Assessment report

Zejula

International non-proprietary name: niraparib

Procedure No. EMEA/H/C/004249/X/0029

Note

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

AE    adverse event
AUC\textsubscript{0-\infty} area under the plasma concentration-time curve (AUC) from time 0 extrapolated to infinity
AUC\textsubscript{0-t} AUC from time 0 to the time of the last quantifiable concentration
BA bioavailability
BE bioequivalence
CI confidence interval
CL/F apparent systemic clearance
C\textsubscript{\text{max}} maximum observed plasma concentration
CPP Critical process parameter
CQA Critical Quality Attribute
critical quality attributes
CSR clinical study report
EU European Union
FDA United States Food and Drug Administration
FMEA Failure mode effects analysis
FT-IR Fourier-transformed infrared
GCP Good Clinical Practice
GMP Good Manufacturing Practice
HDPE High-density polyethylene
HPLC High performance liquid chromatography
ICH International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IPC In-process control
LDPE Low-density polyethylene
LOD Limit of detection
LOQ Limit of quantitation
LSM least-squares mean
MAA Marketing authorization application
MAH Marketing authorization holder
OPA Polyamide nylon
PACMP Post approval change management protocol
PARP poly (adenosine diphosphate-ribose) polymerase
PK pharmacokinetic(s)
PP Process parameter
PVC Poly(vinylpyrrolidone)
PVC Polyvinyl chloride
QTPP quality target product profile
QTPP Quality target product profile
RH Relative humidity
SmPC Summary of Product Characteristics
$\text{t}_{1/2}$ apparent terminal elimination half-life
TEAE Treatment emergent adverse event
$\text{t}_{\text{max}}$ maximum observed plasma concentration
UDU Uniformity of dosage units
Vz/F apparent volume of distribution
XRPD x-ray powder diffraction
1. Background information on the procedure

1.1. Submission of the dossier

GlaxoSmithKline (Ireland) Limited submitted on 26 May 2021 an extension of the marketing authorisation. Extension application to introduce a new pharmaceutical form (100 mg film-coated tablet). The RMP (version 5.1) is updated in accordance.

The MAH applied for the following indication for Zejula 100 mg film-coated tablet:
- 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.
- 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

1.2. Legal basis, dossier content

The legal basis for this application refers to:


Zejula was designated as an orphan medicinal product EU/3/10/760 on 04 Aug 2010 in the following condition: treatment of ovarian cancer.

1.3. Information on Paediatric requirements

At the time of submission of the application, the PIP P/0184/2021 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Protocol assistance

The MAH did not seek Protocol assistance at the CHMP.
### 1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Ingrid Wang

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Jan Neuhauser

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
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<tr>
<td>The application was received by the EMA on</td>
<td>26 May 2021</td>
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<tr>
<td>The procedure started on</td>
<td>17 June 2021</td>
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<td>The CHMP Rapporteur’s first Assessment Report was circulated to all CHMP and PRAC members on</td>
<td>8 September 2021</td>
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<tr>
<td>The PRAC Rapporteur’s first Assessment Report was circulated to all PRAC and CHMP members on</td>
<td>09 September 2021</td>
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<tr>
<td>The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on</td>
<td>14 October 2021</td>
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<tr>
<td>The MAH submitted the responses to the CHMP consolidated List of Questions on</td>
<td>15 October 2021</td>
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<td>The following GMP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality assessment of the product:</td>
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<td>− A GMP inspection at one manufacturing site in China between 8-12 November 2021. The outcome of the inspection carried out was issued on</td>
<td>18 February 2022</td>
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<td>The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on</td>
<td>16 November 2021</td>
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<td>The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on</td>
<td>16 December 2021</td>
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<tr>
<td>The MAH submitted the responses to the CHMP List of Outstanding Issues on</td>
<td>22 February 2022</td>
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<tr>
<td>The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on</td>
<td>09 March 2022</td>
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<td>The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Zejula on</td>
<td>24 March 2022</td>
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2. Scientific discussion

2.1. Problem statement

This is a line extension application to the marketing authorisation of Zejula 100 mg hard capsules (EU/1/17/1235/001-003) to add a new pharmaceutical form, Zejula 100 mg film-coated tablet. Strength (100 mg), dosing and indication are the same as for the previously approved hard capsules.

2.1.1. Disease or condition

Zejula 100 mg film-coated tablet has been developed as a line extension (new formulation) to the reference product Zejula 100 mg hard capsule, and is intended to be used in the same indications as the capsule.

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.
- 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.

2.1.2. Epidemiology

Ovarian cancer is the fifth overall cause of cancer death in women, representing 5% of all cancer deaths. It is also the deadliest of gynaecologic cancers in 2014, 14,270 women in the United States (US) and 18,303 in the European Union (EU) died from ovarian cancer. Across Europe, the estimated age standardised rate of newly diagnosed ovarian cancer cases in 2020 is 15.5/100,000 and the mortality is 10.3/100,000 (ECIS 2020).

2.1.3. Biologic features

Epithelial ovarian cancer represents the majority of malignant ovarian neoplasm (about 90%) (Chan JK et al 2006; Jelovac D et al. 2011). The World Health Organization (WHO) classification of surface epithelial ovarian tumours includes six major histotypes - serous, mucinous, endometrioid, clear cell, transitional cell and epithelial-stromal. The serous subtype of ovarian carcinoma accounts for approximately 60-80% of ovarian cancer cases and is the most aggressive type of ovarian cancer. Grade is an additional prognostic determinant and a number of grading systems currently exist which are derived from reviewing the following tumour characteristics: architectural features, mitotic counts and nuclear atypia (ESMO Clinical Practice Guidelines, 2013). Low grade (grade 1, well differentiated) serous ovarian carcinoma is considered a distinct type of disease compared with high grade (grade 2 and 3 – moderately and poorly differentiated) serous carcinoma based on a number of clinical and molecular features, thus forming a 2 tier classification of low and high grade disease widely accepted and used in clinical practice (Levanon et al 2008; Vang et al 2009).

Breast cancer genes (BRCA) 1 and 2 are tumour suppressors that play a role in DNA repair: a deleterious

Recent research shows that homologous recombination deficiency can also be induced by other genes involved in DNA damage repair or by genetic alterations such as DNA methylation that lead to genomic instability. Approximately 41% to 50% of newly diagnosed ovarian carcinomas are estimated to exhibit homologous recombination deficiency (Elvin et al. 2017, Moschetta et al. 2016) which is also a phenotype that predicts improved rate of responses to platinum-based therapy and PARP inhibitors relative to tumours that are homologous recombination proficient (Kaufman et al. 2015).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Ovarian cancer is often asymptomatic in the early stages and is, therefore, first detected in advanced stages, when prognosis is poor. For women who do experience symptoms in the early stages, ovarian cancer is sometimes misdiagnosed because the majority of symptoms are nonspecific. These symptoms may overlap those of gastrointestinal and other diseases, and as a result, many patients may be treated incorrectly for months or years. The advanced stage at which ovarian cancer is generally detected is reflected in the 5-year survival rates; 46% across all stages and 29% for advanced stages (Siegel et al 2017).

2.1.5. Management

The paradigm for first-line treatment of newly diagnosed ovarian cancer includes a combination of surgery and chemotherapy: either primary debulking surgery (PDS) followed by adjuvant chemotherapy or neoadjuvant chemotherapy (NACT) with subsequent interval debulking surgery (IDS) followed by additional chemotherapy. Worldwide, the use of NACT is increasing in patients with large volume Stage IIIC/IV disease, such that 45-60% of these patients will receive NACT (Epi Flatiron Database EMR Database 2019, Liu et al. 2017, Vergote et al. 2010, Monitor IHGO 2019, Nicklin et al. 2017). The preferred standard of care chemotherapy regimen is carboplatin and paclitaxel, based upon an improved toxicity profile and comparable efficacy when compared to cisplatin and paclitaxel (Ozol et al. 2003, duBois et al. 2005).

Bevacizumab is an additional option for first line treatment. The addition of bevacizumab to every-3-week paclitaxel and carboplatin, followed by continuation of maintenance for up to 15 cycles with bevacizumab improved PFS over placebo in the Phase 3 GOG 218 study (PFS hazard ratio [HR] 0.62) and in the high-risk population subgroup, as defined by Stage and residual disease, in the open-label Phase 3 ICON 7 study (PFS HR 0.68) (Burger et al. 2003, Perren et al. 2011). However, bevacizumab provided no overall survival benefit in the Intent-to-Treat (ITT) population in either study.

Olaparib, a PARP inhibitor, was approved for use as a maintenance treatment in patients with ovarian cancer and a mutation in the breast cancer susceptibility gene (BRCAmut) following complete response (CR) or partial response (PR) to first line platinum based chemotherapy based on an improvement in PFS over placebo (HR 0.30; [OS data is not yet available]) in study SOLO-1 (see SmPC Lynparza).

Data were recently reported from the Phase 3 PAOLA trial, which assessed the combination of bevacizumab plus olaparib versus bevacizumab in the ovarian cancer front line setting. Clinical benefit of the combination was observed in patients with homologous recombination deficiency (HR 0.33) but not in the remaining population (HR 0.92) (Ray-Coquard et al., paper presented at European Society for Medical Oncology 2019).
Observation, or “watch and wait” after response to first line therapy is included in the National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology, and American Society of Assessment report EMA/531223/2020 Page 12/168 Clinical Oncology guidelines and is the approach currently taken for the majority (>75%) of patients with advanced ovarian cancer (Epi Flatiron Database EMR Database 2019, Liu et al. 2017, Colombo et al. 2019).

Despite high response rates to first line standard-of-care platinum-based chemotherapy, 85% of patients with advanced ovarian cancer will experience disease recurrence and ultimately die of the disease. Prolonging the benefit of first line platinum is currently the best chance these patients have to avoid recurrence and potentially improve survival outcomes. Development of new therapies is essential to address the unmet medical need and improve the overall outlook for patients with this lethal cancer (Lorusso et al. 2012).

### 2.2. About the product

Niraparib is an orally available, highly selective poly(adenosine diphosphate-ribose) polymerase (PARP) -1 and -2 inhibitor exhibiting potent anti-tumour activity through the direct inhibition of PARP.

Zejula (niraparib) 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.
- 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.

In first-line ovarian cancer maintenance treatment, the recommended starting dose of Zejula is 200 mg (two 100-mg tablets), taken once daily. However, for those patients who weigh ≥ 77 kg and have baseline platelet count ≥ 150,000/μL, the recommended starting dose of Zejula is 300 mg (three 100-mg tablets), taken once daily (see section 4.4 and 4.8).

In recurrent ovarian cancer maintenance treatment, the dose is three 100 mg tablets once daily, equivalent to a total daily dose of 300 mg.

### 2.3. Type of Application and aspects on development

This is a line extension application to the marketing authorisation of Zejula 100 mg hard capsules (EU/1/17/1235/001-003) to add a new pharmaceutical form, Zejula 100 mg film-coated tablet.

### 2.4. Quality aspects

#### 2.4.1. Introduction

This is a line extension application to the marketing authorisation of Zejula 100 mg hard capsules (EU/1/17/1235/001-003) to add a new pharmaceutical form, Zejula 100 mg film-coated tablet. The strength of the film-coated tablets, dosing and indication are the same as for the previously approved hard capsules.

The finished product is presented as film-coated tablets containing niraparib tosylate monohydrate equivalent to 100 mg niraparib as active substance.
Other ingredients of the tablet core are: crospovidone, lactose monohydrate, magnesium stearate, microcrystalline cellulose (E 460), povidone (E 1201), silica colloidal hydrated. Ingredients of the film coating are: polyvinyl alcohol (E 1203), titanium dioxide (E 171), macrogol (E 1521), talc (E 553b) and iron oxide black (E 172).

The product is available in OPA/aluminium/PVC/aluminium/vinyl/acrylic blister, as described in section 6.5 of the SmPC.

### 2.4.2. Active Substance

The active substance documentation is identical to that of the previously approved capsule formulation and is acceptable.

Physico-chemical properties of the active substance that are relevant for the new tablet formulation have been adequately addressed in the pharmaceutical development of the finished product.

### 2.4.3. Finished Medicinal Product

#### 2.4.3.1. Description of the product and pharmaceutical development

Niraparib Tablets, 100 mg, are immediate release, grey, oval-shaped (12 mm x 8 mm), film coated tablets, debossed with “100” on one side and “Zejula” on the other side.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards, except iron oxide, which complies with the purity criteria concerning colours for use in foodstuffs, CD/231/2012/EC. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.4.3 of this report.

The discriminating ability of the method was assessed by manufacturing and testing batches with intentional variations in different material attributes or process parameters which could impact dissolution performance. The discriminatory power of the dissolution method has been demonstrated.

The primary packaging is OPA/aluminium/PVC/aluminium/vinyl/acrylic blister. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

#### 2.4.3.2. Manufacture of the product and process controls

The process is considered to be a standard manufacturing process and includes blending, granulation, compression and film coating.

As the process is considered to be a standard manufacturing process, major steps of the manufacturing process will be validated in line with provided validation protocol, which was found acceptable.

#### 2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual), identification (FT-IR, HPLC), identification of tosylate ion (HPLC), assay (HPLC), degradation products
(HPLC), uniformity of dosage units (HPLC), dissolution (HPLC), water content (KF) and microbial enumeration (Ph. Eur.).

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

Based on the data presented, niraparib tablets possess very low risk of microbial contamination. Utilizing ICH Q6A decision tree # 8, microbial testing of commercial lots of Zejula 100 mg film-coated tablets during routine release testing is not considered necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided on two pilot scale batches and six commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. **Stability of the product**

Stability data from three reduced scale batches of the finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for description, assay, degradation products, dissolution, water content and microbial enumeration. The analytical procedures used are stability indicating.

No significant changes nor trends have been observed during long term and accelerated conditions.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results demonstrate that the finished product is not light-sensitive.

The stability evaluation of the tablets also includes studies under stress conditions. The stress studies involving storage under frozen conditions, freeze-thaw cycles, high humidity conditions (open dish). The data demonstrate that the finished product must be stored in their original container to protect the tablets from absorption of water under high humidity conditions.

Based on available stability data, the proposed shelf-life of 36 months and storage conditions store in the original package as stated in the SmPC (sections 6.3 & 6.4) are acceptable.
2.4.3.5. Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

No non-clinical data were submitted, This was considered acceptable as the current line extension is only introducing a new tablet formulation.

Ecotoxicity/environmental risk assessment

No Environmental Risk Assessment studies were submitted. This is justified as the introduction of a new table formulation is not considered to result in any increase in the exposure of the environment to the active substance. Thus, the ERA is expected to be similar.

2.6. Clinical aspects

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies
2.6.1. Clinical pharmacology

2.6.1.1. Pharmacokinetics

Study 3000-01-004: is a multicenter, open-label, 2-stage, randomized-sequence, single-crossover study to assess the relative bioavailability (BA) and bioequivalence (BE) of niraparib tablet formulation relative to the capsule formulation in patients with advanced solid tumours.

Methods

- Study design

Figure 1: Study Design: Single-Crossover Study
Both stages of the study consisted of a Screening Period (Day -21 to Day -1), a PK Phase (Study Drug and Washout/PK Period 1 and Study Drug and PK Period 2), an End of Treatment (EOT) Visit, and a Safety Follow-up Visit. When patients completed the PK Phase of the study (at least 7 days after the beginning of PK Period 2), they were eligible to participate in an Extension Phase prior to the EOT and Safety Follow-up Visits, following review of the Extension Phase inclusion criteria and completion of the required screening assessments.

Blood was collected during the study for PK assessments at the following time points relative to niraparib dosing:

Stage 1: predose (30 minutes prior to dosing) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72, 96, 120, and 168 hours postdose.

Stage 2: predose (30 minutes prior to dosing) and at 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 12, 24, 48, 72, 96, 120, and 168 hours postdose.

29 Patients with Advanced Solid Tumours were randomized in Stage 1 (for BA evaluation). In stage 2 (demonstrating bioequivalence), 179 patients were randomized.

- **Test and reference products**

Stage 1: The 100 mg capsules were bulk lot number 1703037, expiry date 31.03.2020. The 300 mg tablets were bulk lot number KH17/0077 (pilot scale batch), expiry date 28.02.2019.

Stage 2: The 100 mg capsules were obtained from bulk lot numbers 1801021, 1808201 or M10642, expiry date ranging from February to July 2021. The 300 mg tablets were bulk lot numbers M10723, M10740 or
M10795 (production scale batches), expiry date ranging from May to July 2020.

- **Population(s) studied**

29 Patients with Advanced Solid Tumors were randomized in Stage 1, and received either a single oral dose of 300 mg niraparib as three 100 mg capsules or one 300 mg tablet. All the patients completed the stage 1 phase, however 23 patients (10 + 13) were included in the BA evaluable population. 5 of the 6 patients who were excluded from the BA evaluable population due to predose level >5% of $C_{\text{max}}$ in period 2 received the tablet in the first period and then the capsule.

In stage 2, 179 patients with Advanced Solid Tumors were randomized, and received either a single oral dose of 300 mg niraparib as three 100 mg capsules or one 300 mg tablet. 130 patients completed the PK phase. The number of discontinued patients was comparable in the two treatment groups.

Another 30 patients were excluded from the BE evaluable population: Patients with clinical events resulting in a high probability of the patients' data being unevaluable for at least 1 parameter in PK Period 1 or 2 were allowed to go into the safety Extension Phase of the study without completing the remainder of the PK phase.

The following population was defined for the safety analysis:

- All patients who received any amount of niraparib during the PK Phase of the study.

The following populations were defined for the PK analysis of niraparib (PK Analysis Plan):

- **PK Population**: All patients who received at least 1 dose of niraparib and have at least 1 measurable concentration.

- **PK Evaluable Population**: All patients who completed at least 1 Study Drug and Washout/PK Period and had sufficient concentration data to accurately estimate PK parameters without significant niraparib carryover (baseline concentration >5% of $C_{\text{max}}$) in at least 1 Period. Patients with carryover were excluded from the analysis of PK Period 2, but were included in the analysis of PK Period 1, as data were available.

- **BA Evaluable Population (stage 1)/ BE Evaluable Population (stage 2)**: All patients who completed both Study Drug and Washout/PK Periods and had sufficient PK sample collection to accurately estimate PK parameters, without significant niraparib carryover (baseline concentration >5% of $C_{\text{max}}$) in both PK Periods. Patients who had significant niraparib carryover from PK Period 1 in PK Period 2 were completely excluded from the BA Evaluable Population.

The following populations were defined for the Stage 1 PK analysis of M1:

- **M1 PK Population**: All patients who received at least 1 dose of niraparib and had at least 1 measurable M1 concentration.

- **M1 PK Evaluable Population**: All patients who completed at least 1 Study Drug and Washout/PK Period and had sufficient M1 concentration data to accurately estimate PK parameters.

- **Analytical methods**

The two stages of the study used two test analytical methods (BAC-KB-L010 and BAC-KB-L012). Both methods are used to measure niraparib and M1 metabolite in human plasma (K$_3$EDTA) by LC-MS/MS.
Analytes are extracted from the human plasma by protein precipitation, subsequently separated chromatographically and detected by the respective mass transitions in MRM scan mode.

Validation of both bioassays (reports KB-0044-RB and KB-0167-RB) is in line with EMA guideline on bioanalytical method (EMEA/CHMP/EWP/192217/2009 Rev.1).

- **Pharmacokinetic variables**

The PK parameters that were estimated for each stage included maximum observed plasma concentration ($C_{\text{max}}$), area under the concentration-time curve from time 0 to the time of the last quantifiable concentration ($AUC_{0-t}$), area under the concentration-time curve from time 0 extrapolated to infinity ($AUC_{0-\infty}$), apparent systemic clearance ($CL/F$), $t_{\text{max}}$, apparent terminal elimination half-life ($t_{1/2}$), apparent volume of distribution ($V_z/F$), and apparent terminal rate constant ($\lambda_z$). To conclude BE of the tablet formulation relative to the capsule formulation, the 90% CIs of the ratios of geometric least squares mean (LSM) of the test (tablet) to reference (capsule) product were to be within 0.800 to 1.250 for $AUC_{0-t}$, $AUC_{0-\infty}$, and $C_{\text{max}}$.

BA of the tablet formulation relative to the capsule formulation was estimated based on $AUC_{0-t}$, $AUC_{0-\infty}$, and $C_{\text{max}}$ obtained during stage 1.

- **Statistical methods**

No formal sample size calculation was performed for Stage 1. Approximately 24 patients were planned to be enrolled in Stage 1. This sample size was considered adequate for preliminary assessment of the relative BA of the tablet compared to the capsules and for estimating the intrasubject CV, after accounting for patient drop-outs and potential carryover. Based on estimates from Stage 1, 100 BE evaluable patients were required in Stage 2.

The PK parameters were derived by noncompartmental methods (Phoenix WinNonlin version 7.0 or higher) using actual sampling times and were summarized descriptively, including the number of observations, arithmetic mean, median, standard deviation, coefficient of variation (CV), minimum, maximum, geometric mean, and geometric CV%. PK parameters were summarized for the BA Evaluable and PK Evaluable Populations for niraparib and for the M1 PK Evaluable Population for M1. The intrasubject variability of $C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\infty}$ was assessed as well as the number of patients with carryover from Period 1 to Period 2.

A comparison of the logarithmically transformed niraparib PK parameters ($C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\infty}$) was carried out to evaluate the relative BA between treatments (test versus reference) by performing an analysis of variance (ANOVA) model, accounting for sources of variation. Geometric least-squares mean (LSM), geometric mean ratios, and 90% CIs were presented.

**Results**

- **Participant flow**
Stage 1:

**Figure 2: Disposition of Patients (Stage 1 PK Phase)**

- N=35 Patients screened
- N=29 Patients randomized

N=15 Patients randomized to tablet/capsule sequence
- N=10 Patients included in the BA-evaluable Population

N=14 Patients randomized to capsule/tablet sequence
- N=13 Patients included in the BA-evaluable Population

N=15 Patients received tablets and capsules
- N=0 Patients discontinued prior to completing the PK Phase

N=14 Patients received capsules and tablets
- N=0 Patients discontinued prior to completing the PK Phase

Screen Failures:
1 Patient did not meet Exclusion Criterion 13 (known hepatic disease).
2 Patients did not meet Inclusion Criterion 01 (ability to understand written informed consent).
3 Patients did not meet Inclusion Criterion 05 (adequate organ function).
Stage 2:

**Figure 3: Disposition of Patients (Stage 2 PK Phase)**

- **Recruitment**
  - Stage 1:
    - First patient enrolled (signed informed consent): 29 November 2017
    - Last patient completed: 14 May 2018
  - Stage 2:
    - First patient enrolled (signed informed consent): 02 January 2019
    - Last patient completed: 02 January 2020

- **Baseline data**
  - In the Stage 1 PK Phase Safety Population, the median weight, height, and BMI for all patients was 75.5 kg (range: 49 to 121 kg), 168.0 cm (range: 142 to 183 cm), and 28.2 kg/m² (range: 19 to 43 kg/m²), respectively. The ECOG performance status at study entry was 0 for 27.6% of patients and 1 for 72.4% of patients.
  
  - In the Stage 2 Safety Population, the median weight, height, and BMI for all patients was 79.6 kg (range: 38 to 147 kg), 168.0 cm (range: 142 to 196 cm), and 27.7 kg/m² (range: 17 to 49 kg/m²), respectively. The ECOG performance status at study entry was 0 for 22.6% of patients, 1 for 72.0% of patients, and 2 for 5.4% of patients.
Relative bioavailability (Stage 1):

In Stage 1, 23 of the 29 randomised patients were included in the BA evaluable population. The six excluded patients had a predose level >5% of $C_{\text{max}}$ in period 2.

The summary of plasma PK parameters of niraparib following administration of tablet and capsule for the BA Evaluable Population is presented in Table 5.

Table 1. Summary of Pharmacokinetics Parameters of Niraparib by Treatment (BA Evaluable Population; Stage 1 PK Phase)

<table>
<thead>
<tr>
<th>PK Parameter, Statistic</th>
<th>Tablet (Test)</th>
<th>Capsule (Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL), Mean (%CV)</td>
<td>494 (42.3)</td>
<td>521 (49.2)</td>
</tr>
<tr>
<td>$t_{\text{max}}$ (hr)$^*$</td>
<td>4.05 (1.98-8.00)</td>
<td>4.00 (1.52-25.02)</td>
</tr>
<tr>
<td>$AUC_{0-t}$ (hr*ng/mL), Mean (%CV)</td>
<td>16,200 (42.4)</td>
<td>17,300 (40.9)</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$ (hr*ng/mL), Mean (%CV)</td>
<td>17,700 (43.9)</td>
<td>18,600 (41.1)</td>
</tr>
<tr>
<td>CL/F (L/hr), Mean (%CV)</td>
<td>20.1 (39.7)</td>
<td>18.8 (38.8)</td>
</tr>
<tr>
<td>$V_{z}/F$ (L), Mean (%CV)</td>
<td>1,370 (40.4)</td>
<td>1,190 (39.3)</td>
</tr>
<tr>
<td>$t_{1/2}$ (hr), Mean (%CV)</td>
<td>48.4 (23.3)</td>
<td>44.9 (23.1)</td>
</tr>
</tbody>
</table>

Abbreviations: $AUC_{0-\infty}$=area under the concentration-time curve from time 0 to the time of the last quantifiable concentration; $AUC_{0-t}$=area under the concentration-time curve from time 0 extrapolated to infinity; BA=bioavailability; CL/F=apparent total body clearance; $C_{\text{max}}$=maximum observed plasma concentration; CV=intersubject coefficient of variation; PK=pharmacokinetics; $t_{1/2}$=terminal half-life; $t_{\text{max}}$=time to reach maximum observed plasma concentration; $V_{z}/F$=apparent terminal volume of distribution.

*Niraparib relative BA was assessed by comparing $C_{\text{max}}$, $AUC_{0-t}$, and $AUC_{0-\infty}$ for capsule (reference treatment) and tablet (test treatment) (Table 6).

Table 2. Analysis of Relative Bioavailability for Niraparib PK Parameters (BA Evaluable Population; Stage 1 PK Phase)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment</th>
<th>n</th>
<th>Geometric LS Mean</th>
<th>Ratio (Test/Reference)</th>
<th>90% CI for Ratio of Geometric LS Means</th>
<th>Intrasubject CV%</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/mL)</td>
<td>Capsule (reference)</td>
<td>23</td>
<td>473.24</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Tablet (test)</td>
<td>23</td>
<td>448.75</td>
<td>0.9483</td>
<td>(0.8489, 1.0593)</td>
<td>21.9</td>
</tr>
<tr>
<td>$AUC_{0-t}$ (hr*ng/mL)</td>
<td>Capsule (reference)</td>
<td>23</td>
<td>16,313.08</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Tablet (test)</td>
<td>23</td>
<td>14,860.55</td>
<td>0.9110</td>
<td>(0.8550, 0.9706)</td>
<td>12.4</td>
</tr>
<tr>
<td>$AUC_{0-\infty}$ (hr*ng/mL)</td>
<td>Capsule (reference)</td>
<td>23</td>
<td>17,489.96</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Tablet (test)</td>
<td>23</td>
<td>16,118.62</td>
<td>0.9216</td>
<td>(0.8631, 0.9841)</td>
<td>12.9</td>
</tr>
</tbody>
</table>

Bioequivalence (Stage 2):
In stage 2, 108 of the 179 randomised patients were included in the BE evaluable population. The number of discontinued patients was comparable in the two treatment groups.

The summary of plasma PK parameters for niraparib following administration of tablet and capsule for the BE Evaluable Population is shown in Table 7.

Table 3. Summary of PK Parameters of Niraparib by Treatment (BE Evaluable Population [N=108]; Stage 2 PK Phase)

<table>
<thead>
<tr>
<th>Parameter, Statistic</th>
<th>n</th>
<th>Tablet (Test)</th>
<th>Capsule (Reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (ng/mL), mean (CV%)</td>
<td>108</td>
<td>580.5 (50.0)</td>
<td>595.2 (44.3)</td>
</tr>
<tr>
<td>tmax (hr), median (minimum, maximum)</td>
<td>108</td>
<td>5.00 (1.55, 8.00)</td>
<td>4.97 (0.970, 23.8)</td>
</tr>
<tr>
<td>AUC0-t (hr*ng/mL), mean (CV%)</td>
<td>107</td>
<td>19,800 (60.3)</td>
<td>20,190 (54.0)</td>
</tr>
<tr>
<td>AUC0-∞ (hr*ng/mL), mean (CV%)</td>
<td>98</td>
<td>20,450 (59.3)</td>
<td>20,990 (54.2)</td>
</tr>
<tr>
<td>CL/F (L/hr), mean (CV%)</td>
<td>98</td>
<td>19.07 (47.4)</td>
<td>18.28 (48.0)</td>
</tr>
<tr>
<td>Vz/F (L), mean (CV%)</td>
<td>98</td>
<td>1,258 (46.4)</td>
<td>1,253 (44.5)</td>
</tr>
<tr>
<td>t1/2 (hr), mean (CV%)</td>
<td>108</td>
<td>49.64 (28.2)</td>
<td>51.88 (27.1)</td>
</tr>
</tbody>
</table>

The statistical evaluation of the PK parameters, Cmax, AUC0-t, and AUC0-∞, for the BE Evaluable Population is presented in Table 8. The geometric LSM ratios for the tablet to capsule comparison were 0.9619, 0.9594, and 0.9566 for Cmax, AUC0-t, and AUC0-∞, respectively, with 90% CIs within the 0.800 to 1.250 limits, demonstrating BE of the test tablet formulation to the reference capsule formulation. The intrasubject variability (CV %) was low and ranged from 18.1% to 23.7%.

Table 4. Analysis of BE of Niraparib PK Parameters (BE Evaluable Population [N=108]; Stage 2 PK Phase)

- **Safety data**

In the Stage 1 PK Phase, observations related to TEAEs were as follows:

- Two (6.9%) patients had dose reductions due to TEAEs. The TEAEs that led to dose reduction occurred during the PK Phase, and the dose reduction was implemented at the first dose of the Extension Phase. The events leading to dose reduction were increased AST (Grade 3) and increased ALT (Grade 2) in 1 patient and increased AST (Grade 3) in 1 patient; these 3 events were considered by the Investigator as related to study drug and were transient in nature as they eventually resolved.

- A total of 19 (65.5%) patients experienced at least 1 TEAE. TEAEs reported in more than 1 patient included nausea (7 [24.1%] patients); vomiting (4 [13.8%] patients); fatigue (3 [10.3%] patients);
and AST increased, back pain, and hypomagnesaemia (2 [6.9%] patients each).

- Overall, related TEAEs were reported for 7 (24.1%) patients. The only TEAEs assessed as related to study drug by the Investigator in more than 1 patient in total were nausea (6 [20.7%] patients), vomiting (3 [10.3%] patients), and AST increased (2 [6.9%] patients).
- In the Stage 1 PK Phase, there were no deaths, SAEs, discontinuations due to AEs, or AESIs reported.

In Stage 2, observations related to TEAEs were as follows:

- A total of 125 (74.4%) patients experienced at least 1 TEAE. The TEAEs reported in ≥10% of patients overall were constipation (32 [19.0%] patients), nausea (31 [18.5%] patients), anemia (19 [11.3%] patients), fatigue (18 [10.7%] patients), and vomiting (17 [10.1%] patients).
- Overall, 60 (35.7%) patients had treatment-related TEAEs, 36 (21.4%) patients had TEAEs with CTCAE toxicity Grade ≥3, and 8 (4.8%) patients had treatment-related TEAEs with CTCAE toxicity Grade ≥3. The TEAEs assessed as related to study drug by the Investigator in ≥5% of patients overall were nausea (21 [12.5%] patients), constipation (12 [7.1%] patients), vomiting (10 [6.0%] patients), and fatigue (9 [5.4%] patients).
- A total of 26 (15.5%) patients had serious TEAEs, 5 (3.0%) patients had TEAEs leading to treatment discontinuation, 3 (1.8%) patients had TEAEs leading to death, and no AESIs were reported.

One patient experienced a TEAE in the Stage 2 PK Phase that led to the dose being reduced in the Extension Phase; the dose reduction could not be implemented in the Stage 2 PK Phase because only a single administered dose of niraparib tablet or capsule was allowed during this phase of the study. Two patients experienced TEAEs in the Stage 2 PK Phase that led to dose interruption. These patients had their study treatment delayed; one of whom eventually discontinued treatment due to disease progression.

2.6.1.2. Pharmacodynamics

No new pharmacodynamic studies were presented and no such studies are required for this application (introduction of a tablet formulation).

Biowaiver for strength

The bioequivalence study was performed on 300 mg dose. A biowaiver for strength was requested for the 100 mg tablet strength that is intended for marketing:

Multimedia comparative dissolution testing performed in support of the biowaiver request demonstrated similarity between the reference product (300-mg tablet biobatch) and test single tablet products (200- and 100-mg tablets) across all physiologically relevant media.

In a Phase 1 food effect study using the capsule formulation, a high fat meal did not have a clinically significant effect on the pharmacokinetics of niraparib.

The niraparib tablet should behave similarly to the capsule formulation in the fed state:

a) niraparib is a BCS class II drug that just narrowly misses BCS class I requirements with high permeability and moderate solubility,
b) the tablet manufacturing process and excipients are not expected to affect fed bioavailability.

c) as the tablet and capsule formulations are bioequivalent, the same clinically insignificant effect of a high fat meal can be inferred on the tablet formulation as was observed for the capsule formulation.

The comparative dissolution testing in support of the request for biowaiver for the 100 (and 200 mg) tablets met the criteria for similarity with $f_2 \geq 50$.

In conclusion, comparable in vitro dissolution was demonstrated between the 100 mg strength to be marketed, and the 300 mg strength that was demonstrated to be bioequivalent to the marketed hard capsule formulation (biobatch).

### 2.6.2. Discussion on clinical aspects

Niraparib exhibits linear PK, and exposure is dose proportional. Absorption and clearance are dose independent (range: 30 to 400 mg). Niraparib is rapidly absorbed following oral dosing, with time to reach maximum observed plasma concentration ($t_{\text{max}}$) occurring within 3 hours. The oral capsule formulation has high bioavailability (BA; approximately 73%), and concomitant intake of a high-fat meal prior to dosing exerts only negligible effects on the extent and rate of absorption.

A BA/BE study was performed to establish the bioequivalence between the previously approved hard capsule formulation and the new tablet formulation. The bioequivalence study was performed using the highest strength that was intended for marketing at the time (300 mg). With the extension of the wash-out period before stage 2, the design of the bioequivalence study was appropriate.

**Stage 1:** Comparable performance of the capsule and tablet formulations was demonstrated; the 90% CIs of the geometric LSMeans for Cmax, $AUC_{0-t}$, and $AUC_{0-\infty}$ were within the 0.80 to 1.25 limits. Pre-dose levels above 5% of Cmax was observed in period 2 in 5 out of 28 patients (18%), indicating that the wash-out period of 7 days was not sufficient. Considering that the wash-out period was increased to 14 days in stage 2 of the study, and that the results from stage 2 are the primary evidence of bioequivalence, this is acceptable. It is considered that the primary objective of stage 1 was met: to obtain preliminary assessment of the relative bioavailability (BA) of 300 mg niraparib administered as a tablet versus capsule formulation and to estimate the intrasubject variability of niraparib pharmacokinetics.

**Stage 2:** The results of stage 2 of this study was found to be consistent with the preliminary values reported in stage 1. BE was established between the niraparib tablet (1×300 mg) and capsule (3×100 mg) formulations using the BE Evaluable Population, which included patients with data in both PK Periods, as predefined in the protocol and the SAP. The 90% CIs of the geometric LSM ratios for tablet compared to capsules fell within the limits of 0.800 and 1.250 for all 3 primary niraparib PK parameters (Cmax, $AUC_{0-t}$, and $AUC_{0-\infty}$). Intrasubject variability was low, ranging from 18.1% to 23.7% for the key PK parameters.

The submitted bioequivalence study demonstrated bioequivalence between 3x100 mg hard capsules and 1x300 mg tablet.

Claiming that all conditions regarding biowaiver as described in the Guideline on the Investigation of Bioequivalence have been fulfilled, biowaiver has been requested for the additional strengths of 100 mg (scope of the application) and 200 mg (initially intended for marketing). It is considered that the conditions for biowaiver have been fulfilled:
• All the three strengths are manufactured at the same site by the same manufacturer and manufacturing process.
• The qualitative composition of the different strengths is the same.
• The composition of the strengths are quantitatively proportional (except for non-functional film coating)
• Comparable in vitro dissolution data (pH 1.2, pH 4.5 and pH 6.8) confirm the adequacy of waiving additional in vivo bioequivalence testing. Dissolution profiles were considered similar as supported by f2 value greater than 50.

Comparative in vitro dissolution testing demonstrated that the 100 mg tablet can be supported by the bioequivalence result obtained with the 300 mg tablet. Consequently, a biowaiver for the additional strengths is considered acceptable.

In conclusion, the combination of data provided establishes the equivalence of the niraparib tablets and the marketed capsule dosage form.

2.6.3. Conclusions on the clinical aspects

Based on the presented bioequivalence study Zejula 3x100 mg hard capsules and 1x300 mg tablets are considered bioequivalent. The biowaiver for strength between the 300 mg tablet and the 100 mg tablet is acceptable.

2.7. Risk Management Plan

The MAH submitted an updated RMP version with this application.

2.7.1. Safety concerns

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Haematological toxicity (thrombocytopenia, anaemia, neutropenia including neutropenic infection and neutropenic sepsis)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hypertension</td>
</tr>
<tr>
<td>Important potential risks</td>
<td>MDS and AML</td>
</tr>
<tr>
<td></td>
<td>SPM other than MDS and AML</td>
</tr>
<tr>
<td>Missing information</td>
<td>None</td>
</tr>
</tbody>
</table>
### 2.7.2. Pharmacovigilance plan

**Table 2.** On-going and planned additional pharmacovigilance activities

<table>
<thead>
<tr>
<th>Study Status</th>
<th>Summary of objectives</th>
<th>Safety concerns addressed</th>
<th>Milestones</th>
<th>Due dates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category 1</strong> - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation</td>
<td>None</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Category 2</strong> – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit risk)</td>
<td>None</td>
<td>None</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Category 3</strong> - Required additional pharmacovigilance activities</td>
<td></td>
<td></td>
<td>Final study report</td>
<td>Q1 2025</td>
</tr>
<tr>
<td>3000-04-002: An integrated meta-analysis of MDS/AML and other SPM incidence in patients with ovarian cancer who have been treated with niraparib</td>
<td>The primary endpoint is to compare the incidence rate of MDS/AML in patients with ovarian cancer treated with niraparib versus any other treatment comparator.</td>
<td>To provide additional safety information about the important potential risks of MDS, AML and SPM.</td>
<td>Final study report</td>
<td>Q1 2025</td>
</tr>
<tr>
<td>Planned</td>
<td>• The secondary endpoint is to compare the incidence rate of SPM in the same population.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• The third endpoint is to estimate incidence of MDS/AML and other SPM in patients with ovarian cancer treated with niraparib in pooled TESARO clinical studies.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3000-04-001: PASS to evaluate the risks of MDS/AML and other SPM in adult patients with platinum-sensitive, relapsed, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer receiving maintenance treatment with Zejula® (Niraparib).</td>
<td>Primary: To estimate the incidence rate of MDS/AML among a cohort of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer treated with Zejula who are in a complete or partial response to platinum-based chemotherapy.</td>
<td>To provide additional safety information about the important potential risks of MDS/AML and SPM other than MDS/AML in patients treated in clinical practice with existing medicines for ovarian cancer and patients treated with niraparib.</td>
<td>Final study report</td>
<td>Q1 2027</td>
</tr>
</tbody>
</table>
Study Status | Summary of objectives | Safety concerns addressed | Milestones | Due dates
---|---|---|---|
Planned | not been treated with a PARP inhibitor. | | |

### 2.7.3. Risk minimisation measures

**Table 3.** Summary table of risk minimisation activities by safety concern

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Important identified risk: Haematological toxicity (thrombocytopenia, anaemia, neutropenia including neutropenic infection and sepsis)</strong></td>
<td><strong>SmPC sections</strong>&lt;br&gt;• Guidance in SmPC section 4.2 on dosing interruptions and adjustments in cases of haematological toxicity&lt;br&gt;• Warning in SmPC section 4.4 that haematological toxicity is expected and to use caution with anticoagulation and antiplatelet drugs&lt;br&gt;• Testing blood counts and monitoring is recommended in SmPC section 4.4&lt;br&gt;• Listed as adverse reactions in SmPC section 4.8&lt;br&gt;&lt;br&gt;<strong>PL Sections</strong>&lt;br&gt;• <strong>Section 2</strong> advises the patient to talk to the practitioner before or while taking Zejula regarding low blood-cell counts.&lt;br&gt;• <strong>Section 3</strong> mentions that the recommended starting dose is 200 mg and if the patient weigh ≥ 77 kg and have platelet count ≥ 150,000/μL before starting treatment, the recommended starting dose is 300 mg.&lt;br&gt;• <strong>Section 4</strong> lists the haematologic side effects under the very common category.&lt;br&gt;&lt;br&gt;<strong>Prescription status</strong>&lt;br&gt;• Prescription only medicine&lt;br&gt;• Use restricted to physicians experienced in the use of anticancer medicinal products&lt;br&gt;&lt;br&gt;<strong>Additional risk minimisation measures:</strong> None</td>
</tr>
<tr>
<td><strong>Important identified risk: Hypertension</strong></td>
<td><strong>Routine risk minimisation measures:</strong>&lt;br&gt;<strong>SmPC sections</strong>&lt;br&gt;• Warning in SmPC section 4.4 that hypertension has been reported with niraparib therapy and that blood pressure should be monitored&lt;br&gt;• Listed as an adverse reaction in SmPC section 4.8&lt;br&gt;&lt;br&gt;<strong>PL sections</strong>&lt;br&gt;• <strong>Section 2</strong> advises the patient to talk to the practitioner before or while taking Zejula regarding high blood pressure.&lt;br&gt;• <strong>Section 4</strong> lists high blood pressure under the very common category.&lt;br&gt;&lt;br&gt;<strong>Prescription status</strong>&lt;br&gt;• Prescription only medicine&lt;br&gt;• Use restricted to physicians experienced in the use of anticancer medicinal products&lt;br&gt;&lt;br&gt;<strong>Additional risk minimisation measures:</strong> None</td>
</tr>
<tr>
<td><strong>Important potential risk: MDS and AML</strong></td>
<td><strong>Routine risk minimisation measures:</strong>&lt;br&gt;<strong>SmPC Sections</strong></td>
</tr>
</tbody>
</table>
2.7.4. Conclusion

The CHMP and PRAC considered that the risk management plan version 5.1 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) (d) - Extensions of marketing authorisations.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:
The content of the new 100 mg film-coated tablet PL will be identical to the approved 100 mg hard capsule PL.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Zejula (niraparib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that his medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

The bioequivalence study forms the pivotal basis with an open-label, 2-stage, randomized-sequence, single-crossover design. The study design was considered adequate to evaluate the bioequivalence of this formulation and was in line with the respective European requirements. Choice of dose, sampling points, overall sampling time as well as wash-out period were adequate. The analytical method was validated. Pharmacokinetic and statistical methods applied were adequate.

The test formulation of Zejula tablet met the protocol-defined criteria for bioequivalence when compared with the Zejula capsule. The point estimates and their 90% confidence intervals for the parameters AUC0-t, AUC0-72h, and Cmax were all contained within the protocol-defined acceptance range. Bioequivalence of the two formulations was demonstrated.

The benefit-risk balance of Zejula 100 mg tablets is comparable to the marketed Zejula 100 mg capsules.

4. Recommendations

Outcome

Based on the review of the data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Zejula 100 mg film-coated tablets is favourable in the following indication(s):

- 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.

- 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.

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.
Conditions or restrictions with regard to the safe and effective use of the medicinal product

Medicinal product subject to restricted medical prescription

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.