue/asthenia and diarrhoea.

An additional comparison was conducted for key toxicities at grade ≥3 using active and placebo data from the olaparib pooled studies and NOVA. Figure 1 shows a forest plot comparing the treatment difference between the pooled olaparib data and the corresponding pooled placebo data, and the niraparib and placebo data in the NOVA study. Points further to the left indicate a more favourable comparison for the drug compared to the placebo group in the study.

Figure 1. Forest plots for key adverse events (grade ≥3) in pooled olaparib data vs. placebo as compared with NOVA vs placebo (from the sponsor's application)



In this comparison, the haematological toxicities in particular show an improved profile for olaparib vs. placebo, compared to niraparib vs. placebo. The discontinuation rates would be more relevant to document the extent of any differences in safety profiles.

The sponsor was requested to elaborate on the extent of the differences in the context of comparability of the two study populations.

4. COMP list of issues

Prevalence

The sponsor invited to elaborate on a) the inclusion of fallopian and primary peritoneal cancer b) the choice of the epidemiological index and the duration of the condition and c) the available RARECARE data.

Significant benefit

The sponsor is arguing a significant benefit on the basis of both improved efficacy and safety.

The sponsor is invited to further elaborate on both of those points by discussing the comparability of the pivotal studies that are juxtaposed, and comment on the extent of any differences in that context.

A comparative discussion versus all authorised products for the condition as applied for is expected.