27 October 2020
EMA/OD/0000031233
EMADOC-1700519818-571923
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Zejula (niraparib)
Treatment of ovarian cancer
EU/3/10/760
Sponsor: GlaxoSmithKline (Ireland) 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	
Designated active substance	(3S)-3-{4-[7-(aminocarbonyl)-2H-indazol-2-yl] phenyl} piperidine tosylate monohydrate salt
International Non-Proprietary Name	Niraparib
Tradename	Zejula
Orphan condition	Treatment of ovarian cancer
Sponsor's details:	GlaxoSmithKline (Ireland) Limited 12 Riverwalk Citywest Business Campus Dublin 24 D24 YK11 Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	Merck Sharp & Dohme Limited
COMP opinion	6 May 2010
EC decision	4 August 2010
EC registration number	EU/3/10/760
Post-designation procedural history	
Transfer of sponsorship	Transfer from Merck Sharp & Dohme Limited to Tesaro U.K. Limited – EC decision of 19 December 2012
COMP opinion on review of orphan designation at the time of marketing authorisation	16 November 2017
Transfer of sponsorship	Transfer from Tesaro U.K. Limited to TESARO Bio Netherlands – EC decision of 10 December 2018
Transfer of sponsorship	Transfer from TESARO Bio Netherlands to GlaxoSmithKline (Ireland) Limited – EC decision of 18 December 2019
Type II variation procedural history	
Rapporteur / Co-rapporteur	Bjorg Bolstad / Alexandre Moreau
Applicant	GlaxoSmithKline (Ireland) Limited
Application submission	10 February 2020
Procedure start	29 February 2020
Procedure number	EMA/H/C/004249/II/0019
Invented name	Zejula

Proposed therapeutic indication	Zejula is indicated as monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy. Further information on Zejula can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/zejula
CHMP opinion	17 September 2020
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Brigitte Schwarzer-Daum / Frauke Naumann-Winter
Sponsor's report submission	9 March 2020
COMP discussion and adoption of list of questions	8-10 September 2020
Oral explanation cancellation	6 October 2020
COMP opinion	8 October 2020

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2010 designation 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 European Union, at the time the application was made;
- the condition is life-threatening and chronically debilitating due to diagnosis of the condition at a late stage and poor overall survival;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that (3S)-3-{4-[7-(aminocarbonyl)-2H-indazol-2-yl] phenyl} piperidine tosylate monohydrate salt may be of significant benefit to those affected by the condition. This appears to be justified on the grounds of a clinically relevant advantage, due to potential improved effect secondary to a novel mechanism of action and in particular inhibition of poly ADP ribose polymerase, as supported by the preclinical data in relevant models and preliminary clinical studies in ovarian cancer patients.

2.2. Review of orphan medicinal product designation at the time of marketing authorisation

The COMP opinion on the initial review of the orphan medicinal product designation in 2017 was based on the following grounds:

- 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 to be 4.3 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating 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, Zejula is of significant benefit to patients in the orphan condition as defined in the granted therapeutic indication. The currently authorised product Lynparza is indicated for maintenance treatment of patients with BRCA mutation. In contrast, maintenance treatment with Zejula improved progression free survival in adult patients with platinum sensitive relapsed high grade serous ovarian cancer independent of BRCA mutation status. Therefore, Zejula provides significant benefit for patients without BRCA mutation, who currently have no authorised maintenance treatment.

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

Ovarian cancer is a varied group of neoplasms characterised as a malignant transformation of tissue on the surface of the ovaries. The majority of cases of ovarian cancer are of epithelial origin (~90%) with the remainder coming from germ cells or sex cord stromal cells.

The exact cause of ovarian cancer remains unknown but many associated risk factors have been identified. A woman's reproductive history appears to contribute significantly to her lifetime risk of ovarian cancer. Family history also plays a very important role in the development of ovarian cancer.

The clinical presentation of epithelial ovarian carcinoma, fallopian tubal carcinoma, and peritoneal carcinoma may be either acute or subacute. Women who present in an acute fashion are typically those with advanced disease who present with a condition that requires urgent care and evaluation (e.g. pleural effusion, bowel obstruction). Most patients with early stage disease are asymptomatic, and in general the symptoms of ovarian cancer are nonspecific and often mimic the presence of upper abdominal disease, making diagnosis of early ovarian cancer difficult. Typically, only patients with more advanced disease present with definitive symptoms such as abdominal distension, effusions (pleural or peritoneal) and the development of respiratory symptoms. Thus, ovarian cancer is rarely

diagnosed in its early stages (stages I/II), often going undetected until it has spread beyond the ovary (stages III/IV).

The proposed condition has been designated previously.

The approved therapeutic indication "for the maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy" falls within the scope of the designated orphan condition "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

Ovarian cancer is the fifth most common cause of cancer in women in the developed world. The median age at diagnosis is 63years. Frequently diagnosed at an advanced stage, symptoms can be vague and sometimes misattributed to irritable bowel syndrome. Median progression free survival (PFS) for patients with advanced ovarian cancer is approximately 18months and overall survival (OS) for all ovarian cancer 40% to 50% at 10years. Prognosis is influenced by age (Flaum et al, Clinical Genetic. 2020;97:54-63).

It has recently been noted that ovarian cancer rates have dropped to 4.2 in 100,000 (-11.5%) since 2015. (Carioli G et al, Annals of Oncology Vol31, issue 5 April 2020).

Number of people affected or at risk

The sponsor has accessed data on the prevalence of ovarian cancer based on a literature search and databases from Nordcan and ECIS. An earlier Rarecare publication has also been used.

Below is a table of selected publications used for the estimate of the prevalence of ovarian cancer in the European Union.

Table 1.

Author	Year	Data source	Comment
Gatta et al.	2018	RARECARENet; cancer diagnosed up to 2007	Provides crude incidence and 5-year relative survival data
Ojamaa et al.	2017	Estonian cancer registry, cases diagnosed 1995-2009	Study of trends in ovarian cancer survival in Estonia
Chirlaque et al.	2018	Data from 9 Spanish cancer registries; cases diagnosed 2000-2007	Compares 5-year relative survival from 1995-1999 and 2000-2007 in Spain
Timmermans et al.	2018	Data from Netherlands cancer registry; cases diagnosed 1989 to 2014	Analysis of long-term survival of ovarian cancer patients in the Netherlands
Tewari et al.	2019	OS from bevacizumab clinical study	Provides overall survival (OS) of 1,873 women from bevacizumab clinical study with median 102.9 months follow-up
Elzakkers et al.	2019	Data from Netherlands cancer registry; cases diagnosed 1990 to 2014	Comparison of OS of patients ≤ 40 years to patients > 40 years
Arnold et al.	2019	Data from cancer registries in Denmark, Ireland, Norway and UK	Progress in ovarian cancer survival, mortality and incidence 1995 to 2014
Dal Maso et al.	2019	Data from Italian cancer registries	Estimate of life expectancy in ovarian cancer diagnosed 1990 to 2000
Botta et al.	2019	Data from Italian cancer registries	Estimate of life expectancy in ovarian cancer diagnosed 1985 to 2011, and follow-up until 2013
Wu et al.	2019	SEER (covering 28% of US population); cases diagnosed 1990 to 2014	Survival trends in epithelial ovarian cancer, US population only
Zhang et al.	2019	GLOBOCAN, SEER, and Cancer Incidence in Five Continents	Temporal trends in ovarian cancer incidence from 1973 to 2015

The sponsor notes that most of the data used in these publications is from epidemiological sources which date around 2010. In order to establish a more current prevalence a calculation based on incidence and duration is therefore proposed.

Incidence

A more current incidence was deduced from primarily two databases: Nordcan and ECIS.

The Nordcan database was accessed in 2019 by the sponsor and had records up to 2016. The average crude incidence rate (based on female population only) for ovarian cancer in the Nordic countries is 17.5 per 100,000 in the period from 2010 to 2016. Of note, there is a continuous decline in crude incidence rate from 18.3 per 100,000 in 2010 to 16.8 in 2016, corresponding to an 8.2% decrease. If the effects of changes due to shifts in the age of the population are removed by standardising to the age of the Nordic population, the same tendency is even more pronounced (16.2 in 2010 to 14.5 in 2016), with a decrease in the Nordic age-standardised rate (ASR) of 10,5%.

Table 2. Incidence of ovarian cancer in the Nordic countries

Year	Incidence (numbers)	Incidence (crude rate, for female population only) per 100,000	European ASR (for female population only) per 100,000	Nordic ASR (for female population only) per 100,000
2010	2,364	18.3	13.7	16.2
2011	2,311	17.8	13.3	15.9
2012	2,325	17.8	13.3	15.7
2013	2,308	17.6	13.1	15.4
2014	2,238	16,9	12.3	14.6
2015	2,336	17.5	12.7	15.1
2016	2,255	16.8	12.2	14.5
Average	**2,305**	**17.5**	**12,9**	**15.3**
Change		**8,2%**		**10,5%**

European ASR: age-standardised rate (standardised for European population); Nordic ASR: age-standardised rate (standardised for European population).
Source: NORDCAN 2019

The European Cancer Information System (ECIS, https://ecis.jrc.ec.europa.eu/index.php) is a data repository for information on cancer in the European Union, set up by the European Commission's Joint Research Centre (JRC) in close collaboration with the Directorate-General for Health and Food Safety (DG SANTE), building on existing experience, competence and cooperation of cancer registries associated to the European Network of Cancer Registries (ENCR), together with other key stakeholders in the cancer information domain.

The project, in its first edition, makes use of data from a call launched in 2015 and addressed to all European population-based cancer registries with the aim of establishing a single European cancer-registry data repository. As of February 2018, a total of 147 population-based cancer registries from 32 European countries responded to the call for data and were included in the dataset.

Due to this methodology, the ECIS dataset is considered the most appropriate set of data on cancer incidence in the EU/EEA.

In total, 45,134 new cases of ovarian cancer were extrapolated by ECIS for the EEA-30 (28 EU Member States plus Iceland and Norway) for 2018. For Liechtenstein, data is not available.

The combined population of EU-28 plus Norway and Island in 2018 was 518,023,294 persons (Eurostat, 2019). For this population, 45,134 cases of newly diagnosed ovarian cancer corresponds to a crude incidence rate (both sexes) of **8.71/100,000 population.**

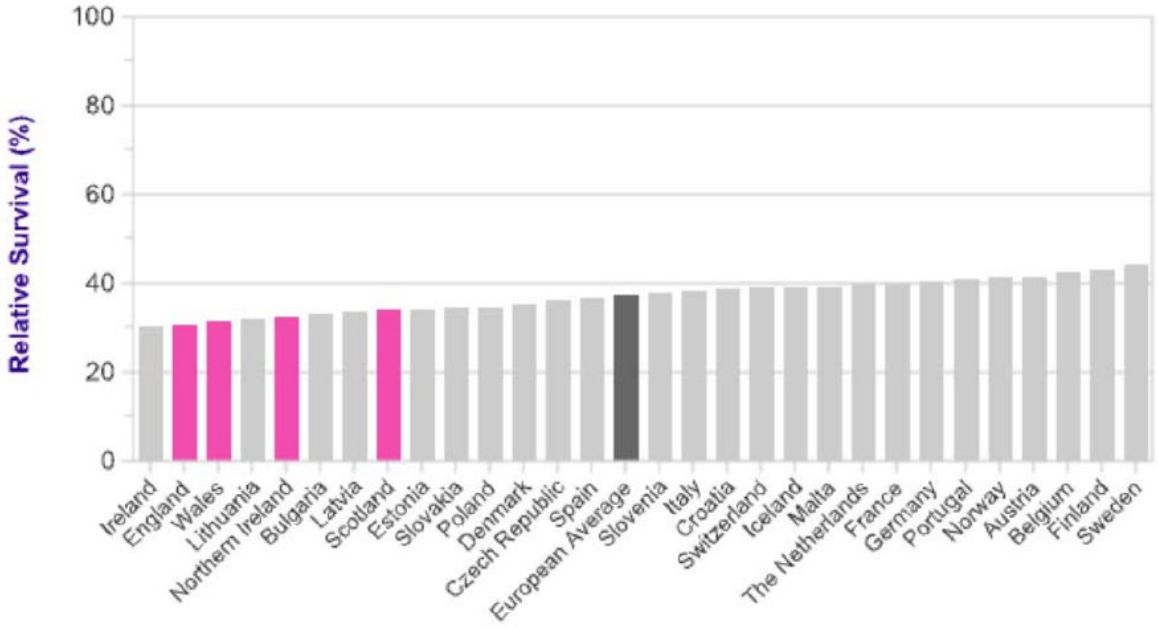
Survival

For the purpose of the calculation of disease duration, real-world data as provided in registry sources is proposed to be more appropriate than data derived from the setting of clinical trials. All registry data presented show a similar pattern of very fast decline in relative survival in the first three years after diagnosis, while for later years the death rates attributable to ovarian cancer decrease continuously. This indicates that a certain (though difficult to quantify) subset of patients is permanently cured from the disease. It has been estimated that less than 10% of patients experience a 10-year disease-free survival (Tewari et al., 2019).

Of the registry data available the data from the sponsor believes that the NORDCAN database is considered the most appropriate since the source registries systematically include most of the Scandinavian population. At the same time, it is based on reported cases (not estimates), and the data is the most recent available (2010 to 2016). This is an important point as survival rates have increased

continuously over the last decades in many member states. Survival rates in the Nordic countries are among the highest in Europe (Figure 4), hence referring to this data is considered a conservative approach.

Figure 1. Ovarian Cancer, age standardised five-years relative survival, 2000-2007



In the Nordic countries, about 20% of patients die within the first year after diagnosis, and, depending on the country, only between 41% (Denmark) and 49% (Sweden) are still alive after 5 years (NORDCAN, 2019).

Based on this data, for the purpose of point prevalence calculation, the duration of disease for ovarian cancer is considered 5 years which is an acceptable estimation.

The sponsor added the incidence of fallopian and primary peritoneal (proportion justified according to a recent publication) and concludes on an estimate of 4.88 in 10.000 which was accepted by the COMP for 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 following authorised treatments: bevacizumab, doxorubicin hydrochloride, topotecan, olaparib, niraparib, rucaparib, trabectedin, gemcitabine, paclitaxel, carboplatin, cisplatin, cyclophosphamide, docetaxel, epirubicin, 5FU, irinotecan, mephalan, methotrexate, mitoxantrone, paclitaxel, and treosulphan, are available in the EU.

There is a current ESMO guideline for the treatment of newly Diagnosed and Relapsed Epithelial Ovarian Carcinoma (Ledermann et al 2013), which is supplemented with an eUpdate addressing and incorporating the approval of Olaparib (Ledermann et al 2016).

- The aim of surgery for early ovarian cancer is to resect the tumour and to undertake adequate staging. This will provide prognostic information and will define whether chemotherapy is needed.
- In advanced epithelial ovarian cancer, the aim is complete cytoreduction of all macroscopic visible disease, since this has been shown to be associated with a significantly increased OS and PFS. The value of surgical cytoreduction in relapsed epithelial ovarian cancer remains controversial and is not regarded as a standard of care, as the evidence for this approach has not been demonstrated in prospective trials.
- Front line: standard chemotherapy consists of a combination of paclitaxel and carboplatin. The combination of cisplatin and paclitaxel is equally effective but is more toxic and less convenient to administer. For those patients who develop an allergy to or do not tolerate paclitaxel, the combination of docetaxel-carboplatin or pegylated liposomal doxorubicin (PLD)-carboplatin can be considered an alternative. The addition of bevacizumab is recommended for patients with advanced ovarian cancer with poor prognostic features such as stage IV.
- Recurrence: Treatment depends on the categorisation into 'platinum-refractory', 'platinum-resistant', 'partially platinum-sensitive' and 'platinum-sensitive' patients.
- E-update: on recurrent 'platinum-sensitive' ovarian cancer: patients with high-grade tumours should be tested for a germline BRCA mutation. Consideration should be given to testing tumours for a somatic BRCA mutation. 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
- The ESMO guidelines have been updated to account for the introduction of PARP inhibitors.

Recommendations:

- Maintenance therapy with a PARP inhibitor (olaparib, niraparib or rucaparib) following a response to platinum-based therapy in patients with recurrent platinum-sensitive high-grade ovarian cancer is a new standard of care option, irrespective of BRCA status [I, A].
- For patients with recurrent platinum-sensitive ovarian cancer and a BRCA mutation unable to receive platinum-based therapy, rucaparib monotherapy is an option [III, A].

Significant benefit

The sponsor is proposing that their product niraparib will offer a significant benefit in the treatment of a specific target patient population which is only partially treated with olaparib. The wording of the proposed amendment to the current niraparib indication is:

"for the maintenance treatment of adult patients with advanced high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy."

The wording of the comparative similar indication for olaparib is:

"maintenance treatment of adult patients with advanced (FIGO stages III and IV) BRCA1/2-mutated (germline and/or somatic) high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy."

The COMP noted that the therapeutic indication for niraparib is for first line maintenance in an "all-comers" (i.e. no specific enrichment approach in addition to requiring either CR or PR after a platinum-

containing regimen) (although the treatment effect size is the largest in the HR-deficient subgroup).

It is not clear whether the claim of SB over bevacizumab is based on improved efficacy and safety because the sponsor highlights safety profile of bevacizumab and no explicit claim for major contribution to patient care is mentioned by the sponsor. As such the claim of SB over bevacizumab and olaparib appear to be based on improved efficacy.

The proposed therapeutic indication corresponds to a broader patient population as compared to the one olaparib is authorised for. As such Niraparib is indicated for a broader patient population than olaparib and brings a clinically relevant advantage in patients who do not have a BRCA1/2 mutation.

Bevacizumab, on the contrary, is used in a broad patient population not restricted by biomarkers or genetic mutations. The sponsor highlights the following limitations of bevacizumab: no survival benefit, safety concerns and data are lacking on its use in the growing number of patients receiving NACT.

The pivotal studies of bevacizumab and niraparib are not comparable neither by design nor by population. Bevacizumab was studied as continued treatment with one of a triple baseline chemotherapy without prospective biomarker assessment and niraparib was studied in a dedicated maintenance study in responding patients with biomarker assessment. In view of the different timing of the performance of the studies, the use of prior neoadjuvant chemotherapy in patients with ovarian cancer was very different. The growing NACT group is considered important.

The comparisons between the biomarker-defined subsets are limited by methodological differences. A retrospective analysis of GOG-218 patients showed that while patients with homologous recombination negative (I.e. proficient) tumours might benefit with bevacizumab therapy (HR 0.71), there was no benefit in the homologous recombination deficient subgroup (HR 0.95-1) (Norquist et al. 2018). This is contrary to the results for niraparib.

In accordance with the need to submit data for the claim for major contribution to patient care the sponsor provided a literature review including dedicated large surveys with patients on maintenance treatment for ovarian cancer (not necessarily niraparib), reporting a preference for oral over iv and a review of COVID recommendations. Preference for oral therapies in the context of the treatment of ovarian cancer has been reported in the literature (Calhoun and Roland 2000; Rohr et al. 2020).

Of particular interest was the recent publication by Rohr et al 2020. It reported on a large European survey of 2,101 patients with ovarian cancer conducted by the European Network of Gynaecological Oncological Trial Groups (ENGOT) in order to explore patients' expectation of maintenance therapies. The results of the study showed that 42.9% of respondents preferred oral tablets, 32.1% had no preference, and 25% preferred IV administration. The study also found that, there was a clear preference for a once daily oral dose (32%) compared to twice daily (15.5%) or twice weekly (13%) oral administration.

The COMP considered that this level of data was sufficient to support the claim for major contribution to patient care when niraparib was compared to bevacizumab, and a clinically relevant advantage over olaparip due to the difference in the target patient population, and recommended maintaining the current 10-year market exclusivity.

4. COMP position adopted on date

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition 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 to be 4.8 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating due to diagnosis of the condition at a late stage and poor overall survival;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Zejula is of significant benefit for those affected by the orphan condition still holds. The sponsor has provided clinical data in a broader patient population compared to olaparib which corresponds to a clinically relevant advantage. In addition, the oral administration of niraparib constitutes a major contribution to patient care over regimens containing bevacizumab, which is administered by intravenous administration in the granted therapeutic indication.

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 Zejula, (3S)-3-{4-[7-(aminocarbonyl)-2H-indazol-2-yl] phenyl} piperidine tosylate monohydrate salt, niraparib for treatment of ovarian cancer (EU/3/10/760) is not removed from the Community Register of Orphan Medicinal Products.