ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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 0.0172 mg of the colouring agent tartrazine (E 102).

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 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.

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

First-line ovarian cancer maintenance treatment
The recommended starting dose of Zejula is 200 mg (two 100-mg capsules), 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 capsules), taken once daily (see section 4.4 and 4.8).

Recurrent ovarian cancer maintenance treatment
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 or toxicity.

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

Dose adjustments for adverse reactions
The recommended dose modifications for adverse reactions are listed in Tables 1, 2 and 3.

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 interrupt the treatment and then resume at the lower 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.

Table 1: Recommended dose modifications for adverse reactions		
Starting dose level	**200 mg**	**300 mg**
First dose reduction	100 mg/day	200 mg/day (two 100-mg capsules)
Second dose reduction	Discontinue Zejula.	100 mg/day* (one 100-mg capsule)

*If further dose reduction below 100 mg/day is required, discontinue Zejula.

Table 2: 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 level per Table 1.
	Second occurrence: • Withhold Zejula for a maximum of 28 days or until resolution of adverse reaction. • Resume Zejula at a reduced dose or discontinue per Table 1.
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 3: 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 per Table 1 based on clinical evaluation. • If platelet count is < 75,000/μL at any time, resume at a reduced dose per Table 1.
	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 per Table 1. • 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 per Table 1. • 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 in recurrent ovarian cancer maintenance treatment
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 adverse reactions (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 hepatic impairment (either aspartate aminotransferase (AST) > upper limit of normal (ULN) and total bilirubin (TB) ≤ ULN or any AST and TB > 1.0 x – 1,5 x ULN). For patients with moderate hepatic impairment (any AST and TB > 1.5 x - 3 x ULN) the recommended starting dose of Zejula is 200 mg once daily. There are no data in patients with severe hepatic impairment (any AST and TB > 3 x ULN); use with caution in these patients (see sections 4.4 and 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

Zejula is for 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

Haematologic adverse reactions (thrombocytopenia, anaemia, neutropenia) have been reported in patients treated with Zejula (see section 4.8). Patients with lower body weight or lower baseline platelet count may be at increased risk of Grade 3+ thrombocytopenia (see section 4.2).
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 including pancytopenia 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

Cases of myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) have been observed in patients treated with Zejula monotherapy or combination therapy in clinical trials and postmarketing.

The duration of Zejula treatment in patients prior to developing MDS/AML varied from 0.5 months to > 4.9 years. The cases were typical of secondary, cancer therapy-related MDS/AML. All patients

had received 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 (see section 4.8). Pre-existing hypertension should be adequately controlled before starting Zejula treatment. Blood pressure should be monitored at least weekly for two months, monitored monthly afterwards for the first year and periodically thereafter during treatment with Zejula. Home blood pressure monitoring may be considered for appropriate patients with instruction to contact their health care provider in case of rise in blood pressure.

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.

Posterior reversible encephalopathy syndrome (PRES)

There have been reports of PRES in patients receiving Zejula (see section 4.8). PRES is a rare, reversible, neurological disorder which can present with rapidly evolving symptoms including seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI).

In case of PRES, it is recommended to discontinue Zejula and to treat specific symptoms including hypertension. The safety of reinitiating Zejula therapy in patients previously experiencing PRES is not known.

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.

Hepatic impairment

Patients with severe hepatic impairment could have increased exposure of niraparib based on data from patients with moderate hepatic impairment and should be carefully monitored (see sections 4.2 and 5.2).

Lactose

Zejula hard capsules contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total 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, BSEP, MRP2, 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), or multidrug resistance-associated protein 2 (MRP2). The major primary metabolite M1 is not a substrate of P-gp, BCRP, BSEP, or MRP2. Niraparib is not a substrate of multidrug and toxin extrusion (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 uptake transporters (e.g. cimetidine, quinidine).

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).

Inhibition of UDP-glucuronosyltransferases (UGTs)
Niraparib did not exhibit inhibitory effect against the UGT isoforms (UGT1A1, UGT1A4, UGT1A9, and UGT2B7) up to 200 µM *in vitro*. Therefore, the potential for a clinically relevant inhibition of UGTs by niraparib is minimal.

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 could 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, MRP2, and MATE1/2)
Niraparib is not an inhibitor of BSEP or MRP2. *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, MRP2 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, dizziness or difficulties concentrating. Patients who experience these symptoms should observe caution when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

ADRs of all grades occurring in ≥ 10 % of the 851 patients receiving Zejula monotherapy in the pooled PRIMA (either 200 mg or 300 mg starting dose) and NOVA trials were nausea, anaemia, thrombocytopenia, fatigue, constipation, vomiting, headache, insomnia, platelet count decreased, neutropenia, abdominal pain, decreased appetite, diarrhoea, dyspnoea, hypertension, asthenia, dizziness, neutrophil count decreased, cough, arthralgia, back pain, white blood cell count decreased, and hot flush.

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 based on clinical trials and post-marketing surveillance in patients receiving Zejula monotherapy (see Table 4). Frequencies of occurrence of undesirable effects are based on pooled adverse events data generated from the PRIMA and NOVA studies (fixed starting dose of 300 mg/day) where patient exposure is known and 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); and very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 4: Tabulated list of adverse reactions

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, leukopenia **Uncommon** Pancytopenia, febrile neutropenia	**Very common** Thrombocytopenia, anaemia, neutropenia **Common** Leukopenia **Uncommon** Pancytopenia, febrile neutropenia

System Organ Class	Frequency of all CTCAE* grades	Frequency of CTCAE* grade 3 or 4
Immune system disorders	**Common** Hypersensitivity†	**Uncommon** Hypersensitivity
Metabolism and nutrition disorders	**Very common** Decreased appetite **Common** Hypokalemia	**Common** Hypokalemia **Uncommon** Decreased appetite
Psychiatric disorders	**Very common** Insomnia **Common** Anxiety, depression, cognitive impairment†† **Uncommon** Confusional state	**Uncommon** Insomnia, anxiety, depression, confusional state
Nervous system disorders	**Very common** Headache, dizziness **Common** Dysgeusia **Rare** Posterior Reversible Encephalopathy Syndrome (PRES)**	**Uncommon** Headache
Cardiac disorders	**Very common** Palpitations **Common** Tachycardia	
Vascular disorders	**Very common** Hypertension **Rare** Hypertensive crisis	**Common** Hypertension
Respiratory, thoracic and mediastinal disorders	**Very common** Dyspnoea, cough, nasopharyngitis **Common** Epistaxis **Uncommon** Pneumonitis	**Uncommon** Dyspnoea, epistaxis, pneumonitis
Gastrointestinal disorders	**Very common** Nausea, constipation, vomiting, abdominal pain, diarrhoea, dyspepsia **Common** Dry mouth, abdominal distension, mucosal inflammation, stomatitis	**Common** Nausea, vomiting, abdominal pain **Uncommon** Diarrhoea, constipation, mucosal inflammation, 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

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

*CTCAE=Common Terminology Criteria for Adverse Events version 4.02
** Based on niraparib clinical trial data. This is not limited to pivotal ENGOT-OV16 monotherapy study.
† Includes hypersensitivity, drug hypersensitivity, anaphylactoid reaction, drug eruption, angioedema, and urticaria.
†† Includes memory impairment, concentration impairment.

The adverse reactions noted in the group of patients who were administered a 200 mg starting dose of Zejula based on baseline weight or platelet count were of similar or lesser frequency compared to the group administered a fixed starting dose of 300 mg (Table 4).

See below for specific information regarding frequency of thrombocytopenia, anaemia and neutropenia.

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.

In the NOVA and PRIMA studies, 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 (NOVA) or ≥ 10 g/dL (PRIMA) prior to therapy. In the clinical programme, haematologic adverse reactions were managed with laboratory monitoring and dose modifications (see section 4.2).

In PRIMA, patients who were administered a starting dose of Zejula based on baseline weight or platelet count, Grade ≥3 thrombocytopenia, anaemia and neutropenia were reduced from 48% to 21%, 36% to 23% and 24% to 15%, respectively, compared to the group administered a fixed starting dose of 300 mg. Discontinuation due to thrombocytopenia, anaemia, and neutropenia occurred, respectively, in 3%, 3%, and 2% of patients.

Thrombocytopenia
In PRIMA, 39% of Zejula-treated patients experienced Grade 3-4 thrombocytopenia compared to 0.4% of placebo-treated patients with a median time from first dose to first onset of 22 days (range: 15 to 335 days) and with a median duration of 6 days (range: 1 to 374 days). Discontinuation due to thrombocytopenia occurred in 4% of patients receiving niraparib.

In NOVA, 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.

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 reaction 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.

Anaemia
In PRIMA, 31% of Zejula-treated patients experienced Grade 3-4 anaemia compared to 2% of placebo-treated patients with a median time from first dose to first onset of 80 days (range: 15 to 533 days) and with a median duration of 7 days (range: 1 to 119 days). Discontinuation due to anaemia occurred in 2% of patients receiving niraparib.

In NOVA, 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
In PRIMA, 21% of Zejula-treated patients experienced Grade 3-4 neutropenia compared to 1% of placebo-treated patients with a median time from first dose to first onset of 29 days (range: 15 to 421 days) and with a median duration of 8 days (range: 1 to 42 days). Discontinuation due to neutropenia occurred in 2% of patients receiving niraparib.

In NOVA, 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 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
In PRIMA, Grade 3-4 hypertension occurred in 6% of Zejula-treated patients compared to 1% of placebo-treated patients with a median time from first dose to first onset of 50 days (range: 1 to 589 days) and with a median duration of 12 days (range: 1 to 61 days). Discontinuation due to hypertension occurred in 0% of patients.

In NOVA, hypertension of any grade occurred in 19.3 % of patients treated with Zejula. Grade 3/4 hypertension occurred in 8.2 % of patients. 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: antineoplastic agents, other antineoplastic agents, ATC code: L01XK02.

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

First-line ovarian cancer maintenance treatment
PRIMA was a Phase 3 double-blind, placebo-controlled trial in which patients (n=733) in complete or partial response to first-line platinum-based chemotherapy were randomised 2:1 to niraparib or matched placebo. PRIMA was initiated with a starting dose of 300 mg QD in 475 patients (whereof 317 was randomised to the niraparib arm vs. 158 in the placebo arm) in continuous 28-day cycles. The starting dose in PRIMA was changed with Amendment 2 of the Protocol. From that point forward, patients with a baseline body weight ≥77 kg and baseline platelet count ≥150,000/μL were administered niraparib 300 mg (n=34) or placebo daily (n=21) while patients with a baseline body weight <77 kg or baseline platelet count <150,000/μL were administered niraparib 200 mg (n=122) or placebo daily (n=61).

Patients were randomised post completion of first-line platinum-based chemotherapy plus/minus surgery. Subjects were randomised within 12 weeks of the first day of the last cycle of chemotherapy. Subjects had ≥6 and ≤9 cycles of platinum-based therapy. Following interval debulking surgery subjects had ≥2 post-operative cycles of platinum-based therapy. Patients who had received bevacizumab with chemotherapy but could not receive bevacizumab as maintenance therapy were not excluded from the study. Patients could not have received prior PARP inhibitor therapy, includingniraparib. Patients who had neoadjuvant chemotherapy followed by interval debulking surgery could have visible residual or no residual disease. Patients with Stage III disease who had complete cytoreduction (i.e., no visible residual disease) after primary debulking surgery were excluded. Randomisation was stratified by best response during the front-line platinum regimen (complete response vs partial response), neoadjuvant chemotherapy (NACT) (Yes vs No); and homologous recombination deficiency (HRD) status [positive (HR deficient) vs negative (HR proficient) or not determined]. Testing for HRD was performed using the HRD test on tumour tissue obtained at the time of initial diagnosis. The CA-125 levels should be in the normal range (or a CA-125 decrease by > 90 %) during the patient's front-line therapy, and be stable for at least 7 days.

Patients began treatment on Cycle 1/Day 1 (C1/D1) with niraparib 200 or 300 mg or matched placebo administered QD in continuous 28-day cycles. Clinic visits occurred each cycle (4 weeks ± 3 days).

The primary endpoint was progression-free survival (PFS), as determined by blinded independent central review (BICR) per RECIST, version 1.1. Overall survival (OS) was a key secondary objective. PFS testing was performed hierarchically: first in the HR deficient population, then in the overall population. The median age of 62 ranged from 32 to 85 years among patients randomised with niraparib and 33 to 88 years among patients randomised with placebo. 89 percent of all patients were white. 69 percent of patients randomised with niraparib and 71% of patients randomised with placebo had an ECOG of 0 at study baseline. In the overall population, 65% of patients had stage III disease and 35% had stage IV disease. In the overall population, the primary tumour site in most patients (≥ 80 %) was the ovary; most patients (> 90 %) had tumours with serous histology. 67 percent of the patients received NACT. 69 percent of the patients had a complete response to the first-line platinum-based chemotherapy. A total of 6 niraparib patients had received bevacizumab as prior treatment for their ovarian cancer.

PRIMA demonstrated a statistically significant improvement in PFS for patients randomised to niraparib as compared with placebo in the HR deficient and overall population (Table 5, and Figures 1 and 2).

Secondary efficacy endpoints included PFS after the first subsequent therapy (PFS2) and OS (Table 5).

Table 5: Efficacy results – PRIMA (determined by BICR)

	HR deficient population		Overall population	
	niraparib (N=247)	placebo (N=126)	niraparib (N=487)	placebo (N=246)
PFS median (95% CI)	21.9 (19.3, NE)	10.4 (8.1, 12.1)	13.8 (11.5, 14.9)	8.2 (7.3, 8.5)
Hazard ratio (HR) (95% CI)	0.43 (0.31, 0.59)		0.62 (0.50, 0.76)	
p-value	<0.0001		<0.0001	
PFS2 Hazard ratio (HR) (95% CI)	0.84 (0.485, 1.453)		0.81 (0.577, 1.139)	
OS* Hazard ratio (HR) (95% CI)	0.61 (0.265, 1.388)		0.70 (0.44, 1.11)	

*At the time of primary PFS analysis, an estimated survival at two years after randomization of 84% for patients receiving Zejula, as compared to 77% for patients receiving placebo in the overall population.
Data of PFS2 and OS are currently not mature.

Figure 1: Progression-free survival in patients with HR deficient tumours (ITT population, N=373)

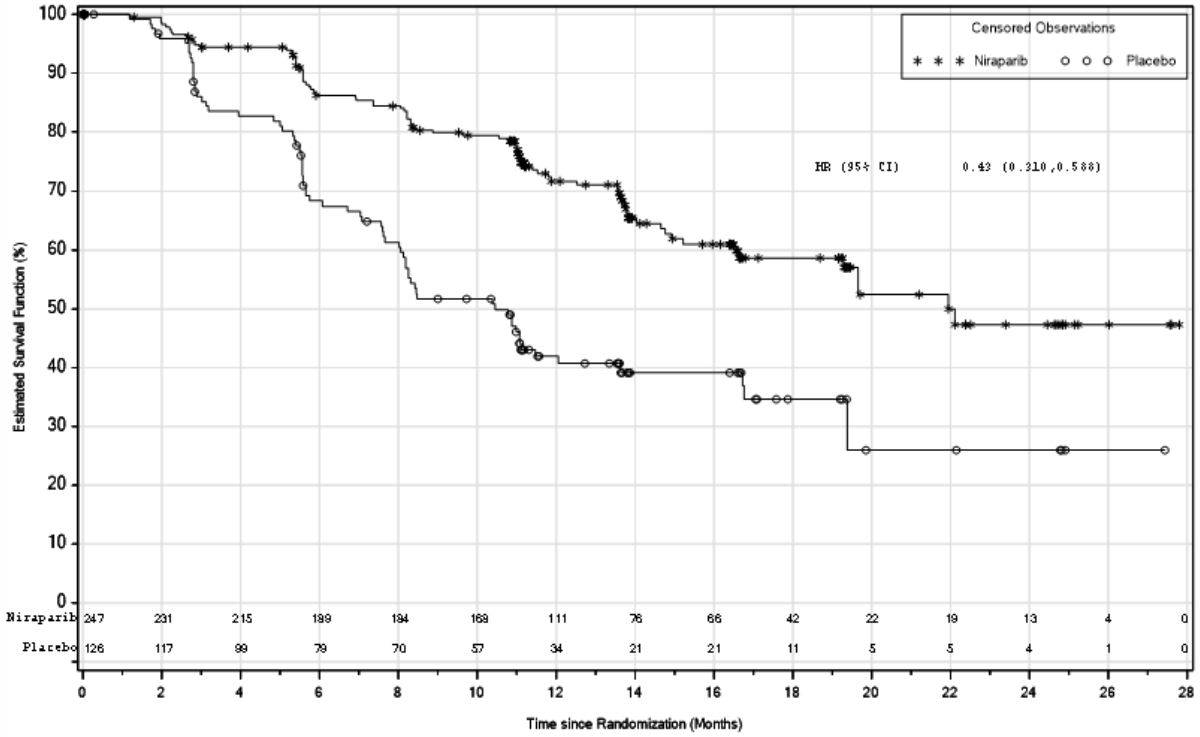
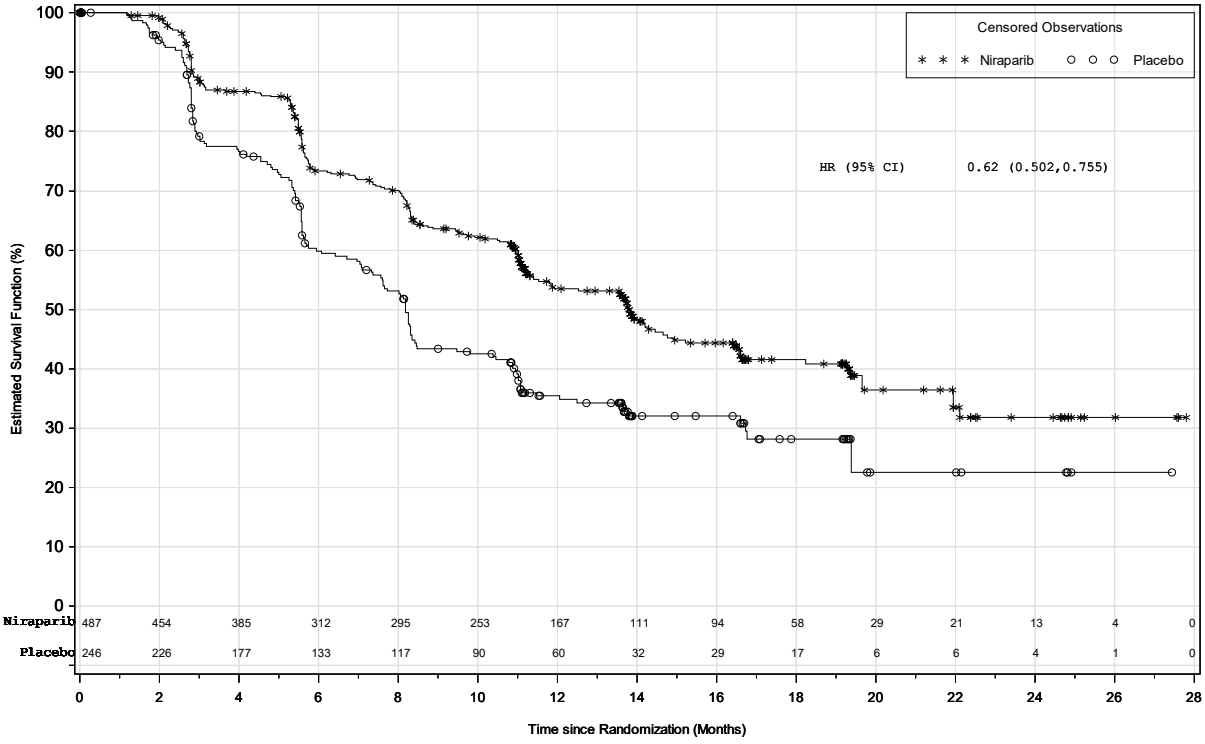


Figure 2: Progression-free survival in the overall population (ITT population, N=733)



Subgroup analyses

Within the HR deficient population, a hazard ratio of 0.40 (95% CI [0.27, 0.62]) was observed in the subgroup of patients with *BRCA*mut ovarian cancer (N = 223). In the subgroup of HR deficient patients without a *BRCA* mutation (N = 150), a hazard ratio of 0.50 (95% CI [0.31, 0.83]) was

observed. In the HR proficient population (N= 249), a hazard ratio of 0.68 (95% CI [0.49, 0.94]) was observed.

In exploratory subgroup analyses of patients who were administered 200 or 300 mg dose of Zejula based on baseline weight or platelet count, comparable efficacy (investigator-assessed PFS) was observed with a hazard ratio of 0.54 (95% CI [0.33, 0.91]) in the HR deficient population, and with a hazard ratio of 0.68 (95% CI [0.49, 0.94]) in the overall population. In the HR proficient subgroup, the dose of 200 mg appeared to give a lower treatment effect compared to the 300 mg dose.

Recurrent ovarian cancer maintenance treatment

The safety and efficacy of niraparib as maintenance therapy was studied in a Phase 3 randomised, double-blind, placebo-controlled international trial (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 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 enrolment (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 6 and Figures 3 and 4 show 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 6: Summary of primary objective outcomes in the NOVA 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 HR deficient group, the hazard ratio was 0.38 (95 % CI, 0.243, 0.586; $p < 0.0001$). In the HR proficient 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 3: Kaplan-Meier plot for progression-free survival in the g*BRCA*mut cohort based on IRC assessment (ITT population, N = 203)

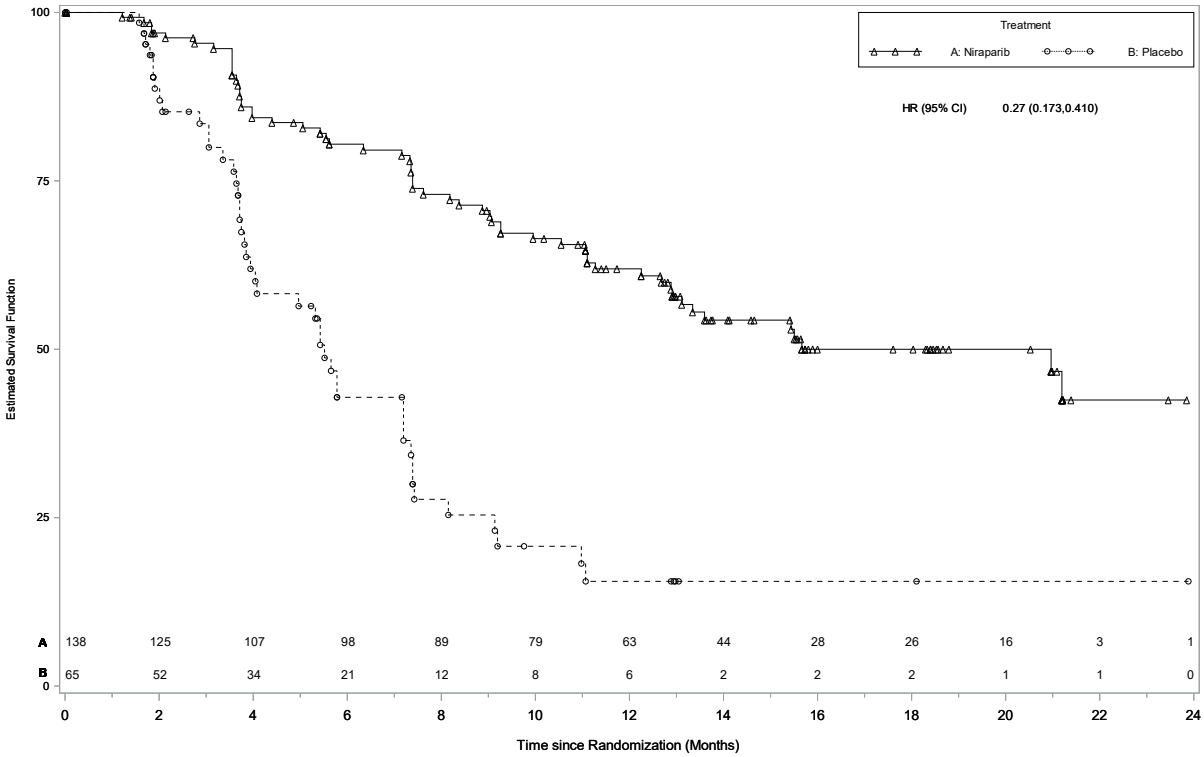
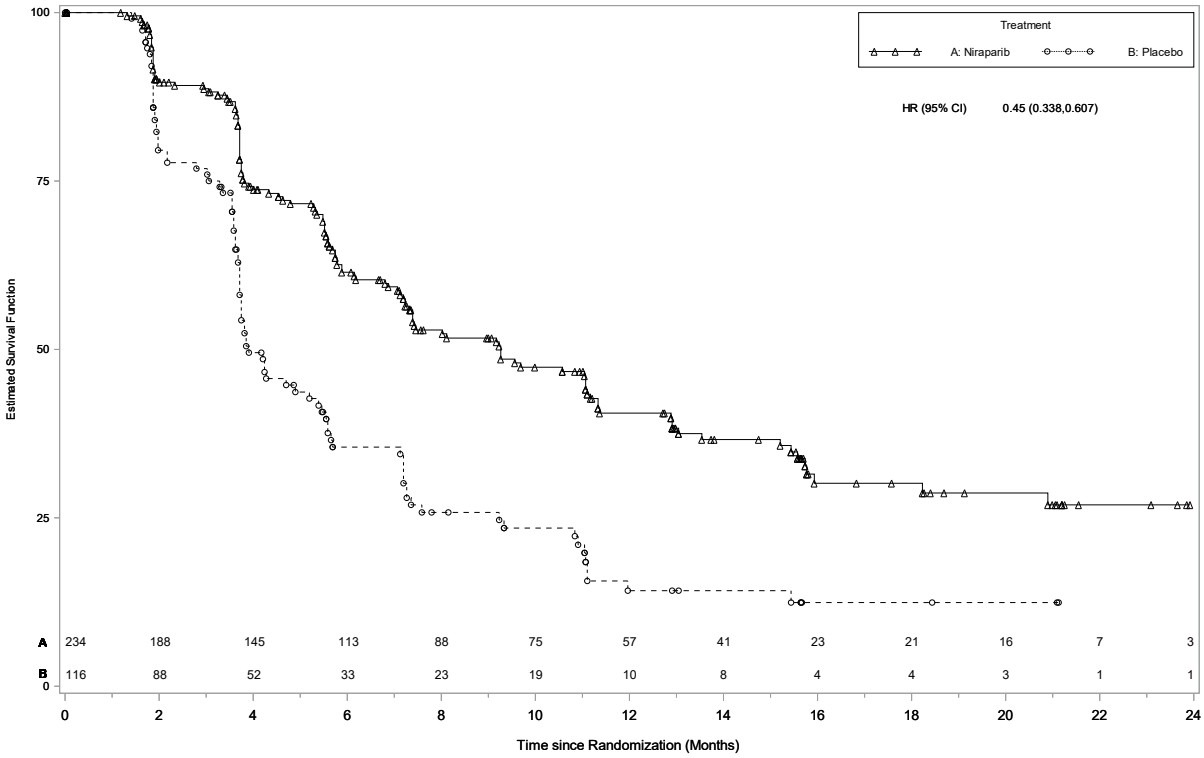


Figure 4: Kaplan-Meier plot for progression-free survival in the non-g*BRCA*mut cohort overall based on IRC assessment (ITT population, N = 350)



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 7).

Table 7: Secondary endpoints*

	g*BRCA*mut		non-g*BRCA*mut	
Endpoint	**niraparib N = 138**	**Placebo N = 65**	**niraparib 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	
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. In a population pharmacokinetic analysis of niraparib, the inter-individual variability in bioavailability was estimated to a coefficient of variation (CV) of 31%.

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

The tablet and capsule formulations have been demonstrated to be bioequivalent. Following administration of either one 300 mg tablet or three 100 mg capsules of niraparib in 108 patients with solid tumours under fasting conditions, the 90% confidence intervals of the geometric mean ratios for tablet compared to capsules for C_{max}, AUC_{last} and AUC_{∞} fell within the limits of bioequivalence (0.80 and 1.25).

Distribution

Niraparib was moderately protein bound in human plasma (83.0 %), mainly with serum albumin. In a population pharmacokinetic analysis of niraparib, the apparent volume of distribution (V_d/F) was 1,311 L (based on a 70 kg patient) in cancer patients (CV 116%), 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 16.5 L/h in cancer patients (CV 23.4%).

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 faeces over 21 days. Radioactive recovery in the urine accounted for 47.5 % (range 33.4 % to 60.2 %) and in the faeces 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 faeces primarily as unchanged niraparib.

Special populations

Renal impairment
In the population pharmacokinetic analysis, patients with mild (creatinine clearance 60-90 ml/min) and moderate (30-60 mL/min) renal impairment had mildly reduced niraparib clearance compared to individuals with normal renal function (7-17% higher exposure in mild and 17-38% higher exposure in moderate renal impairment). The difference in exposure is not considered to warrant dose adjustment. 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 hepatic impairment (n=155) did not influence the clearance of niraparib. In a clinical study of cancer patients using NCI-ODWG criteria to classify the degree of hepatic impairment, niraparib AUC_{inf} in patients with moderate hepatic impairment (n=8) was 1.56 (90% CI: 1.06 to 2.30) times the niraparib AUC_{inf} in patients with normal hepatic function (n=9) following administration of a single 300 mg dose. Niraparib dose adjustment is recommended for patients with moderate hepatic impairment (see section 4.2). Moderate hepatic impairment did not have an effect on niraparib C_{max} or on niraparib protein binding. The pharmacokinetics of niraparib have not been assessed in patients with severe hepatic impairment (see sections 4.2 and 4.4).

Weight, age and race
Increasing weight was found to increase niraparib volume of distribution in the population pharmacokinetic analysis. No impact of weight was identified on niraparib clearance or overall exposure. Dose adjustment according to body weight is not warranted from a pharmacokinetic point of

view.

Increasing age was found to decrease niraparib clearance in the population pharmacokinetic analysis. The average exposure in a 91-year old patient was predicted to be 23% higher than in a 30-year old patient. The impact of age is not considered to warrant dose adjustment.

There is insufficient data across races to conclude on the impact of race on niraparib pharmacokinetics.

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

5.3 Preclinical safety data

Safety 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

Decreased spermatogenesis was observed in rats and dogs at exposure levels below those seen clinically and was 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)
Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 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

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

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
Date of latest renewal: 18 July 2022

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.

1. NAME OF THE MEDICINAL PRODUCT

Zejula 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains niraparib tosylate monohydrate equivalent to 100 mg niraparib.

Excipients with known effect

Each film-coated tablet contains 34.7 mg of lactose monohydrate (see section 4.4).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Grey, oval-shaped (12 mm x 8 mm), film-coated tablet debossed with “100” on one side and “Zejula” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

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

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).

Recurrent ovarian cancer maintenance treatment
The dose is three 100 mg tablets 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 or toxicity.

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

Dose adjustments for adverse reactions
The recommended dose modifications for adverse reactions are listed in Tables 1, 2 and 3.

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 interrupt the treatment and then resume at the lower 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.

Table 1: Recommended dose modifications for adverse reactions

Starting dose level	**200 mg**	**300 mg**
First dose reduction	100 mg/day	200 mg/day (two 100-mg tablets)
Second dose reduction	Discontinue Zejula.	100 mg/day* (one 100-mg tablet)

*If further dose reduction below 100 mg/day is required, discontinue Zejula.

Table 2: 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 level per Table 1.
	Second occurrence: • Withhold Zejula for a maximum of 28 days or until resolution of adverse reaction. • Resume Zejula at a reduced dose or discontinue per Table 1.
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 3: 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 per Table 1 based on clinical evaluation. • If platelet count is < 75,000/μL at any time, resume at a reduced dose per Table 1.
	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 per Table 1. • 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 per Table 1. • 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 in recurrent ovarian cancer maintenance treatment
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 adverse reactions (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 hepatic impairment (either aspartate aminotransferase (AST) > upper limit of normal (ULN) and total bilirubin (TB) ≤ ULN or any AST and TB > 1.0 x – 1,5 x ULN). For patients with moderate hepatic impairment (any AST and TB > 1.5 x - 3 x ULN) the recommended starting dose of Zejula is 200 mg once daily. There are no data in patients with severe hepatic impairment (any AST and TB > 3 x ULN); use with caution in these patients (see sections 4.4 and 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

Zejula is for oral use.

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

Haematologic adverse reactions (thrombocytopenia, anaemia, neutropenia) have been reported in patients treated with Zejula (see section 4.8). Patients with lower body weight or lower baseline platelet count may be at increased risk of Grade 3+ thrombocytopenia (see section 4.2).
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 including pancytopenia 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

Cases of myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) have been observed in patients treated with Zejula monotherapy or combination therapy in clinical trials and postmarketing.

The duration of Zejula treatment in patients prior to developing MDS/AML varied from 0.5 months to > 4.9 years. The cases were typical of secondary, cancer therapy-related MDS/AML. All patients had received 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 (see section 4.8). Pre-existing hypertension should be adequately controlled before starting Zejula treatment. Blood pressure should be monitored at least weekly for two months, monitored monthly afterwards for the first year and periodically thereafter during treatment with Zejula. Home blood pressure monitoring may be considered for appropriate patients with instruction to contact their health care provider in case of rise in blood pressure.

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.

Posterior reversible encephalopathy syndrome (PRES)

There have been reports of PRES in patients receiving Zejula (see section 4.8). PRES is a rare, reversible, neurological disorder which can present with rapidly evolving symptoms including seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI).

In case of PRES, it is recommended to discontinue Zejula and to treat specific symptoms including hypertension. The safety of reinitiating Zejula therapy in patients previously experiencing PRES is not known.

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.

Hepatic impairment

Patients with severe hepatic impairment could have increased exposure of niraparib based on data from patients with moderate hepatic impairment and should be carefully monitored (see sections 4.2 and 5.2).

Lactose

Zejula film-coated tablets contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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, BSEP, MRP2, 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), or multidrug resistance-associated protein 2 (MRP2). The major primary metabolite M1 is not a substrate of P-gp, BCRP, BSEP, or MRP2. Niraparib is not a substrate of multidrug and toxin extrusion (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 uptake transporters (e.g. cimetidine, quinidine).

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).

Inhibition of UDP-glucuronosyltransferases (UGTs)
Niraparib did not exhibit inhibitory effect against the UGT isoforms (UGT1A1, UGT1A4, UGT1A9, and UGT2B7) up to 200 µM *in vitro*. Therefore, the potential for a clinically relevant inhibition of UGTs by niraparib is minimal.

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 could 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, MRP2, and MATE1/2)
Niraparib is not an inhibitor of BSEP or MRP2. *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, MRP2 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, dizziness or difficulties concentrating. Patients who experience these symptoms should observe caution when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

ADRs of all grades occurring in ≥ 10 % of the 851 patients receiving Zejula monotherapy in the pooled PRIMA (either 200 mg or 300 mg starting dose) and NOVA trials were nausea, anaemia, thrombocytopenia, fatigue, constipation, vomiting, headache, insomnia, platelet count decreased, neutropenia, abdominal pain, decreased appetite, diarrhoea, dyspnoea, hypertension, asthenia, dizziness, neutrophil count decreased, cough, arthralgia, back pain, white blood cell count decreased, and hot flush.

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 based on clinical trials and post-marketing surveillance in patients receiving Zejula monotherapy (see Table 4). Frequencies of occurrence of undesirable effects are based on pooled adverse events data generated from the PRIMA and NOVA studies (fixed starting dose of 300 mg/day) where patient exposure is known and 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); and very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 4: Tablutaed list of adverse reactions

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, leukopenia **Uncommon** Pancytopenia, febrile neutropenia	**Very common** Thrombocytopenia, anaemia, neutropenia **Common** Leukopenia **Uncommon** Pancytopenia, febrile neutropenia

System Organ Class	Frequency of all CTCAE* grades	Frequency of CTCAE* grade 3 or 4
Immune system disorders	**Common** Hypersensitivity†	**Uncommon** Hypersensitivity
Metabolism and nutrition disorders	**Very common** Decreased appetite **Common** Hypokalemia	**Common** Hypokalemia **Uncommon** Decreased appetite
Psychiatric disorders	**Very common** Insomnia **Common** Anxiety, depression, cognitive impairment†† **Uncommon** Confusional state	**Uncommon** Insomnia, anxiety, depression, confusional state
Nervous system disorders	**Very common** Headache, dizziness **Common** Dysgeusia **Rare** Posterior Reversible Encephalopathy Syndrome (PRES)**	**Uncommon** Headache
Cardiac disorders	**Very common** Palpitations **Common** Tachycardia	
Vascular disorders	**Very common** Hypertension **Rare** Hypertensive crisis	**Common** Hypertension
Respiratory, thoracic and mediastinal disorders	**Very common** Dyspnoea, cough, nasopharyngitis **Common** Epistaxis **Uncommon** Pneumonitis	**Uncommon** Dyspnoea, epistaxis, pneumonitis
Gastrointestinal disorders	**Very common** Nausea, constipation, vomiting, abdominal pain, diarrhoea, dyspepsia **Common** Dry mouth, abdominal distension, mucosal inflammation, stomatitis	**Common** Nausea, vomiting, abdominal pain **Uncommon** Diarrhoea, constipation, mucosal inflammation, 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

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

*CTCAE=Common Terminology Criteria for Adverse Events version 4.02
** Based on niraparib clinical trial data. This is not limited to pivotal ENGOT-OV16 monotherapy study.
† Includes hypersensitivity, drug hypersensitivity, anaphylactoid reaction, drug eruption, angioedema, and urticaria.
†† Includes memory impairment, concentration impairment.

The adverse reactions noted in the group of patients who were administered a 200 mg starting dose of Zejula based on baseline weight or platelet count were of similar or lesser frequency compared to the group administered a fixed starting dose of 300 mg (Table 4).

See below for specific information regarding frequency of thrombocytopenia, anaemia and neutropenia.

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.

In the NOVA and PRIMA studies, 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 (NOVA) or ≥ 10 g/dL (PRIMA) prior to therapy. In the clinical programme, haematologic adverse reactions were managed with laboratory monitoring and dose modifications (see section 4.2).

In PRIMA, patients who were administered a starting dose of Zejula based on baseline weight or platelet count, Grade ≥3 thrombocytopenia, anaemia and neutropenia were reduced from 48% to 21%, 36% to 23% and 24% to 15%, respectively, compared to the group administered a fixed starting dose of 300 mg. Discontinuation due to thrombocytopenia, anaemia, and neutropenia occurred, respectively, in 3%, 3%, and 2% of patients.

Thrombocytopenia
In PRIMA, 39% of Zejula-treated patients experienced Grade 3-4 thrombocytopenia compared to 0.4% of placebo-treated patients with a median time from first dose to first onset of 22 days (range: 15 to 335 days) and with a median duration of 6 days (range: 1 to 374 days). Discontinuation due to thrombocytopenia occurred in 4% of patients receiving niraparib.

In NOVA, 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.

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 reaction 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.

Anaemia
In PRIMA, 31% of Zejula-treated patients experienced Grade 3-4 anaemia compared to 2% of placebo-treated patients with a median time from first dose to first onset of 80 days (range: 15 to 533 days) and with a median duration of 7 days (range: 1 to 119 days). Discontinuation due to anaemia occurred in 2% of patients receiving niraparib.

In NOVA, 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
In PRIMA, 21% of Zejula-treated patients experienced Grade 3-4 neutropenia compared to 1% of placebo-treated patients with a median time from first dose to first onset of 29 days (range: 15 to 421 days) and with a median duration of 8 days (range: 1 to 42 days). Discontinuation due to neutropenia occurred in 2% of patients receiving niraparib.

In NOVA, 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 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
In PRIMA, Grade 3-4 hypertension occurred in 6% of Zejula-treated patients compared to 1% of placebo-treated patients with a median time from first dose to first onset of 50 days (range: 1 to 589 days) and with a median duration of 12 days (range: 1 to 61 days). Discontinuation due to hypertension occurred in 0% of patients.

In NOVA, hypertension of any grade occurred in 19.3 % of patients treated with Zejula. Grade 3/4 hypertension occurred in 8.2 % of patients. 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: antineoplastic agents, other antineoplastic agents, ATC code: L01XK02.

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

First-line ovarian cancer maintenance treatment
PRIMA was a Phase 3 double-blind, placebo-controlled trial in which patients (n=733) in complete or partial response to first-line platinum-based chemotherapy were randomised 2:1 to niraparib or matched placebo. PRIMA was initiated with a starting dose of 300 mg QD in 475 patients (whereof 317 was randomised to the niraparib arm vs. 158 in the placebo arm) in continuous 28-day cycles. The starting dose in PRIMA was changed with Amendment 2 of the Protocol. From that point forward, patients with a baseline body weight ≥77 kg and baseline platelet count ≥150,000/μL were administered niraparib 300 mg (n=34) or placebo daily (n=21) while patients with a baseline body weight <77 kg or baseline platelet count <150,000/μL were administered niraparib 200 mg (n=122) or placebo daily (n=61).

Patients were randomised post completion of first-line platinum-based chemotherapy plus/minus surgery. Subjects were randomised within 12 weeks of the first day of the last cycle of chemotherapy. Subjects had ≥6 and ≤9 cycles of platinum-based therapy. Following interval debulking surgery subjects had ≥2 post-operative cycles of platinum-based therapy. Patients who had received bevacizumab with chemotherapy but could not receive bevacizumab as maintenance therapy were not excluded from the study. Patients could not have received prior PARP inhibitor therapy, including niraparib. Patients who had neoadjuvant chemotherapy followed by interval debulking surgery could have visible residual or no residual disease. Patients with Stage III disease who had complete cytoreduction (i.e., no visible residual disease) after primary debulking surgery were excluded. Randomisation was stratified by best response during the front-line platinum regimen (complete response vs partial response), neoadjuvant chemotherapy (NACT) (Yes vs No); and homologous recombination deficiency (HRD) status [positive (HR deficient) vs negative (HR proficient) or not determined]. Testing for HRD was performed using the HRD test on tumour tissue obtained at the time of initial diagnosis. The CA-125 levels should be in the normal range (or a CA-125 decrease by > 90 %) during the patient's front-line therapy, and be stable for at least 7 days.

Patients began treatment on Cycle 1/Day 1 (C1/D1) with niraparib 200 or 300 mg or matched placebo administered QD in continuous 28-day cycles. Clinic visits occurred each cycle (4 weeks ± 3 days).

The primary endpoint was progression-free survival (PFS), as determined by blinded independent central review (BICR) per RECIST, version 1.1. Overall survival (OS) was a key secondary objective. PFS testing was performed hierarchically: first in the HR deficient population, then in the overall population. The median age of 62 ranged from 32 to 85 years among patients randomised with niraparib and 33 to 88 years among patients randomised with placebo. 89 percent of all patients were white. 69 percent of patients randomised with niraparib and 71% of patients randomised with placebo had an ECOG of 0 at study baseline. In the overall population, 65% of patients had stage III disease and 35% had stage IV disease. In the overall population, the primary tumour site in most patients (≥ 80 %) was the ovary; most patients (> 90 %) had tumours with serous histology. 67 percent of the patients received NACT. 69 percent of the patients had a complete response to the first-line platinum-based chemotherapy. A total of 6 niraparib patients had received bevacizumab as prior treatment for their ovarian cancer.

PRIMA demonstrated a statistically significant improvement in PFS for patients randomised to niraparib as compared with placebo in the HR deficient and overall population (Table 5, and Figures 1 and 2).

Secondary efficacy endpoints included PFS after the first subsequent therapy (PFS2) and OS (Table 5).

Table 5: Efficacy results – PRIMA (determined by BICR)

	HR deficient population		Overall population	
	niraparib (N=247)	placebo (N=126)	niraparib (N=487)	placebo (N=246)
PFS median (95% CI)	21.9 (19.3, NE)	10.4 (8.1, 12.1)	13.8 (11.5, 14.9)	8.2 (7.3, 8.5)
Hazard ratio (HR) (95% CI)	0.43 (0.31, 0.59)		0.62 (0.50, 0.76)	
p-value	<0.0001		<0.0001	
PFS2 Hazard ratio (HR) (95% CI)	0.84 (0.485, 1.453)		0.81 (0.577, 1.139)	
OS* Hazard ratio (HR) (95% CI)	0.61 (0.265, 1.388)		0.70 (0.44, 1.11)	

*At the time of primary PFS analysis, an estimated survival at two years after randomization of 84% for patients receiving Zejula, as compared to 77% for patients receiving placebo in the overall population.
Data of PFS2 and OS are currently not mature.

Figure 1: Progression-free survival in patients with HR deficient tumours (ITT population, N=373)

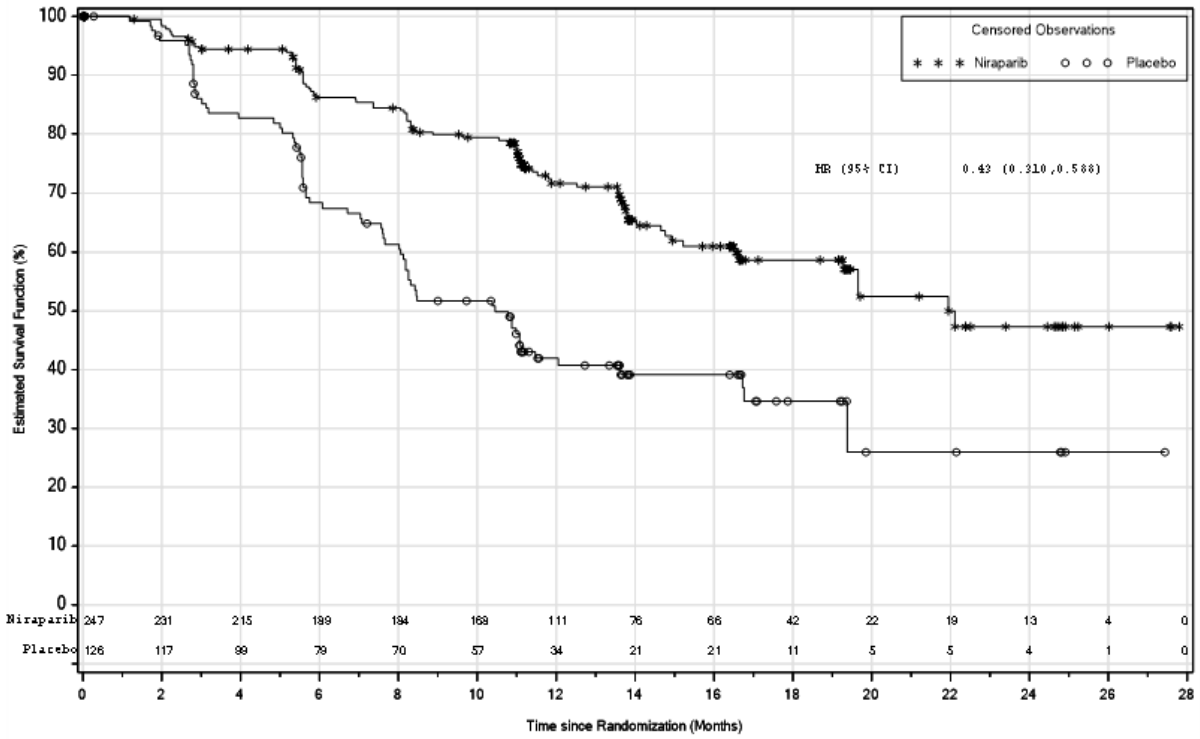
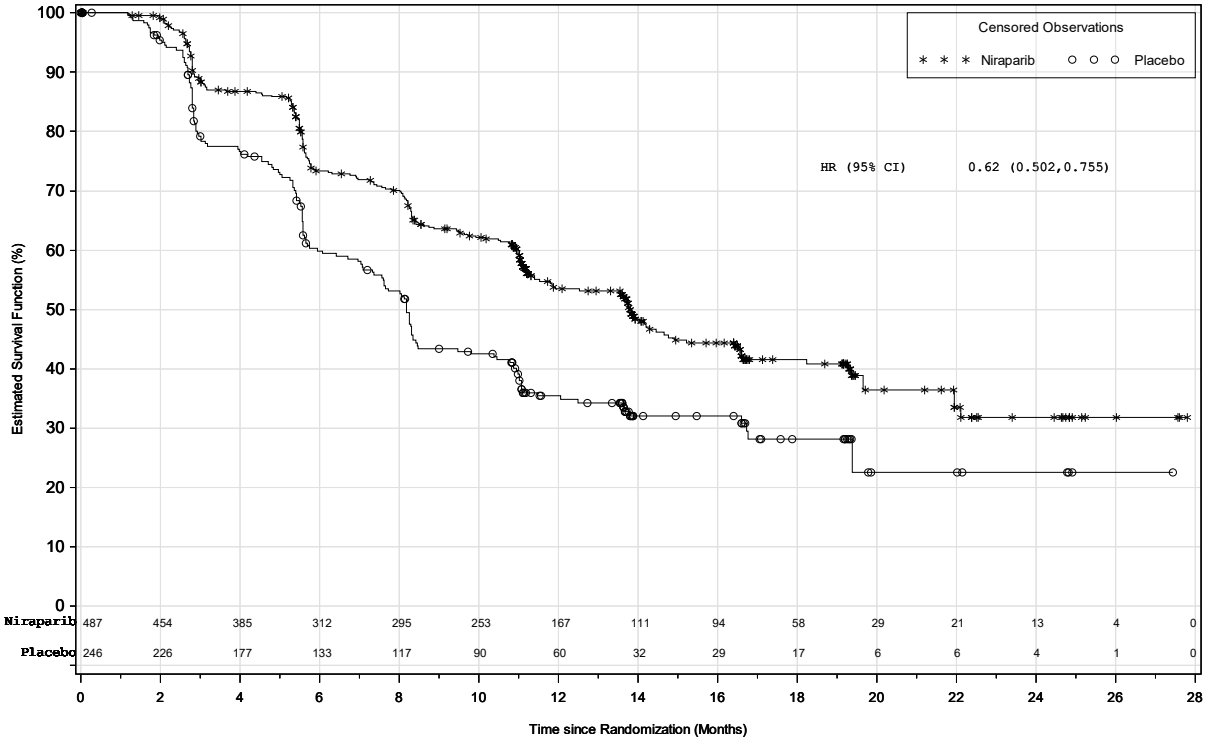


Figure 2: Progression-free survival in the overall population (ITT population, N=733)



Subgroup analyses

Within the HR deficient population, a hazard ratio of 0.40 (95% CI [0.27, 0.62]) was observed in the subgroup of patients with *BRCA*mut ovarian cancer (N = 223). In the subgroup of HR deficient patients without a *BRCA* mutation (N = 150), a hazard ratio of 0.50 (95% CI [0.31, 0.83]) was

observed. In the HR proficient population (N= 249), a hazard ratio of 0.68 (95% CI [0.49, 0.94]) was observed.

In exploratory subgroup analyses of patients who were administered 200 or 300 mg dose of Zejula based on baseline weight or platelet count, comparable efficacy (investigator-assessed PFS) was observed with a hazard ratio of 0.54 (95% CI [0.33, 0.91]) in the HR deficient population, and with a hazard ratio of 0.68 (95% CI [0.49, 0.94]) in the overall population. In the HR proficient subgroup, the dose of 200 mg appeared to give a lower treatment effect compared to the 300 mg dose.

Recurrent ovarian cancer maintenance treatment
The safety and efficacy of niraparib as maintenance therapy was studied in a Phase 3 randomised, double-blind, placebo-controlled international trial (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 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 enrolment (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 6 and Figures 3 and 4 show 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 6: Summary of primary objective outcomes in the NOVA 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 HR deficient group, the hazard ratio was 0.38 (95 % CI, 0.243, 0.586; $p < 0.0001$). In the HR proficient 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 3: Kaplan-Meier plot for progression-free survival in the g*BRCA*mut cohort based on IRC assessment (ITT population, N = 203)

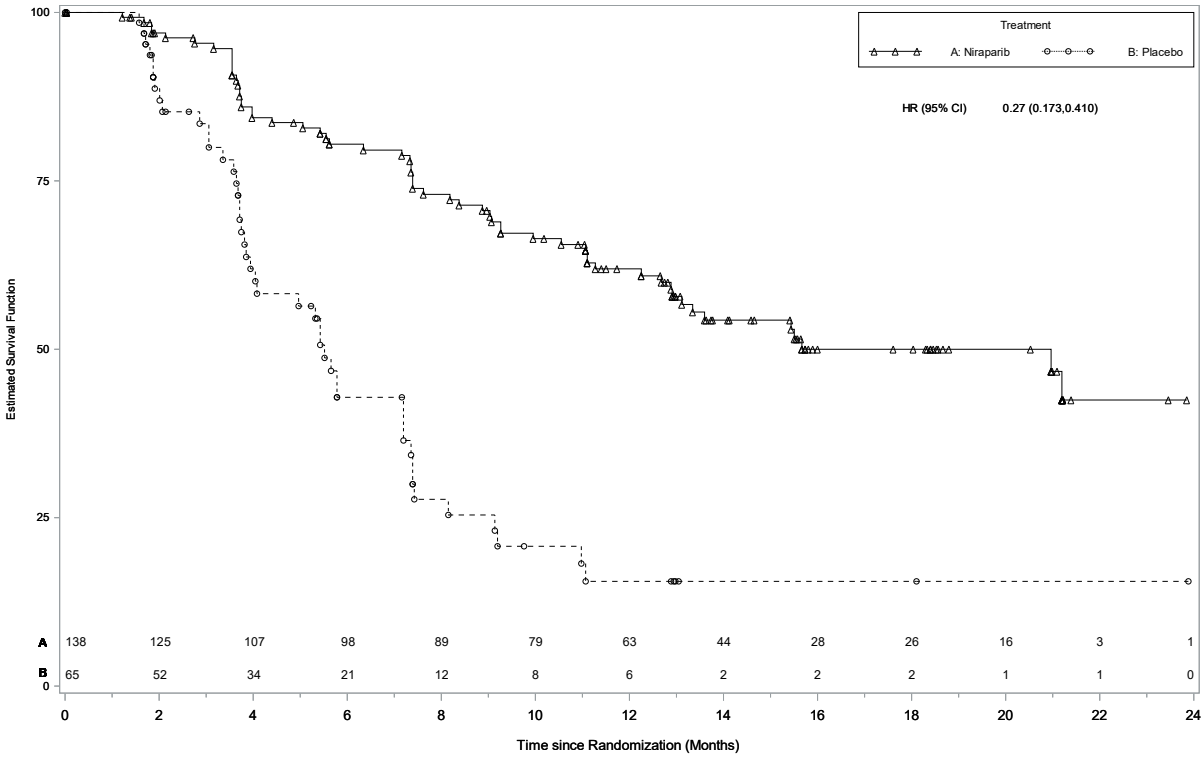
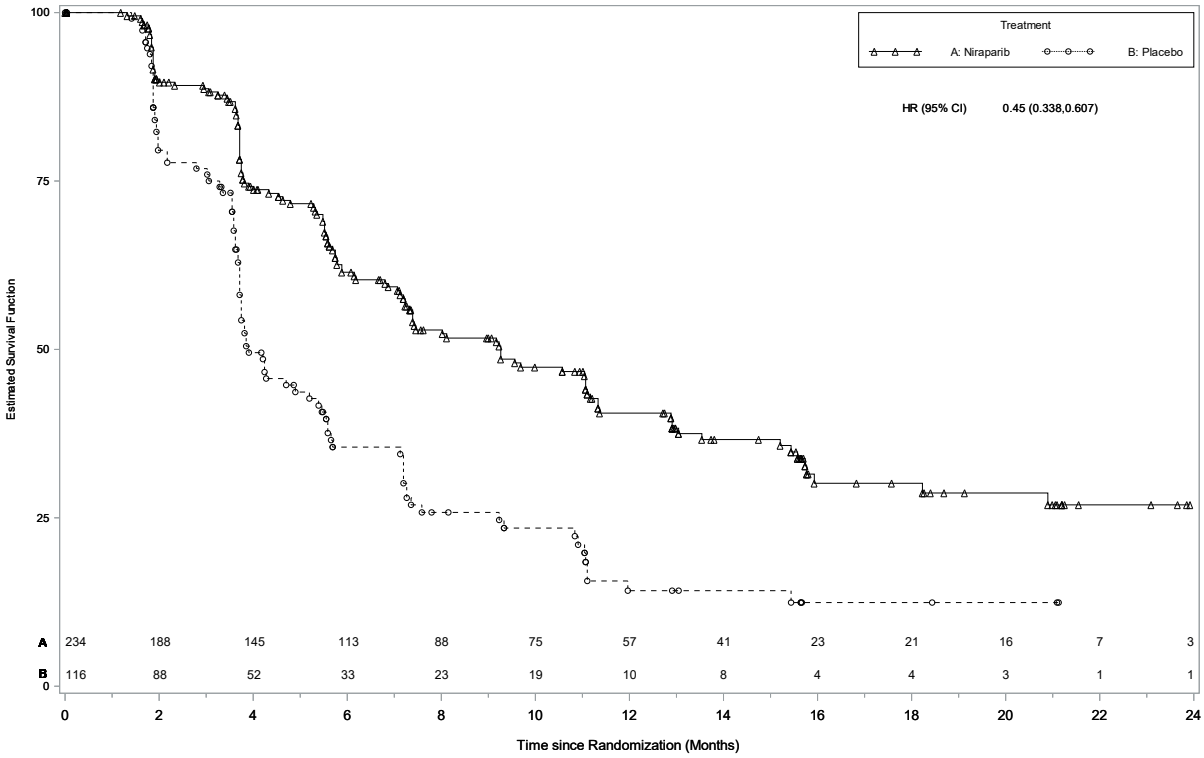


Figure 4: Kaplan-Meier plot for progression-free survival in the non-g*BRCA*mut cohort overall based on IRC assessment (ITT population, N = 350)



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 7).

Table 7: Secondary endpoints*

	g*BRCA*mut		non-g*BRCA*mut	
Endpoint	**niraparib N = 138**	**Placebo N = 65**	**niraparib 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	
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. In a population pharmacokinetic analysis of niraparib, the inter-individual variability in bioavailability was estimated to a coefficient of variation (CV) of 31%.

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

The tablet and capsule formulations have been demonstrated to be bioequivalent. Following administration of either one 300 mg tablet or three 100 mg capsules of niraparib in 108 patients with solid tumours under fasting conditions, the 90% confidence intervals of the geometric mean ratios for tablet compared to capsules for C_{max}, AUC_{last} and AUC_{∞} fell within the limits of bioequivalence (0.80 and 1.25).

Distribution

Niraparib was moderately protein bound in human plasma (83.0 %), mainly with serum albumin. In a population pharmacokinetic analysis of niraparib, the apparent volume of distribution (V_d/F) was 1,311 L (based on a 70 kg patient) in cancer patients (CV 116%), 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 16.5 L/h in cancer patients (CV 23.4%).

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 faeces over 21 days. Radioactive recovery in the urine accounted for 47.5 % (range 33.4 % to 60.2 %) and in the faeces 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 faeces primarily as unchanged niraparib.

Special populations

Renal impairment
In the population pharmacokinetic analysis, patients with mild (creatinine clearance 60-90 ml/min) and moderate (30-60 mL/min) renal impairment had mildly reduced niraparib clearance compared to individuals with normal renal function (7-17% higher exposure in mild and 17-38% higher exposure in moderate renal impairment). The difference in exposure is not considered to warrant dose adjustment. 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 hepatic impairment (n=155) did not influence the clearance of niraparib. In a clinical study of cancer patients using NCI-ODWG criteria to classify the degree of hepatic impairment, niraparib AUC_{inf} in patients with moderate hepatic impairment (n=8) was 1.56 (90% CI: 1.06 to 2.30) times the niraparib AUC_{inf} in patients with normal hepatic function (n=9) following administration of a single 300 mg dose. Niraparib dose adjustment is recommended for patients with moderate hepatic impairment (see section 4.2). Moderate hepatic impairment did not have an effect on niraparib C_{max} or on niraparib protein binding. The pharmacokinetics of niraparib have not been assessed in patients with severe hepatic impairment (see sections 4.2 and 4.4).

Weight, age and race
Increasing weight was found to increase niraparib volume of distribution in the population

pharmacokinetic analysis. No impact of weight was identified on niraparib clearance or overall exposure. Dose adjustment according to body weight is not warranted from a pharmacokinetic point of view.

Increasing age was found to decrease niraparib clearance in the population pharmacokinetic analysis. The average exposure in a 91-year old patient was predicted to be 23% higher than in a 30-year old patient. The impact of age is not considered to warrant dose adjustment.

There is insufficient data across races to conclude on the impact of race on niraparib pharmacokinetics.

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

5.3 Preclinical safety data

Safety 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

Decreased spermatogenesis was observed in rats and dogs at exposure levels below those seen clinically and was 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

Tablet core
Crospovidone
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose (E 460)
Povidone (E 1201)
Silica, colloidal hydrated

Tablet coat
Polyvinyl alcohol (E 1203)
Titanium dioxide (E 171)
Macrogol (E 1521)
Talc (E 553b)
Iron oxide black (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions, store in the original package to protect the tablets from absorption of water under high humidity conditions.

6.5 Nature and contents of container

OPA/aluminium/PVC/aluminium/vinyl/acrylic blisters in cartons of 84 × 1 and 56 × 1 film-coated tablets.

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

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1235/004
EU/1/17/1235/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 November 2017
Date of latest renewal: 18 July 2022

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

Hard Capsules and Film-coated Tablets:
GlaxoSmithKline Trading Services Ltd.
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

Film-coated Tablets:
Millmount Healthcare Ltd.
Block 7, City North Business Campus,
Stamullen, Co Meath
Ireland

OR

Glaxo Wellcome, S.A.
Avda. Extremadura, 3
09400 Aranda de Duero
Burgos
Spain

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 (PSURs)**

The requirements for submission of PSURs 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.

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

- **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.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Post-authorisation efficacy study (PAES): In order to further investigate the efficacy of niraparib in 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, the MAH should submit the final analysis for OS and updated analyses for TFST, PFS-2 and outcomes for next anticancer therapy from study PRIMA.	31 December 2025

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CAPSULE 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

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1235/001 84 hard capsules
EU/1/17/1235/002 56 hard capsules
EU/1/17/1235/003 28 hard capsules

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

CAPSULE BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Zejula 100 mg capsules
niraparib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

TABLET CARTON

1. NAME OF THE MEDICINAL PRODUCT

Zejula 100 mg film-coated tablets
niraparib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains niraparib tosylate monohydrate equivalent to 100 mg of niraparib.

3. LIST OF EXCIPIENTS

Also contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
56 film-coated tablets
84 film-coated tablets

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

Store in the original package.

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

GlaxoSmithKline (Ireland) Limited
12 Riverwalk
Citywest Business Campus
Dublin 24
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1235/004 56 film-coated tablets
EU/1/17/1235/005 84 film-coated tablets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zejula tablet

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

TABLET BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Zejula 100 mg tablets
niraparib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

GlaxoSmithKline (Ireland) Limited

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

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 the first treatment with platinum-based chemotherapy, or
- come back (recurred) 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. Your doctor may advise home blood pressure monitoring and instruction on when to contact him or her in case of a rise in blood pressure.

Posterior reversible encephalopathy syndrome (PRES)
A rare neurological side effect named PRES has been associated with Zejula treatment. If you have headache, vision changes, confusion or seizure with or without high blood pressure, please contact your doctor.

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, unfocused, 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 medicinal product.

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.

For ovarian cancer that has responded to the first treatment with platinum-based chemotherapy
The recommended starting dose is 200 mg (two 100 mg capsules), taken together once a day, with or without food. If you weigh ≥ 77 kg and have platelet count ≥ 150,000/µL before starting treatment, the recommended starting dose is 300 mg (three 100 mg capsules), taken together once a day, with or without food.

For ovarian cancer that has come back (recurred)
The recommended starting dose is 300 mg (three 100 mg capsules), taken together once a day, with or without food.

Take Zejula at approximately the same time each day. Taking Zejula at bedtime may help you to manage nausea.

Your doctor may adjust your starting dose if you have problems with your liver.

Swallow the capsules whole, with some water. Do not chew or crush the capsules. This will ensure the medicine works as well as possible.

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 <u>straight away</u> 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.
- Reduction in the number of white cells in the blood (leukopenia)

Common (may affect up to 1 in 10 people)
- Allergic reaction (including severe allergic reaction that can be life-threatening). Signs include raised and itchy rash (hives) and swelling—sometimes of the face or mouth (angioedema), causing difficulty in breathing, and collapse or loss of consciousness.

Rare (may affect up to 1 in 1000 people)
- A sudden increase in blood pressure, which may be a medical emergency that could lead to organ damage or can be life-threatening.
- A brain condition with symptoms including seizures (fits), headache, confusion, and changes in vision (Posterior Reversible Encephalopathy Syndrome or PRES), which is a medical emergency that could lead to organ damage or can be life-threatening.

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 (nausea)
- Heartburn (dyspepsia)
- Decreased number of white cells in the blood
- Decreased number of platelets in the blood
- Decreased number of red cells in the blood (anaemia)
- Feeling tired
- Feeling of weakness
- Constipation
- Vomiting
- Stomach pain
- Inability to sleep
- Headache
- Decreased appetite
- Runny or stuffy nose
- Diarrhoea
- Shortness of breath
- Back pain
- Joint pain
- High blood pressure
- Indigestion
- Dizziness
- Cough
- Urinary tract infection
- Palpitations (feeling like your heart is skipping beats or beating harder than usual)

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
- Impaired concentration, understanding, memory and thinking (cognitive impairment)
- 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
- Abnormal taste in mouth

Uncommon (may affect up to 1 in 100 people)
- Reduction in the number of red blood cells, white blood cells and platelets
- Confusional state
- Inflammation of the lungs which can cause shortness of breath and difficulty breathing (non-infectious pneumonitis)

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 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), povidone (E 1201), and titanium dioxide (E 171).

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 unit dose blister packs of
- 84 × 1 hard capsules
- 56 × 1 hard capsules
- 28 × 1 hard capsules

Not all pack sizes may be marketed.

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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.

Package leaflet: Information for the patient

Zejula 100 mg film-coated tablets
niraparib

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 the first treatment with platinum-based chemotherapy, or
- come back (recurred) 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. Your doctor may advise home blood pressure monitoring and instruction on when to contact him or her in case of a rise in blood pressure.

Posterior reversible encephalopathy syndrome (PRES)
A rare neurological side effect named PRES has been associated with Zejula treatment. If you have headache, vision changes, confusion or seizure with or without high blood pressure, please contact your doctor.

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, unfocused, 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 medicinal product.

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.

For ovarian cancer that has responded to the first treatment with platinum-based chemotherapy
The recommended starting dose is 200 mg (two 100 mg tablets), taken together once a day, with or without food. If you weigh ≥ 77 kg and have platelet count ≥ 150,000/µL before starting treatment, the recommended starting dose is 300 mg (three 100 mg tablets), taken together once a day, with or without food.

For ovarian cancer that has come back (recurred)
The recommended starting dose is 300 mg (three 100 mg tablets), taken together once a day, with or without food.

Take Zejula at approximately the same time each day. Taking Zejula at bedtime may help you to manage nausea.

Your doctor may adjust your starting dose if you have problems with your liver.

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.
- Reduction in the number of white cells in the blood (leukopenia)

Common (may affect up to 1 in 10 people)
- Allergic reaction (including severe allergic reaction that can be life-threatening). Signs include raised and itchy rash (hives) and swelling—sometimes of the face or mouth (angioedema), causing difficulty in breathing, and collapse or loss of consciousness.

Rare (may affect up to 1 in 1000 people)
- A sudden increase in blood pressure, which may be a medical emergency that could lead to organ damage or can be life-threatening.
- A brain condition with symptoms including seizures (fits), headache, confusion, and changes in vision (Posterior Reversible Encephalopathy Syndrome or PRES), which is a medical emergency that could lead to organ damage or can be life-threatening.

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 (nausea)
- Heartburn (dyspepsia)
- Decreased number of white cells in the blood
- Decreased number of platelets in the blood
- Decreased number of red cells in the blood (anaemia)
- Feeling tired
- Feeling of weakness
- Constipation
- Vomiting
- Stomach pain
- Inability to sleep
- Headache
- Decreased appetite
- Runny or stuffy nose
- Diarrhoea
- Shortness of breath
- Back pain
- Joint pain
- High blood pressure
- Indigestion
- Dizziness
- Cough
- Urinary tract infection
- Palpitations (feeling like your heart is skipping beats or beating harder than usual)

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
- Impaired concentration, understanding, memory and thinking (cognitive impairment)
- 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
- Abnormal taste in mouth

Uncommon (may affect up to 1 in 100 people)
- Reduction in the number of red blood cells, white blood cells and platelets
- Confusional state
- Inflammation of the lungs which can cause shortness of breath and difficulty breathing (non-infectious pneumonitis)

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.

This medicine does not require any special storage temperature conditions.

Store in the original package to protect the tablets from absorption of water under high humidity conditions.

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 film-coated tablet contains niraparib tosylate monohydrate equivalent to 100 mg niraparib.

- The other ingredients (excipients) are:
  Tablet core: crospovidone, lactose monohydrate, magnesium stearate, microcrystalline cellulose (E 460), povidone (E 1201), colloidal hydrated silica.
  Tablet coating: polyvinyl alcohol (E 1203), titanium dioxide (E 171), macrogol (E 1521), talc (E 553b), black iron oxide (E 172).

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

What Zejula looks like and contents of the pack

Zejula 100 mg film-coated tablets are grey, oval-shaped, film-coated tablet debossed with “100” on one side and “Zejula” on the other.

The film-coated tablets are packed in blister packs of
- 84 × 1 film-coated tablets
- 56 × 1 film-coated tablets

Not all pack sizes may be marketed.

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Other sources of information

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