EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 July 2018
EMA/COMP/138404/2016
Committee for Orphan Medicinal Products

Withdrawal Assessment Report – Orphan Maintenance

Apealea, Paclitaxel (micellar)
Treatment of ovarian cancer
EU/3/06/422 (EMA/OD/061/06)
Sponsor: Oasmia Pharmaceutical AB

Note

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

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1. Product and administrative information

Product	
Active substance	Paclitaxel (micellar)
International Non-Proprietary Name	Paclitaxel (micellar)
Orphan indication	Treatment of ovarian cancer
Pharmaceutical form	Powder for solution for infusion
Route of administration	Intravenous use
Pharmaco-therapeutic group (ATC Code)	L01CD01
Sponsor's details:	Oasmia Pharmaceutical AB Vallongatan 1 SE 753 17 Uppsala Sweden
Orphan medicinal product designation procedural history	
Sponsor/applicant	Oasmia Pharmaceutical AB
COMP opinion date	9 November 2006
EC decision date	18 December 2006
EC registration number	EU/3/06/422
Marketing authorisation procedural history	
Rapporteur / co-Rapporteur	B. Van der Schueren, E. Balkowiec Iskra
Applicant	Oasmia Pharmaceutical AB
Application submission date	5 February 2016
Procedure start date	25 February 2016
Procedure number	EMA/H/C/0004154
Invented name	Apealea
Therapeutic indication	Apealea in combination with carboplatin is indicated for the treatment of adult patients with first relapse of platinum-sensitive epithelial ovarian cancer, primary peritoneal cancer and fallopian tube cancer. Further information on Apealea 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	20 September 2018
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinator	F. Naumann-Winter
Sponsor's report submission date	17 February 2016
COMP discussion and adoption of list of questions	19-21 June 2018
Oral explanation	19 July 2018

Following communication of the outcome of the discussion, the sponsor formally requested the withdrawal of the orphan designation on 24 July 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 2006 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 in particular 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 paclitaxel (micellar) may be of significant benefit to those affected by the condition.

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

The orphan condition affects predominantly 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.

The proposed indication is: "Apealea is indicated for the treatment of epithelial ovarian cancer, primary peritoneal cancer and Fallopian tube cancer in combination with carboplatin as second- or third-line therapy".

The issue therefore arises as to whether primary peritoneal and faloppian are spanned by the "ovarian cancer" designation. This is not specifically addressed in the old 2006 summary report for the designation step. However 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)". This has been the basis that the inclusion of fallopian and primary peritoneal cancer has been explicitly included in other "ovarian cancer" orphan procedure, on the basis of common tissue origin, molecular pathology, clinical characteristics and natural history leading to the same staging and treatment.

Therefore the propsoed therapeutic indication “Apealea is indicated for the treatment of epithelial ovarian cancer, primary peritoneal cancer and Fallopian tube cancer in combination with carboplatin as second- or third-line therapy” may be eventually considered to fall within the scope of the designated orphan indication “treatment of ovarian cancer”.

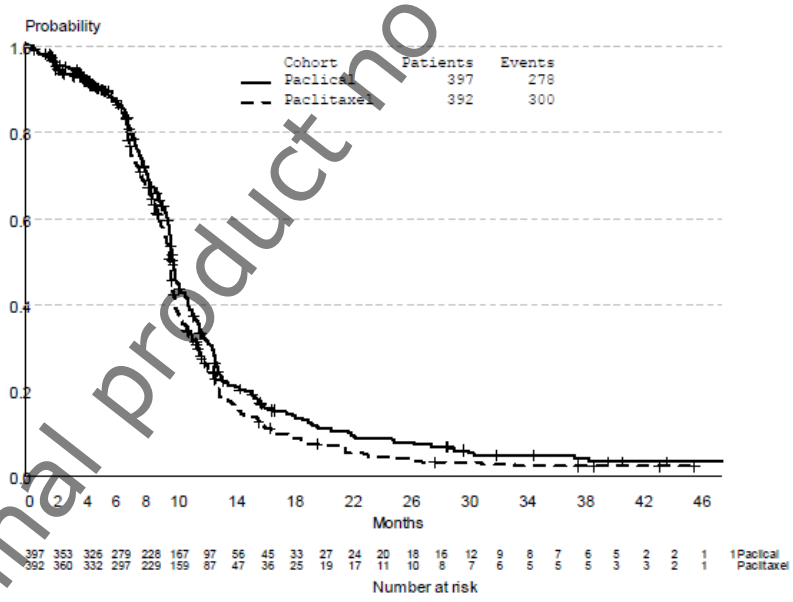
Intention to diagnose, prevent or treat

Conditional to a positive CHMP assessment, the intention to treat the condition will be considered justified. Study OAS-07OVA was an open-label, parallel group, randomised, comparator-controlled, non-inferiority, Phase III study in patients with ovarian fallopian or primary peritoneal cancer, relapsing > 6 months after end of first or second line treatment.

Eligible subjects were randomly assigned in a 1:1 ratio to receive either Apealea 250 mg/m2 plus carboplatin 5-6 AUC or Taxol 175 mg/m2 plus carboplatin 5-6 AUC during 6 cycles with 3 weeks between the cycles. The treatment period started at day of first dose and ended 22 days after the sixth dose. During the follow-up period, which started on cycle 6 day 23, the patients were followed on a monthly basis with start at six months after first dose until progression or leaving the study.

Primary endpoint was PFS, defined as the time from randomisation to progression, based on CT scans evaluated according to RECIST 1.0 by blinded central review, or death from any cause. The study met its primary endpoint for non-inferiority of efficacy in terms of PFS based on central review of CT scans evaluated according to RECIST.

Figure 1. Adopted from the sponsor’s application. Kaplan-Meier plot of PFS based on CT scans according to RECIST – ITT population



Chronically debilitating and / or life-threatening nature

The applicant refers to EUCAN data citing annual mortality rates of approximately 9 per 1000 for 2012.

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

The sponsor states that the prevalence is "not expected to increase the estimates to more than 3 patients per 10,000". This is based on a 5 year partial prevalence for ovarian cancer, calculated in two ways a) directly from EUCAN 2012 data (2.08 per 10,000), and b) from incidence by assuming a 38% 5 year survival (2.82 per 10,000). The sponsor explicitly cannot be specific about fallopian and primary peritoneal.

Table 1. (Adopted from the sponsor's maintenance report, second methodology)

Year	Proportion alive	Increment in prevalence *(inhabitants)*	Mortality *(inhabitants)*
0		44 149	44 149
-1	87.6	38 675	
-2	75.2	33 200	
-3	62.8	30 021	
-4	50.4	22 251	
-5	38	16 777	
	Total patients:	140 924	
5-year Prevalence (EU)		**=140 924/499 784 361=2.82 per 10, 000**	

There are however some limitations to be further explored:

- There is no account of the alleged 38% of patients that are alive after 5 years. Literature reports late relapses and it is not justified why these patients are not considered as affected by the condition.
- The data used go up to 2012. As such, any recent changes in survival, because of diagnostic earlier detection and/or treatment advancements, are not taken into consideration. Updated calculations will be needed.
- In NORDCAN the number of people living with the diagnosis of ovarian cancer is 17.1 per 10,000 women, which gives approximately 9 in 10,000 people altogether.
- In RARECARE 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 on Nov 29, cited a 5.9 per 10,000 including ovarian and fallopian cancer.
- 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).

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 and rucaparib.

- Niraparib 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.
- Olaparib 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.
- Rucaparib 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

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 macroscopically 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

Significant benefit is argued mainly on the basis of improved safety versus the authorised paclitaxel. Several arguments are put forward in that regard:

a) Improved hypersensitivity reactions based on Study OAS-07OVA

With regards to the first point, it is reported that there was no difference in incidence of hypersensitivity reactions overall. In the study, the Investigator was given an opportunity to assess whether the hypersensitivity reactions were caused by paclitaxel (Apealea or Paclitaxel (Taxol)) or by the carboplatin. It is reported that more patients experienced hypersensitivity reactions attributed to carboplatin in the Apealea group than in the Paclitaxel (Taxol) group (p=0.0296). The sponsor however notes that interpretation of the data should be made with caution as the 30 minutes between the infusions of paclitaxel and carboplatin could have made it difficult to assess the relation of reactions that developed during or after the infusion of carboplatin. Additionally, the incidence of hypersensitivity events during carboplatin could have been influenced by a carry-over of the effects of premedication prescribed to control the risks with Taxol. Therefore the argument for improved hypersensitivity profile is difficult to accept, and the gravity and outcomes of the adverse reactions, as well as the size of the population affected, should be further elaborated.

b) No need for routine premedication to avoid frequent or severe hypersensitivity reactions

The sponsor notes freedom from the need to provide premedication potentially shortens patient visits to the hospital, as no time needs to be allowed for the effect of the pre-medications or for their effect to wear off. This argument is in effect a major contribution to patient care argument, which is not qualified or documented by any patient reported outcomes or other means. This would be necessary in order to appreciate the size of any effect.

c) Shorter infusion times

The reduction of the duration of the infusion with Apealea compared with classical paclitaxel formulations such as Taxol is a benefit for the patient, reducing the time that they need to spend at their hospital or infusion centre. It is argued that with a shorter infusion time, some measures that can reduce alopecia (a recognised adverse reaction to paclitaxel) such as “cold caps” become feasible. Shorter infusion times are also a benefit to the hospital, which can accommodate more patients needing infusions. Again the argument is in effect a major contribution to patient care argument, which is not qualified or documented by any patient reported outcomes or other means. This would be necessary in order to appreciate the size of any effect and prescribe significant benefit.

d) No need for a special infusion set

The sponsor recommends use of an ethylene-vinyl acetate (EVA) bag for the administration of the reconstituted Apealea solution. The product information warns that compatibility with di-(2-ethylhexyl) phthalate (DEHP) containing administration sets has not been demonstrated. The use of administration sets with an in-line filter with a microporous membrane of 5 to 15 micrometres is recommended. The applicant goes on to argue that in the case of the classical paclitaxel formulation, the product information warns that to minimise patient exposure to DEHP, which may be leached from plasticised PVC infusion bags, sets, or other medical instruments. It is considered by the applicant that the freedom to use non-specialised infusion sets may be of benefit to the hospital or infusion centre. As in the above cases, clinical data are missing to on the one hand document the serious problems with the available formulations as well as data to document the expected improvements.

In the absence of clinical data to justify any of the claims put forwards, the significant benefit cannot be considered met. Furthermore, the discussion versus other comparators authorised for the targeted

indication is also pending. A previous protocol assistance recommendation on SB also informed the sponsor that a clinically relevant difference in hypersensitivity reactions would be required (and the product otherwise equivalent to authorised paclitaxel) and that merely reducing premedication/infusion time would not be sufficient to maintain orphan status.

4. COMP list of issues

Prevalence

The applicant is invited to: a) justify the epidemiological index used taking into consideration the duration of the condition b) comment on the available European databases and c) provide a crude point prevalence estimate at the time of the orphan maintenance procedure taking into consideration ongoing demographic change. Recent time trends in crude incidence or improvements of survival should be presented and discussed.

Significant benefit

Significant benefit is argued on the basis of improved safety versus the authorised paclitaxel. The COMP has noted that the data submitted do not support improvement in hypersensitivity reactions in the pivotal study presented.

The applicant discusses perceived issues regarding infusion of paclitaxel, including premedication requirements and technical aspects of the proposed paclitaxel formulation. The committee expects clinical data to justify serious and documented difficulties arising from the claimed issues and clinical data with the product to confirm that they would be addressed, also in the setting of a combination therapy with carboplatin.

In the absence of clinical data to justify any of the claims put forwards, significant benefit may not be considered met.