ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Zejula 100 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each hard capsule contains niraparib tosylate monohydrate equivalent to 100 mg niraparib.

Excipients with known effect

Each hard capsule contains 254.5 mg of lactose monohydrate (see section 4.4).

Each hard capsule shell also contains the colouring agent tartrazine (E 102) [0.0172 mg].

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsule (capsule).

Hard capsule of approximately 22 mm × 8 mm; white body with “100 mg” printed in black ink and purple cap with “Niraparib” printed in white ink.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zejula is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

4.2 Posology and method of administration

Treatment with Zejula should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Posology

The dose is three 100 mg hard capsules once daily, equivalent to a total daily dose of 300 mg.

Patients should be encouraged to take their dose at approximately the same time each day. Bedtime administration may be a potential method for managing nausea.

It is recommended that treatment should be continued until disease progression.

Missing dose
If patients miss a dose, they should take their next dose at its regularly scheduled time.

Dose adjustments for adverse reactions
Recommendations for the management of adverse reactions are provided in Table 1. In general, it is recommended to first interrupt the treatment (but no longer than 28 consecutive days) to allow the patient to recover from the adverse reaction and then restart at the same dose. In the case that the adverse reaction recurs, it is recommended to reduce the dose. If adverse reactions persist beyond a 28-day dose interruption, it is recommended that Zejula be discontinued. If adverse reactions are not manageable with this strategy of dose interruption and reduction, it is recommended that Zejula be discontinued.

Dose reductions may be implemented based on adverse reactions. The recommended dose reductions are first from three hard capsules daily (300 mg) to two hard capsules daily (200 mg). If further dose reduction is needed, a second dose reduction from two hard capsules daily (200 mg) to one capsule daily (100 mg) may be implemented.

The recommended dose modifications for adverse reactions are listed in Tables 1 and 2.

Table 1: Dose modifications for non-haematologic adverse reactions	
Non-haematologic CTCAE* ≥ Grade 3 treatment-related adverse reaction where prophylaxis is not considered feasible or adverse reaction persists despite treatment	First occurrence: • Withhold Zejula for a maximum of 28 days or until resolution of adverse reaction. • Resume Zejula at a reduced dose (200 mg/day).
	Second occurrence: • Withhold Zejula for a maximum of 28 days or until resolution of adverse reaction. • Resume Zejula at a reduced dose (100 mg/day).
CTCAE ≥ Grade 3 treatment-related adverse reaction lasting more than 28 days while patient is administered Zejula 100 mg/day	Discontinue treatment.

*CTCAE=Common Terminology Criteria for Adverse Events

Table 2: Dose modifications for haematologic adverse reactions	
Haematologic adverse reactions have been observed during the treatment with Zejula especially during the initial phase of the treatment. It is therefore recommended to monitor complete blood counts (CBCs) weekly during the first month of treatment and modify the dose as needed. After the first month, it is recommended to monitor CBCs monthly and periodically after this time (see section 4.4). Based on individual laboratory values, weekly monitoring for the second month may be warranted.	
Haematologic adverse reaction requiring transfusion or haematopoietic growth factor support	• For patients with platelet count ≤ 10,000/μL, platelet transfusion should be considered. If there are other risk factors for bleeding such as co-administration of anticoagulation or antiplatelet medicinal products, consider interrupting these substances and/or transfusion at a higher platelet count. • Resume Zejula at a reduced dose.
Platelet count < 100,000/μL	First occurrence: • Withhold Zejula for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥ 100,000/μL. • Resume Zejula at same or reduced dose based on clinical evaluation. • If platelet count is < 75,000/μL at any time, resume at a reduced dose.

Table 2: Dose modifications for haematologic adverse reactions	
	Second occurrence: • Withhold Zejula for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥ 100,000/µL. • Resume Zejula at a reduced dose. • Discontinue Zejula if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Neutrophil < 1,000/µL or Haemoglobin < 8 g/dL	• Withhold Zejula for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥ 1,500/µL or haemoglobin returns to ≥ 9 g/dL. • Resume Zejula at a reduced dose. • Discontinue Zejula if neutrophils and/or haemoglobin have not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Confirmed diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML)	• Permanently discontinue Zejula.

Patients with low body weight
Approximately 25 % of patients in the NOVA study weighed less than 58 kg, and approximately 25 % of patients weighed more than 77 kg. The incidence of Grade 3 or 4 ADRs was greater among low body weight patients (78 %) than high body weight patients (53 %). Only 13 % of low body weight patients remained at a dose of 300 mg beyond Cycle 3. A starting dose of 200 mg for patients weighing less than 58 kg may be considered.

Elderly
No dose adjustment is necessary for elderly patients (≥ 65 years). There are limited clinical data in patients aged 75 or over.

Renal impairment
No dose adjustment is necessary for patients with mild to moderate renal impairment. There are no data in patients with severe renal impairment or end stage renal disease undergoing haemodialysis; use with caution in these patients (see section 5.2).

Hepatic impairment
No dose adjustment is needed in patients with mild to moderate hepatic impairment. There are no data in patients with severe hepatic impairment; use with caution in these patients (see section 5.2).

Patients with ECOG performance status 2 to 4
Clinical data are not available in patients with ECOG performance status 2 to 4.

Paediatric population
The safety and efficacy of niraparib in children and adolescents below 18 years of age have not yet been established. No data are available.

Method of administration

Oral use. The capsules should be swallowed whole with water. The capsules should not be chewed or crushed.

Zejula can be taken without regard to meals.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Haematologic adverse reactions

In the NOVA study, patients eligible for Zejula therapy had the following baseline haematologic parameters: absolute neutrophil count (ANC) ≥ 1,500 cells/µL; platelets ≥ 100,000 cells/µL and haemoglobin ≥ 9 g/dL prior to therapy. Haematologic adverse reactions (thrombocytopenia, anaemia, neutropenia) have been reported in patients treated with Zejula. In the NOVA study, 48 of 367 (13 %) of patients experienced bleeding with concurrent thrombocytopenia; all bleeding events concurrent with thrombocytopenia were Grade 1 or 2 in severity except for one event of Grade 3 petechiae and haematoma observed concurrently with a serious adverse event of pancytopenia. Thrombocytopenia occurred more commonly in patients whose baseline platelet count was less than 180×10^9/L. Approximately 76 % of patients with lower baseline platelets ($< 180 \times 10^9$/L) who received Zejula experienced thrombocytopenia of any grade, and 45 % of the patients experienced Grade 3/4 thrombocytopenia. Pancytopenia has been observed in < 1 % of patients receiving niraparib. If a patient develops severe persistent haematologic toxicity including pancytopenia that does not resolve within 28 days following interruption, Zejula should be discontinued.

Testing complete blood counts weekly for the first month, followed by monthly monitoring for the next 10 months of treatment and periodically after this time is recommended to monitor for clinically significant changes in any haematologic parameter during treatment (see section 4.2).

If a patient develops severe persistent haematologic toxicity that does not resolve within 28 days following interruption, Zejula should be discontinued.

Due to the risk of thrombocytopenia, anticoagulants and medicinal products known to reduce the thrombocyte count should be used with caution (see section 4.8).

Myelodysplastic syndrome/acute myeloid leukaemia

Myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML), including cases with fatal outcome, have been reported in a small number of patients who received Zejula or placebo. In the pivotal Phase 3 international trial (ENGOT-OV16), the incidence of MDS/AML in patients who received niraparib (1.4 %) was similar to that in patients who received placebo (1.1 %). Overall, MDS/AML has been reported in 7 out of 751 (0.9 %) patients treated with Zejula in clinical studies.

The duration of Zejula treatment in patients prior to developing MDS/AML varied from 1 month to > 2 years. The cases were typical of secondary, cancer therapy-related MDS/AML. All patients had received multiple platinum-containing chemotherapy regimens and many had also received other DNA damaging agents and radiotherapy. Some of the patients had a history of bone marrow dysplasia.

If MDS and/or AML are confirmed while on treatment with Zejula, treatment should be discontinued and the patient treated appropriately.

Hypertension, including hypertensive crisis

Hypertension, including hypertensive crisis, has been reported with the use of Zejula. Pre-existing hypertension should be adequately controlled before starting Zejula treatment. Blood pressure should be monitored monthly for the first year and periodically thereafter during treatment with Zejula.

Hypertension should be medically managed with antihypertensive medicinal products as well as adjustment of the Zejula dose (see section 4.2), if necessary. In the clinical programme, blood pressure measurements were obtained on Day 1 of each 28-day cycle while the patient remained on Zejula. In most cases, hypertension was controlled adequately using standard antihypertensive treatment with or without Zejula dose adjustment (see section 4.2). Zejula should be discontinued in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy.

Pregnancy/contraception

Zejula should not be used during pregnancy or in women of childbearing potential not willing to use reliable contraception during therapy and for 1 month after receiving the last dose of Zejula (see section 4.6). A pregnancy test should be performed on all women of childbearing potential prior to treatment.

Lactose

Zejula hard capsules contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Tartrazine (E 102)

This medicinal product contains tartrazine (E 102), which may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

The combination of niraparib with vaccines or immunosuppressant agents has not been studied.

The data on niraparib in combination with cytotoxic medicinal products are limited. Therefore, caution should be taken if niraparib is used in combination with vaccines, immunosuppressant agents or with other cytotoxic medicinal products.

Pharmacokinetic interactions

Effect of other medicinal products on niraparib

Niraparib as a substrate of CYPs (CYP1A2 and CYP3A4)
Niraparib is a substrate of carboxylesterases (CEs) and UDP-glucuronosyltransferases (UGTs) *in vivo*. Oxidative metabolism of niraparib is minimal *in vivo*. No dose adjustment for Zejula is required when administered concomitantly with medicinal products known to inhibit (e.g. itraconazole, ritonavir, and clarithromycin) or induce CYP enzymes (e.g. rifampin, carbamazepine, and phenytoin).

Niraparib as a substrate of efflux transporters (P-gp, BCRP, and MATE1/2)
Niraparib is a substrate of P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP). However, due to its high permeability and bioavailability, the risk of clinically relevant interactions with medicinal products that inhibit these transporters is unlikely. Therefore, no dose adjustment for Zejula is required when administered concomitantly with medicinal products known to inhibit P-gp (e.g. amiodarone, verapamil) or BCRP (e.g. osimertinib, velpatasvir, and eltrombopag).

Niraparib is not a substrate of bile salt export pump (BSEP). The major primary metabolite M1 is not a substrate of P-gp, BCRP, or BSEP. Niraparib is not a substrate of MATE 1 or 2, while M1 is a substrate of both.

Niraparib as a substrate of hepatic uptake transporters (OATP1B1, OATP1B3, and OCT1)

Neither niraparib nor M1 is a substrate of organic anion transport polypeptide 1B1 (OATP1B1), 1B3 (OATP1B3), or organic cation transporter 1 (OCT1). No dose adjustment for Zejula is required when administered concomitantly with medicinal products known to inhibit OATP1B1 or 1B3 (e.g. gemfibrozil, ritonavir), or OCT1 (e.g. dolutegravir) uptake transporters.

Niraparib as a substrate of renal uptake transporters (OAT1, OAT3, and OCT2)
Neither niraparib nor M1 is a substrate of organic anion transporter 1 (OAT1), 3 (OAT3), and organic cation transporter 2 (OCT2). No dose adjustment for Zejula is required when administered concomitantly with medicinal products known to inhibit OAT1 (e.g. probenecid) or OAT3 (e.g. probenecid, diclofenac), or OCT2 (e.g. cimetidine, quinidine) uptake transporters.

Effect of niraparib on other medicinal products

Inhibition of CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4)
Neither niraparib nor M1 is an inhibitor of any active substance-metabolising CYP enzymes, namely CYP1A1/2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5.

Even though inhibition of CYP3A4 in the liver is not expected, the potential to inhibit CYP3A4 at the intestinal level has not been established at relevant niraparib concentrations. Therefore, caution is recommended when niraparib is combined with active substances the metabolism of which is CYP3A4-dependent and, notably, those having a narrow therapeutic range (e.g. ciclosporin, tacrolimus, alfentanil, ergotamine, pimozide, quetiapine, and halofantrine).

Induction of CYPs (CYP1A2 and CYP3A4)
Neither niraparib nor M1 is a CYP3A4 inducer *in vitro*. *In vitro*, niraparib weakly induces CYP1A2 at high concentrations and the clinical relevance of this effect would not be completely ruled out. M1 is not a CYP1A2 inducer. Therefore, caution is recommended when niraparib is combined with active substances the metabolism of which is CYP1A2-dependent and, notably, those having a narrow therapeutic range (e.g. clozapine, theophylline, and ropinirole).

Inhibition of efflux transporters (P-gp, BCRP, BSEP, and MATE1/2)
Niraparib is not an inhibitor of BSEP. *In vitro*, niraparib inhibits P-gp very weakly and BCRP with an IC_{50} = 161 µM and 5.8 µM, respectively. Therefore, a clinically meaningful interaction related to an inhibition of these efflux transporters although unlikely, cannot be excluded. Caution is then recommended when niraparib is combined with substrates of BCRP (irinotecan, rosuvastatin, simvastatin, atorvastatin, and methotrexate).

Niraparib is an inhibitor of MATE1 and -2 with IC_{50} of 0.18 µM and ≤ 0.14 µM, respectively. Increased plasma concentrations of co-administered medicinal products that are substrates of these transporters (e.g. metformin) cannot be excluded.

The major primary metabolite M1 does not appear to be an inhibitor of P-gp, BCRP, BSEP, or MATE1/2.

Inhibition of hepatic uptake transporters (OATP1B1, OATP1B3, and OCT1)
Neither niraparib nor M1 is an inhibitor of organic anion transport polypeptide 1B1 (OATP1B1) or 1B3 (OATP1B3).

In vitro, niraparib weakly inhibits the organic cation transporter 1 (OCT1) with an IC_{50} = 34.4 µM. Caution is recommended when niraparib is combined with active substances that undergo an uptake transport by OCT1 such as metformin.

Inhibition of renal uptake transporters (OAT1, OAT3, and OCT2)
Neither niraparib nor M1 inhibits organic anion transporter 1 (OAT1), 3 (OAT3), and organic cation transporter 2 (OCT2).

All clinical studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/contraception in females

Women of childbearing potential should not become pregnant while on treatment and should not be pregnant at the beginning of treatment. A pregnancy test should be performed on all women of childbearing potential prior to treatment. Women of childbearing potential must use effective contraception during therapy and for 1 month after receiving the last dose of Zejula.

Pregnancy

There are no or limited amount of data from the use of niraparib in pregnant women. Animal reproductive and developmental toxicity studies have not been conducted. However, based on its mechanism of action, niraparib could cause embryonic or foetal harm, including embryo-lethal and teratogenic effects, when administered to a pregnant woman. Zejula should not be used during pregnancy.

Breast-feeding

It is unknown whether niraparib or its metabolites are excreted in human milk. Breast-feeding is contraindicated during administration of Zejula and for 1 month after receiving the last dose (see section 4.3).

Fertility

There are no clinical data on fertility. A reversible reduction of spermatogenesis was observed in rats and dogs (see section 5.3).

4.7 Effects on ability to drive and use machines

Zejula has moderate influence on the ability to drive or use machines. Patients who take Zejula may experience asthenia, fatigue and dizziness. Patients who experience these symptoms should observe caution when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

In the pivotal ENGOT-OV16 study, adverse reactions (ADRs) occurring ≥ 10 % of patients receiving Zejula monotherapy were nausea, thrombocytopenia, fatigue/asthenia, anaemia, constipation, vomiting, abdominal pain, neutropenia, insomnia, headache, decreased appetite, nasopharyngitis, diarrhoea, dyspnea, hypertension, dyspepsia, back pain, dizziness, cough, urinary tract infection, arthralgia, palpitations, and dysgeusia.

The most common serious adverse reactions > 1 % (treatment-emergent frequencies) were thrombocytopenia and anaemia.

Tabulated list of adverse reactions

The following adverse reactions have been identified in the ENGOT-OV16 study in patients receiving Zejula monotherapy (see Table 3).

Frequencies of occurrence of undesirable effects are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3: Adverse drug reactions: frequencies based on all-causality adverse events*

System Organ Class	Frequency of all CTCAE grades	Frequency of CTCAE grade 3 or 4
Infections and infestations	**Very common** Urinary tract infection **Common** Bronchitis, conjunctivitis	**Uncommon** Urinary tract infection, bronchitis
Blood and lymphatic system disorders	**Very common** Thrombocytopenia, anaemia, neutropenia **Common** Leukopenia **Uncommon** Pancytopenia, febrile neutropenia	**Very common** Thrombocytopenia, anaemia, neutropenia **Common** Leukopenia **Uncommon** Pancytopenia, febrile neutropenia
Metabolism and nutrition disorders	**Very common** Decreased appetite **Common** Hypokalemia	**Common** Hypokalemia **Uncommon** Decreased appetite
Psychiatric disorders	**Very common** Insomnia **Common** Anxiety, depression	**Uncommon** Insomnia, anxiety, depression
Nervous system disorders	**Very common** Headache, dizziness, dysgeusia	**Uncommon** Headache
Cardiac disorders	**Very common** Palpitations **Common** Tachycardia	
Vascular disorders	**Very common** Hypertension	**Common** Hypertension
Respiratory, thoracic and mediastinal disorders	**Very common** Dyspnea, cough, nasopharyngitis **Common** Epistaxis	**Common** Dyspnea
Gastrointestinal disorders	**Very common** Nausea, constipation, vomiting, abdominal pain, diarrhoea, dyspepsia **Common** Dry mouth, abdominal distension, mucosal inflammation (including mucositis), stomatitis	**Common** Nausea, vomiting, abdominal pain **Uncommon** Diarrhoea, constipation, mucosal inflammation (including mucositis), stomatitis, dry mouth
Skin and subcutaneous tissue disorders	**Common** Photosensitivity, rash	**Uncommon** Photosensitivity, rash
Musculoskeletal and connective tissue disorders	**Very common** Back pain, arthralgia **Common** Myalgia	**Uncommon** Back pain, arthralgia, myalgia
General disorders and administration site conditions	**Very common** Fatigue, asthenia **Common** Oedema peripheral	**Common** Fatigue, asthenia
Investigations	**Common**	**Uncommon**

System Organ Class	Frequency of all CTCAE grades	Frequency of CTCAE grade 3 or 4
	Gamma-glutamyl transferase increased, AST increased, blood creatinine increased, ALT increased, blood alkaline phosphatase increased, weight decreased	AST increased, ALT increased, blood alkaline phosphatase increased **Common** Gamma-glutamyl transferase increased

* Frequencies are based on percent of patients using all-causality adverse events.

Description of selected adverse reactions

Haematologic adverse reactions (thrombocytopenia, anaemia, neutropenia) including clinical diagnoses and/or laboratory findings generally occurred early during niraparib treatment with the incidence decreasing over time.

Thrombocytopenia
Approximately 60 % of patients receiving Zejula experienced thrombocytopenia of any grade, and 34 % of patients experienced Grade 3/4 thrombocytopenia. In patients with baseline platelet count less than 180×10^9/L, thrombocytopenia of any grade and Grade 3/4 occurred in 76 % and 45 % of the patients, respectively. The median time to onset of thrombocytopenia regardless of grade and Grade 3/4 thrombocytopenia was 22 and 23 days, respectively. The rate of new incidences of thrombocytopenia after intensive dose modifications were performed during the first two months of treatment from Cycle 4 was 1.2 %. The median duration of thrombocytopenia events of any grade was 23 days, and the median duration of Grade 3/4 thrombocytopenia was 10 days. Patients treated with Zejula who develop thrombocytopenia might have an increased risk of haemorrhage. In the clinical programme, thrombocytopenia was managed with laboratory monitoring, dose modification and platelet transfusion where appropriate (see section 4.2). Discontinuation due to thrombocytopenia events (thrombocytopenia and platelet count decreased) occurred in approximately 3 % of the patients.

Anaemia
Approximately 50 % of patients experienced anaemia of any grade, and 25 % experienced Grade 3/4 anaemia. The median time to onset of anaemia of any grade was 42 days, and 85 days for Grade 3/4 events. The median duration of anaemia of any grade was 63 days, and 8 days for Grade 3/4 events. Anaemia of any grade might persist during Zejula treatment. In the clinical programme, anaemia was managed with laboratory monitoring, dose modification (see section 4.2), and where appropriate with red blood cell transfusions. Discontinuation due to anaemia occurred in 1 % of patients.

Neutropenia
Approximately 30 % of patients receiving Zejula experienced neutropenia of any grade, and 20 % of patients experienced Grade 3/4 neutropenia. The median time to onset of neutropenia of any grade was 27 days, and 29 days for Grade 3/4 events. The median duration of neutropenia of any grade was 26 days, and 13 days for Grade 3/4 events. In the clinical programme, neutropenia was managed with laboratory monitoring and dose modifications (see section 4.2). In addition, Granulocyte-Colony Stimulating Factor (G-CSF) was administered to approximately 6 % of patients treated with niraparib as concomitant therapy for neutropenia. Discontinuation due to neutropenia events occurred in 2 % of patients.

Hypertension
Hypertension, including hypertensive crisis, has been reported with Zejula therapy. Hypertension of any grade occurred in 19.3 % of patients treated with Zejula. Grade 3/4 hypertension occurred in 8.2 % of patients. In the clinical programme, hypertension was readily managed with anti-hypertensive medicinal products. Discontinuation due to hypertension occurred in < 1 % of patients.

Paediatric population
No studies have been conducted in paediatric patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no specific treatment in the event of Zejula overdose, and symptoms of overdose are not established. In the event of an overdose, physicians should follow general supportive measures and should treat symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other antineoplastic agents, ATC code: L01XX54.

Mechanism of action and pharmacodynamic effects

Niraparib is an inhibitor of poly(ADP-ribose) polymerase (PARP) enzymes, PARP-1 and PARP-2, which play a role in DNA repair. *In vitro* studies have shown that niraparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage, apoptosis and cell death. Increased niraparib-induced cytotoxicity was observed in tumour cell lines with or without deficiencies in the BReast CAncer (*BRCA)* 1 and 2 tumour suppressor genes. In orthotopic high-grade serous ovarian cancer patient-derived xenograft tumours (PDX) grown in mice, niraparib has been shown to reduce tumour growth in *BRCA* 1 and 2 mutant, *BRCA* wild-type but homologous recombination (HR) deficient, and in tumours that are *BRCA* wild-type and without detectable HR deficiency.

Clinical efficacy and safety

The safety and efficacy of niraparib as maintenance therapy was studied in a Phase 3 randomised, double-blind, placebo-controlled international trial (ENGOT-OV16 / NOVA) in patients with relapsed predominantly high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who were platinum sensitive, defined by complete response (CR) or partial response (PR) for more than six months to their penultimate (next to last) platinum-based therapy. To be eligible for niraparib treatment, the patient should be in response (CR or PR) following completion of last platinum based chemotherapy. The CA-125 levels should be normal (or a > 90 % decrease in CA-125 from baseline) following their last platinum treatment, and be stable for at least 7 days. Patients could not have received prior PARP inhibitor therapy, including Zejula. Eligible patients were assigned to one of two cohorts based on the results of a germline *BRCA* mutation test. Within each cohort, patients were randomised using a 2:1 allocation of niraparib and placebo. Patients were assigned to the g*BRCA*mut cohort based on blood samples for g*BRCA* analysis that were taken prior to randomisation. Testing for tBRCA mutation and homologous recombination deficiency (HRD) was performed using the HRD test on tumour tissue obtained at the time of initial diagnosis or at the time of recurrence. Randomisation within each cohort was stratified by time to progression after the penultimate platinum therapy before study enrollment (6 to < 12 months and ≥ 12 months); use or not of bevacizumab in conjunction with the penultimate or last platinum regimen; and best response during the most recent platinum regimen (complete response and partial response).

Patients began treatment on Cycle 1/Day 1 (C1/D1) with niraparib 300 mg or matched placebo administered QD in continuous 28-day cycles. Clinic visits occurred each cycle (4 weeks ± 3 days).

In the NOVA study, 48 % of patients had a dose interruption in Cycle 1. Approximately 47 % of patients restarted at a reduced dose in Cycle 2.

The most commonly used dose in niraparib-treated patients in the NOVA study was 200 mg.

Progression-free survival was determined per RECIST (Response Evaluation Criteria in Solid Tumors, version 1.1) or clinical signs and symptoms and increased CA-125. PFS was measured from the time of randomisation (which occurred up to 8 weeks after completion of the chemotherapy regimen) to disease progression or death.

The primary efficacy analysis for PFS was determined by blinded central independent assessment and was prospectively defined and assessed for the g*BRCA*mut cohort and the non-g*BRCA*mut cohort separately.

Secondary efficacy endpoints included chemotherapy-free interval (CFI), time to first subsequent therapy (TFST), PFS after the first subsequent therapy (PFS2), time to second subsequent therapy (TSST) and OS (overall survival).

Demographics, baseline disease characteristics, and prior treatment history were generally well balanced between the niraparib and placebo arms in the g*BRCA*mut (n = 203) and the non-g*BRCA*mut cohorts (n = 350). Median ages ranged from 57 to 63 years across treatments and cohorts. The primary tumour site in most patients (> 80 %) within each cohort was the ovary; most patients (> 84 %) had tumours with serous histology. A high proportion of patients in both treatment arms in both cohorts had received 3 or more prior lines of chemotherapy, including 49 % and 34 % of niraparib patients in the g*BRCA*mut and non-g*BRCA*mut cohorts, respectively. Most patients were age 18 to 64 years (78 %), Caucasian (86 %) and had an ECOG performance status of 0 (68 %).

In the g*BRCA*mut cohort, the median number of treatment cycles was higher in the niraparib arm than the placebo arm (14 and 7 cycles, respectively). More patients in the niraparib group continued treatment for more than 12 months than patients in the placebo group (54.4 % and 16.9 % respectively).

In the overall non-g*BRCA*mut cohort, the median number of treatment cycles was higher in the niraparib arm than in the placebo arm (8 and 5 cycles, respectively). More patients in the niraparib group continued treatment for more than 12 months than patients in the placebo group (34.2 % and 21.1 %, respectively).

The study met its primary objective of statistically significantly improved PFS for niraparib maintenance monotherapy compared with placebo in the g*BRCA*mut cohort (HR 0.27; 95 % CI* 0.173, 0.410; p < 0.0001) as well as in the overall non-g*BRCA*mut cohort (HR 0.45; 95 % CI* 0.338, 0.607; p < 0.0001). Table 4 shows the results for the PFS primary endpoint for the primary efficacy populations (g*BRCA*mut cohort and the overall non-g*BRCA*mut cohort). A sensitivity analysis of investigator PFS showed the following results for the g*BRCA*mut cohort: HR 0.27 (95 % CI*, 0.182, 0.401; p < 0.0001); median PFS 14.8 months (95% CI*, 12.0, 16.6) for niraparib and median PFS 5.5 months (95% CI*, 4.9, 7.2) for placebo, and for the non-g*BRCA*mut cohort: HR 0.53 (95 % CI*, 0.405, 0.683; p < 0.0001); median PFS 8.7 months (95 % CI*, 7.3, 10.0) for niraparib and median PFS 4.3 months (95% CI*, 3.7, 5.5) for placebo.

Table 4: Summary of primary objective outcomes in the ENGOT-OV16 study

	g*BRCA*mut cohort		**Non-g*BRCA*mut cohort**	
	niraparib (N = 138)	**placebo (N = 65)**	**niraparib (N = 234)**	**placebo (N = 116)**
PFS median (95% CI*)	**21.0** (12.9, NR)	**5.5** (3.8, 7.2)	**9.3** (7.2, 11.2)	**3.9** (3.7, 5.5)
p-value	**< 0.0001**		**< 0.0001**	
Hazard ratio (HR) (Nir:plac) (95 % CI*)	**0.27** (0.173, 0.410)		**0.45** (0.338, 0.607)	

* CI denotes confidence interval.

Prior to unblinding of the study, tumours of patients were tested for the presence of HRD using an experimental HRD test, which evaluates three indirect measures of tumour genome instability: loss of heterozygosity, telomeric allelic imbalance (TAI), and large-scale state transitions. In the HRDpos group, the hazard ratio was 0.38 (95 % CI, 0.243, 0.586; p < 0.0001). In the HRDneg group, the hazard ratio was 0.58 (95 % CI, 0.361, 0.922; p = 0.0226). The experimental test was not able to discriminate which patients would or would not benefit from niraparib maintenance therapy.

Figure 1: Kaplan-Meier plot for progression-free survival in the g*BRCA*mut cohort based on IRC assessment (ITT population, N = 203)

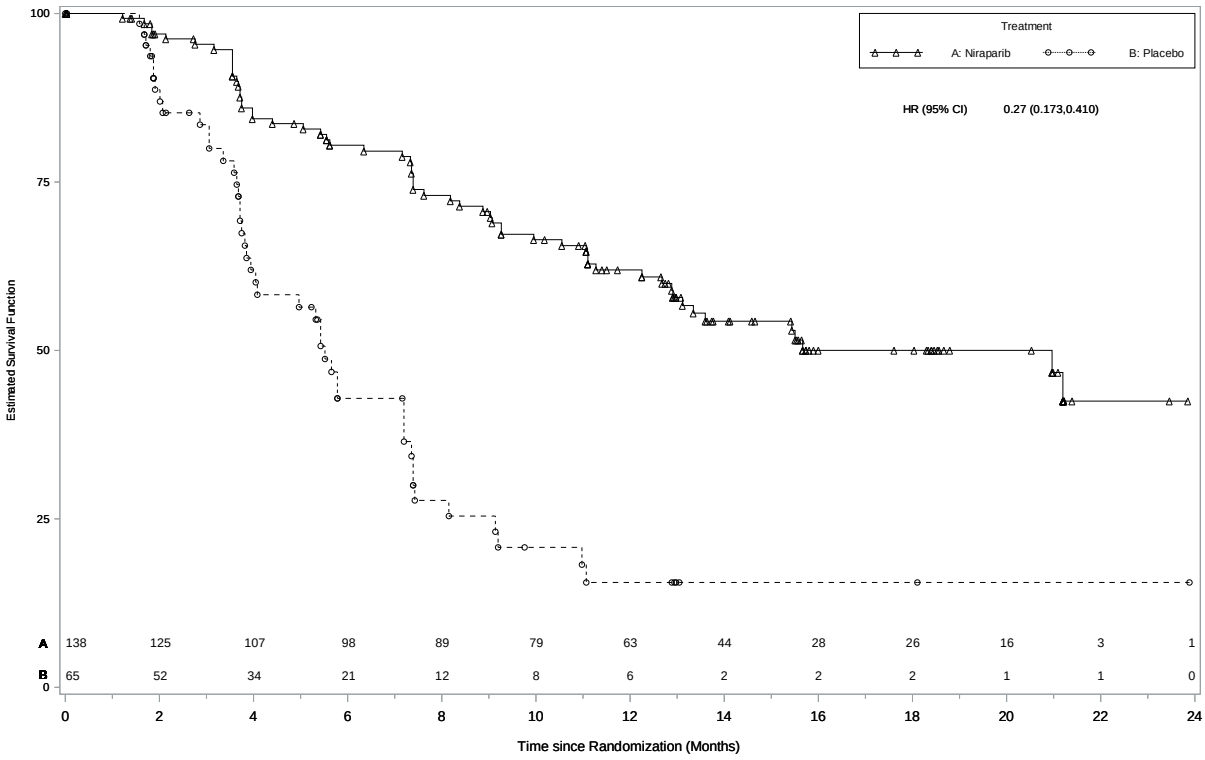
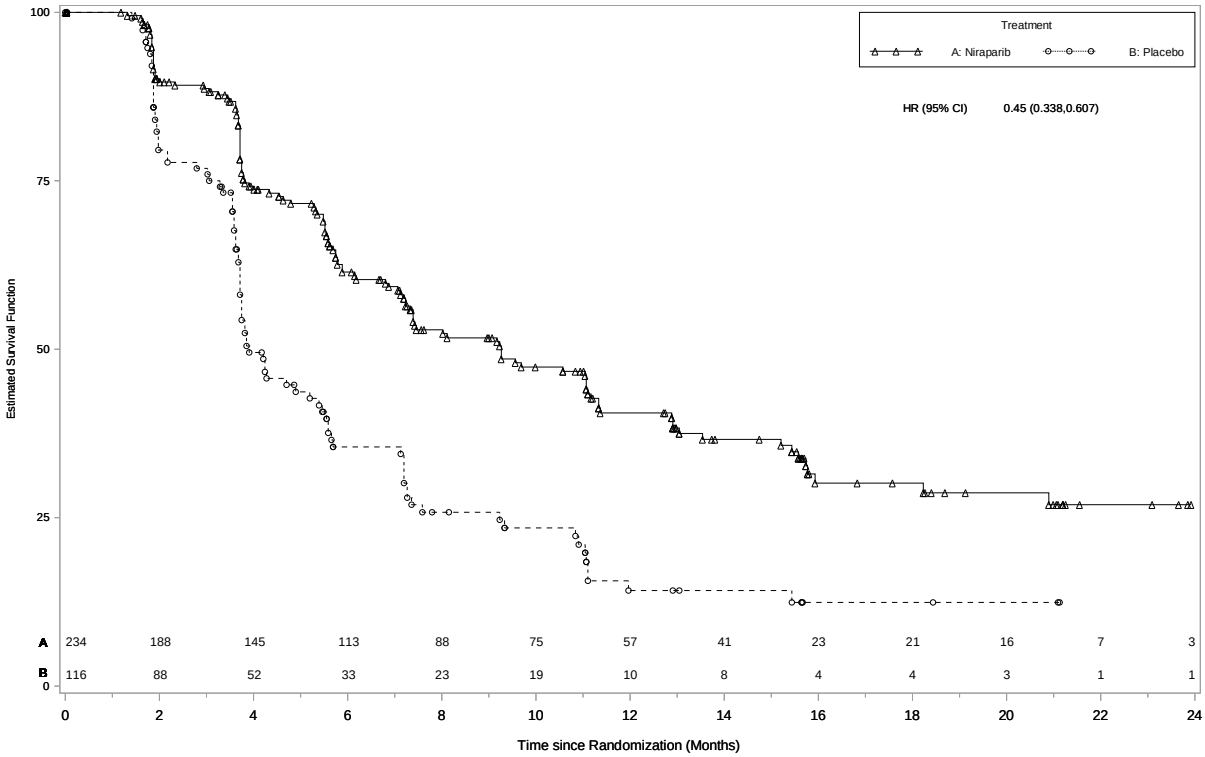


Figure 2: Kaplan-Meier plot for progression-free survival in the non-g*BRCA*mut cohort overall based on IRC assessment (ITT population, N = 350)



The secondary endpoints CFI, TFST, and PFS2 demonstrated a statistically significant and persistent treatment effect in favour of the niraparib treatment arm in the g*BRCA*mut cohort and the overall non-*gBRCA*mut cohort (Table 5).

Table 5: Secondary endpoints*

	g*BRCA*mut		**non-g*BRCA*mut**	
Endpoint	**Zejula N = 138**	**Placebo N = 65**	**Zejula N = 234**	**Placebo N = 116**
Chemotherapy-free interval				
Median (95 % CI) – mo	22.8 (17.9-NR)	9.4 (7.9-10.6)	12.7 (11.0-14.7)	8.6 (6.9-10.0)
P value	< 0.001		< 0.001	
Hazard ratio (95 % CI)	0.26 (0.17-0.41)		0.50 (0.37-0.67)	
Time to first subsequent treatment				
Median (95 % CI) – mo	21.0 (17.5-NR)	8.4 (6.6-10.6)	11.8 (9.7-13.1)	7.2 (5.7-8.5)
P value	< 0.001		< 0.001	
Hazard ratio (95 % CI)	0.31 (0.21-0.48)		0.55 (0.41-0.72)	
Progression-free survival 2				
Median (95 % CI) – mo	25.8 (20.3-NR)	19.5 (13.3-NR)	18.6 (16.2-21.7)	15.6 (13.2-20.9)
P value	0.006		0.03	

	g*BRCA*mut		non-g*BRCA*mut	
Endpoint	**Zejula N = 138**	**Placebo N = 65**	**Zejula N = 234**	**Placebo N = 116**
Hazard ratio (95 % CI)	0.48 (0.28-0.82)		0.69 (0.49-0.96)	

*CI denotes confidence interval, g*BRCA*mut germline *BRCA* mutation, and NR not reached

Patient-reported outcome (PRO) data from validated survey tools (FOSI and EQ-5D) indicate that niraparib-treated patients reported no difference from placebo in measures associated with quality of life (QoL).

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Zejula in all subsets of the paediatric population in ovarian carcinoma (excluding rhabdomyosarcoma and germ cell tumours).

5.2 Pharmacokinetic properties

Absorption

Following a single-dose administration of 300 mg niraparib under fasting conditions, niraparib was measurable in plasma within 30 minutes and the mean peak plasma concentration (C_{max}) for niraparib was reached in about 3 hours [804 ng/mL (% CV:50.2 %)]. Following multiple oral doses of niraparib from 30 mg to 400 mg once daily, accumulation of niraparib was approximately 2 to 3 folds.

The systemic exposures (C_{max} and AUC) to niraparib increased in a dose-proportional manner when the dose of niraparib increased from 30 mg to 400 mg. The absolute bioavailability of niraparib is approximately 73 %, indicating minimal first pass effect.

A concomitant high-fat meal did not significantly affect the pharmacokinetics of niraparib after administration of 300 mg of niraparib.

Distribution

Niraparib was moderately protein bound in human plasma (83.0 %), mainly with serum albumin. In a population pharmacokinetic analysis of niraparib, the V_d/F was 1,074 L in cancer patients, indicating extensive tissue distribution of niraparib.

Biotransformation

Niraparib is metabolised primarily by carboxylesterases (CEs) to form a major inactive metabolite, M1. In a mass balance study, M1 and M10 (the subsequently formed M1 glucuronides) were the major circulating metabolites.

Elimination

Following a single oral 300-mg dose of niraparib, the mean terminal half-life ($t_{½}$) of niraparib ranged from 48 to 51 hours (approximately 2 days). In a population pharmacokinetic analysis, the apparent total clearance (CL/F) of niraparib was 16.2 L/h in cancer patients.

Niraparib is eliminated primarily through the hepatobiliary and renal routes. Following an oral administration of a single 300-mg dose of [^{14}C]-niraparib, on average 86.2 % (range 71 % to 91 %) of the dose was recovered in urine and feces over 21 days. Radioactive recovery in the urine accounted for 47.5 % (range 33.4 % to 60.2 %) and in the feces for 38.8 % (range 28.3 % to 47.0 %) of the dose. In pooled samples collected over 6 days, 40.0 % of the dose was recovered in the urine primarily as metabolites and 31.6 % of the dose was recovered in the feces primarily as unchanged niraparib.

Special populations

Renal impairment
In the population pharmacokinetic analysis of data from clinical studies in patients, pre-existing mild (CLCr < 90 - ≥ 60 ml/min) and moderate (CLCr < 60 - ≥ 30 mL/min) renal impairment did not influence the clearance of niraparib. No patients with pre-existing severe renal impairment or end-stage renal disease undergoing hemodialysis were identified in clinical studies (see section 4.2).

Hepatic impairment
In the population pharmacokinetic analysis of data from clinical studies in patients, pre-existing mild and moderate hepatic impairment did not influence the clearance of niraparib. The pharmacokinetics of niraparib have not been assessed in patients with severe hepatic impairment (see section 4.2).

Age, weight and race
Population pharmacokinetic analyses indicated that age, weight and race had no significant impact on the pharmacokinetics of niraparib.

Paediatric population
No studies have been conducted to investigate the pharmacokinetics of niraparib in paediatric patients.

5.3 Preclinical safety data

Secondary pharmacology

In vitro, niraparib inhibited the dopamine transporter DAT at concentration levels below human exposure levels. In mice, single doses of niraparib increased intracellular levels of dopamine and metabolites in cortex. Reduced locomotor activity was seen in one of two single dose studies in mice. The clinical relevance of these findings is not known. No effect on behavioural and/or neurological parameters have been observed in repeat-dose toxicity studies in rats and dogs at estimated CNS exposure levels similar to or below expected therapeutic exposure levels.

Repeat-dose toxicity

In repeat-dose oral toxicity studies, niraparib was administered daily for up to 3 months' duration in rats and dogs. The major primary target organ for toxicity in both species was the bone marrow, with associated changes in peripheral haematology parameters. Additionally, decreased spermatogenesis was seen in both species. These findings occurred at exposure levels below those seen clinically, and were largely reversible within 4 weeks of cessation of dosing.

Genotoxicity

Niraparib was not mutagenic in a bacterial reverse mutation assay (Ames) test but was clastogenic in an *in vitro* mammalian chromosomal aberration assay and in an *in vivo* rat bone marrow micronucleus assay. This clastogenicity is consistent with genomic instability resulting from the primary pharmacology of niraparib and indicates potential for genotoxicity in humans.

Reproductive toxicology

Reproductive and developmental toxicity studies have not been conducted with niraparib.

Carcinogenicity

Carcinogenicity studies have not been conducted with niraparib.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content
Magnesium stearate
Lactose monohydrate

Capsule shell
Titanium dioxide (E 171)
Gelatin
Brilliant blue FCF (E 133)
Erythrosine (E 127)
Tartrazine (E 102)

Printing ink
Shellac (E 904)
Propylene glycol (E 1520)
Potassium hydroxide (E 525)
Black iron oxide (E 172)
Sodium hydroxide (E 524)
Povidone (E 1201)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 30 °C.

6.5 Nature and contents of container

Aclar/PVC/aluminium foil perforated unit dose blisters in cartons of 84 × 1, 56 × 1 and 28 × 1 hard capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

TESARO Bio Netherlands B.V.
Joop Geesinkweg 901
1114 AB Amsterdam-Duivendrecht
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1235/001

EU/1/17/1235/002
EU/1/17/1235/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 November 2017

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Manufacturing Packaging Farmaca (MPF) B.V.
Appelhof 13
8465 RX Oudehaske
Netherlands

TESARO Bio Netherlands B.V.
Joop Geesinkweg 901
1114 AB Amsterdam-Duivendrecht
Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- 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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- Risk Management Plan (RMP)

The 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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zejula 100 mg hard capsules
niraparib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each hard capsule contains niraparib tosylate monohydrate equivalent to 100 mg of niraparib.

3. LIST OF EXCIPIENTS

Also contains lactose and tartrazine (E 102). See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Hard capsule
84 × 1 hard capsules
56 × 1 hard capsules
28 × 1 hard capsules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Do not store above 30 °C.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

TESARO Bio Netherlands B.V.
Joop Geesinkweg 901
1114 AB Amsterdam-Duivendrecht
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1235/001
EU/1/17/1235/002
EU/1/17/1235/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ZEJULA

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Zejula 100 mg capsules
niraparib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

TESARO Bio Netherlands B.V.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Zejula 100 mg hard capsules
niraparib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zejula is and what it is used for

What Zejula is and how it works
Zejula contains the active substance niraparib. Niraparib is a type of anti-cancer medicine called a PARP inhibitor. PARP inhibitors block an enzyme called poly [adenosine diphosphate-ribose] polymerase (PARP). PARP helps cells repair damaged DNA so blocking it means that the DNA of cancer cells cannot be repaired. This results in tumour cell death, helping to control the cancer.

What Zejula is used for
Zejula is used in adult women for the treatment of cancer of the ovary, the fallopian tubes (part of the female reproductive system that connects the ovaries to the uterus), or the peritoneum (the membrane lining the abdomen). It is used after the cancer has responded to previous treatment with standard platinum-based chemotherapy.

2. What you need to know before you take Zejula

Do not take Zejula:
- if you are allergic to niraparib or any of the other ingredients of this medicine (listed in section 6).
- if you are breast-feeding.

Warnings and precautions
Talk to your doctor, pharmacist or nurse <u>before or while</u> taking this medicine if any of the following could apply to you:

<u>Low blood-cell counts</u>
Zejula lowers your blood-cell counts, such as your red blood-cell count (anaemia), white blood-cell count (neutropenia), or blood-platelet count (thrombocytopenia). Signs and symptoms you need to

look out for include fever or infection, and abnormal bruising or bleeding (see section 4 for more information). Your doctor will test your blood regularly throughout your treatment.

Myelodysplastic syndrome/acute myeloid leukaemia
Rarely, low blood-cell counts may be a sign of more serious problems with the bone marrow such as 'myelodysplastic syndrome' (MDS) or 'acute myeloid leukaemia' (AML). Your doctor may want to test your bone marrow to check for these problems.

High blood pressure
Zejula can cause high blood pressure, which in some cases, could be severe. Your doctor will measure your blood pressure regularly throughout your treatment. He or she may also give you medicine to treat high blood pressure and adjust your Zejula dose, if necessary.

Children and adolescents
Children under 18 years of age should not be given Zejula. This medicine has not been studied in this age group.

Other medicines and Zejula
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy
Zejula should not be taken during pregnancy as it could harm your baby. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

If you are a woman who could become pregnant you must use reliable contraception while you are taking Zejula, and you must continue to use reliable contraception for 1 month after taking your last dose. Your doctor will ask you to confirm that you are not pregnant with a pregnancy test before starting your treatment. Contact your doctor straightaway if you become pregnant while you are taking Zejula.

Breast-feeding
Zejula should not be taken if you are breast-feeding as it is not known if it passes into breast milk. If you are breast-feeding, you must stop before you start taking Zejula and you must not begin breast-feeding again until 1 month after taking your last dose. Ask your doctor for advice before taking this medicine.

Driving and using machines
When you are taking Zejula it may make you feel weak, tired or dizzy and therefore influence your ability to drive and use machines. Observe caution when driving or using machines.

Zejula contains lactose
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Zejula contains tartrazine (E 102)
It may cause allergic reactions.

3. How to take Zejula

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The recommended starting dose is 3 capsules taken together once a day (total daily dose of 300 mg), with or without food. Take Zejula at approximately the same time each day. Taking Zejula at bedtime

may help you to manage nausea.

Swallow the capsules whole, with some water. Do not chew or crush the capsules.

Your doctor may recommend a lower dose if you experience side effects (such as nausea, tiredness, abnormal bleeding/bruising, anaemia).

Your doctor will check you on a regular basis, and you will normally continue to take Zejula as long as you experience benefit, and do not suffer unacceptable side effects.

If you take more Zejula than you should
If you take more than your normal dose, contact your doctor immediately.

If you forget to take Zejula
Do not take an additional dose if you miss a dose or vomit after taking Zejula. Take your next dose at its scheduled time. Do not take a double dose to make up for a forgotten dose.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor straight away if you notice any of the following SERIOUS side effects - you may need urgent medical treatment:

Very common (may affect more than 1 in 10 people)
- Bruising or bleeding for longer than usual if you hurt yourself -- these may be signs of a low blood platelet count (thrombocytopenia).
- Being short of breath, feeling very tired, having pale skin, or fast heartbeat -- these may be signs of a low red blood cell count (anaemia).
- Fever or infection – low white blood cell count (neutropenia) can increase your risk for infection. Signs may include fever, chills, feeling weak or confused, cough, pain or burning feeling when passing urine. Some infections can be serious and may lead to death.

Common (may affect up to 1 in 10 people)
Reduction in the number of white cells in the blood (leukopenia)
Talk to your doctor if you get any other side effects. These can include:

Very common (may affect more than 1 in 10 people)
- Feeling sick
- Feeling tired
- Feeling of weakness
- Constipation
- Vomiting
- Stomach pain
- Inability to sleep
- Headache
- Decreased appetite
- Runny or stuffy nose
- Diarrhoea
- Shortness of breath
- High blood pressure
- Indigestion
- Dizziness

- Cough
- Urinary tract infection
- Palpitations (feeling like your heart is skipping beats or beating harder than usual)
- Abnormal taste in mouth

Common (may affect up to 1 in 10 people)
- Sunburn-like reactions following exposure to light
- Swelling in the feet, ankles, legs, and/or hands
- Low potassium levels in the blood
- Inflammation or swelling of the air passages between the mouth and nose and the lungs, bronchitis
- Abdominal bloating
- Feeling of worry, nervousness, or unease
- Feelings of sadness, depressed
- Nose bleed
- Decrease in weight
- Muscle pain
- Back pain
- Joint pain
- Pink eye
- Fast heart beat may cause dizziness, chest pain or breathlessness
- Dry mouth
- Inflammation of the mouth and/or digestive tract
- Rash
- Elevated blood tests
- Abnormal blood tests

Uncommon (may affect up to 1 in 100 people)
- Reduction in the number of red blood cells, white blood cells and platelets

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zejula

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blister after EXP. The expiry date refers to the last day of that month.

Do not store above 30 °C.

Do not use this medicine if you notice any damage or signs of tampering to the pack.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Zejula contains

- The active substance is niraparib. Each hard capsule contains niraparib tosylate monohydrate equivalent to 100 mg niraparib.

- The other ingredients (excipients) are:
  capsule content: magnesium stearate, lactose monohydrate
  capsule shell: titanium dioxide (E 171), gelatin, brilliant blue FCF (E 133), erythrosine (E 127), tartrazine (E 102)
  printing ink: shellac (E 904), propylene glycol (E 1520), potassium hydroxide (E 525), black iron oxide (E 172), sodium hydroxide (E 524), and povidone (E 1201).

This medicine contains lactose and tartrazine - see section 2 for more information.

What Zejula looks like and contents of the pack

Zejula hard capsules have a white opaque body and a purple opaque cap. The white opaque capsule body is printed with '100 mg' in black ink, and the purple capsule cap is printed with 'Niraparib' in white ink. The capsules contain a white to off-white powder.

The hard capsules are packed in blister packs of
- 84 × 1 hard capsules
- 56 × 1 hard capsules
- 28 × 1 hard capsules

Marketing Authorisation Holder
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Netherlands

Manufacturer
Manufacturing Packaging Farmaca (MPF) B.V.
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Netherlands

TESARO Bio Netherlands B.V.
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This leaflet was last revised in MM/YYYY.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

ANNEX IV

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for niraparib, the scientific conclusions of CHMP are as follows:

Following a signal regarding sepsis with niraparib, a number of relevant cases were identified. Overall, in almost half of the presented cases, the causality could not be excluded or was related to the study drug. Niraparib can cause haematological toxicity that includes febrile neutropenia. A possible cause for sepsis is a low neutrophil count and there is a potential association between niraparib and developing sepsis. Overall, the PRAC considered that the preferred term febrile neutropenia was adequate to describe the cases reviewed within this PSUSA. Febrile neutropenia was reported in 2 out of 367 patients in the NOVA trial leading to the frequency uncommon. Therefore, the PRAC concluded that “febrile neutropenia” should be added as a new adverse drug reaction in section 4.8 of the SmPC with the frequency “uncommon.” The package leaflet should be updated accordingly.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for niraparib, the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing niraparib is unchanged subject to the proposed changes to the product information.

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.