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 34.66 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 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 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.

- 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.

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[a] (one 100-mg tablet)

[a]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 per Table 1
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 daily
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 daily.
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 an Eastern Cooperative Oncology Group (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.

It is advised to take Zejula tablets without food (at least 1 hour before or 2 hours after a meal) or with a light meal (see section 5.2).

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), including cases with fatal outcome, have been observed in patients treated with Zejula monotherapy or combination therapy in clinical trials and postmarketing (see section 4.8).

In clinical trials, 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 patients had a history of bone marrow suppression. In the NOVA trial, the incidence of MDS/AML was higher in the g*BRCA*mut cohort (7.4%) than in the non-g*BRCA*mut cohort (1.7%).

For suspected MDS/AML or prolonged haematological toxicities, the patient should be referred to a haematologist for further evaluation. If MDS/AML is confirmed 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 highly effective contraception during therapy and for 6 months 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

No clinical drug interaction studies have been performed with niraparib.

Effect of other medicinal products on niraparib

Induction of CYP1A2 In vitro, niraparib induces CYP1A2 . 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-glycoprotein (P-gp), Breast Cancer Resistance Protein (BCRP), and MATE1 2K)]

In vitro, niraparib is an inhibitor of P-gp .As no clinical data are available, it cannot be excluded that niraparib may increase the systemic exposure of other medicines transported by P-gp that are sensitive to intestinal P-gp inhibition (e.g., dabigatran etexilate).

In vitro, niraparib is an inhibitor of BCRP . A clinically relevant interaction with BCRP substrates cannot be excluded. Caution is therefore recommended when niraparib is combined with substrates of BCRP (e.g. irinotecan, rosuvastatin, simvastatin, atorvastatin, and methotrexate)due to risk of increased systemic exposure.

Niraparib is an inhibitor of MATE1 and -2K *in vitro.* Plasma concentrations of metformin may increase when concomitantly administered with niraparib .

Close monitoring of glycaemia is recommended when starting or stopping niraparib in patients receiving metformin. A dose adjustment of metformin may be necessary.

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 highly effective contraception during therapy and for 6 months 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

Adverse reactions 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)
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
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**Common** Myelodysplastic syndrome/ acute myeloid leukaemia[a]	**Common** Myelodysplastic syndrome/ acute myeloid leukaemia[a]
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
Immune system disorders	**Common** Hypersensitivity[b]	**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[c] **Uncommon** Confusional state	**Uncommon** Insomnia, anxiety, depression, confusional state
Nervous system disorders	**Very common** Headache, dizziness **Common** Dysgeusia **Rare** Posterior Reversible Encephalopathy Syndrome (PRES)[a]	**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
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
[a] Based on niraparib clinical trial data. This is not limited to pivotal ENGOT-OV16 monotherapy study.
[b] Includes hypersensitivity, drug hypersensitivity, anaphylactoid reaction, drug eruption, angioedema, and urticaria.
[c] 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 NOVA and PRIMA , 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, in 3%, 3%, and 2% of patients respectively.

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 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 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 NOVA , 13% (48/367) 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 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 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.

Myelodysplastic syndrome/Acute myeloid leukaemia
In clinical studies, MDS/AML occurred in 1% patients treated with Zejula, with 41% of cases having a fatal outcome. The incidence was higher in patients with relapsed ovarian cancer who had received 2

or more lines of prior platinum chemotherapy and with *gBRCA*mut following 75 months survival follow-up. All patients had potential contributing factors for the development of MDS/AML, having received previous chemotherapy with platinum agents. Many had also received other DNA damaging agents and radiotherapy. The majority of reports were in g*BRCA*mut carriers. Some patients had a history of previous cancer or of bone marrow suppression.

In PRIMA , the incidence of MDS/AML was 2.3%in patients receiving Zejula and 1.6% in patients receiving placebo with a follow-up of 74 months.

In NOVA in patients with relapsed ovarian cancer who had received at least two prior lines of platinum chemotherapy, the overall incidence of MDS/AML was 3.8% in patients receiving Zejula and 1.7% in patients receiving placebo with a follow-up of 75 months. In g*BRCA*mut and non-g*BRCA*mut cohorts, the incidence of MDS/AML was 7.4% and 1.7% in patients receiving Zejula and 3.1% and 0.9% in patients receiving placebo, respectively.

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). No patients discontinued Zejula due to hypertension.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

There is no specific treatment in the event of overdose with Zejula, 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 daily 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 or 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 (PARPi) 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 daily 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. .

PFS testing was performed hierarchically: first in the HR-deficient population, then in the overall population. Secondary efficacy endpoints included PFS after the first subsequent therapy (PFS2) and overall survival (OS) (Table 5). The median age was 62 years among patients randomised to niraparib (range 32 to 85 years) or placebo (range 33 to 88 years). Eighty-nine percent of all patients were white. Sixty-nine percent of patients randomised to niraparib and 71% of patients randomised to 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. Sixty-seven percent of patients received NACT. Sixty-nine percent of patients had a complete response to the first-line platinum-based chemotherapy. A total of 6 patients in the Zejula group had received bevacizumab as prior treatment for their ovarian cancer.

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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).Efficacy results for the final analysis of OS data are presented in Table 5.

Table 5: Efficacy results – PRIMA

	HR -deficient population		Overall population	
	Zejula (N=247)	**Placebo (N=126)**	**Zejula (N=487)**	**Placebo (N=246)**
Primary endpoint (determined by BICR)				
PFS median months (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 (95% CI)	0.43 (0.31, 0.59)		0.62 (0.50, 0.76)	
p-value	<0.0001		<0.0001	
Secondary endpoints[a, b, c]				
PFS2 median, months (95% CI)	43.4 (37.2, 54.1)	39.3 (30.3, 55.7)	30.1 (27.1, 33.1)	27.6 (24.2, 33.1)
Hazard ratio (95% CI)	0.87 (0.66, 1.17)		0.96 (0.79, 1.17)	
OS median, months[d] (95% CI)	71.9 (55.5, NE)	69.8 (51.6, NE)	46.6 (43.7, 52.8)	48.8 (43.1, 61.0)
Hazard ratio (95% CI)	0.95 (0.70, 1.29)		1.01 (0.84, 1.23)	

PFS = progression-free survival; CI = confidence interval; NE = not evaluable; PFS2 = PFS after the first subsequent therapy; OS = overall survival.

[a] Data based on final analysis.

[b] In the HR-deficient population and overall population, 15.8% and 11.7% of patients in the Zejula arm received subsequent PARPi therapy, respectively.

[c] In the HR-deficient population and overall population, 48.4% and 37.8% of placebo patients received subsequent PARPi therapy, respectively.

[d] The maturity of the OS data for the HR-deficient population and overall population was 49.6% and 62.5%, respectively.

Figure 1: Progression-free survival in patients the HR- deficient population - PRIMA (ITT)

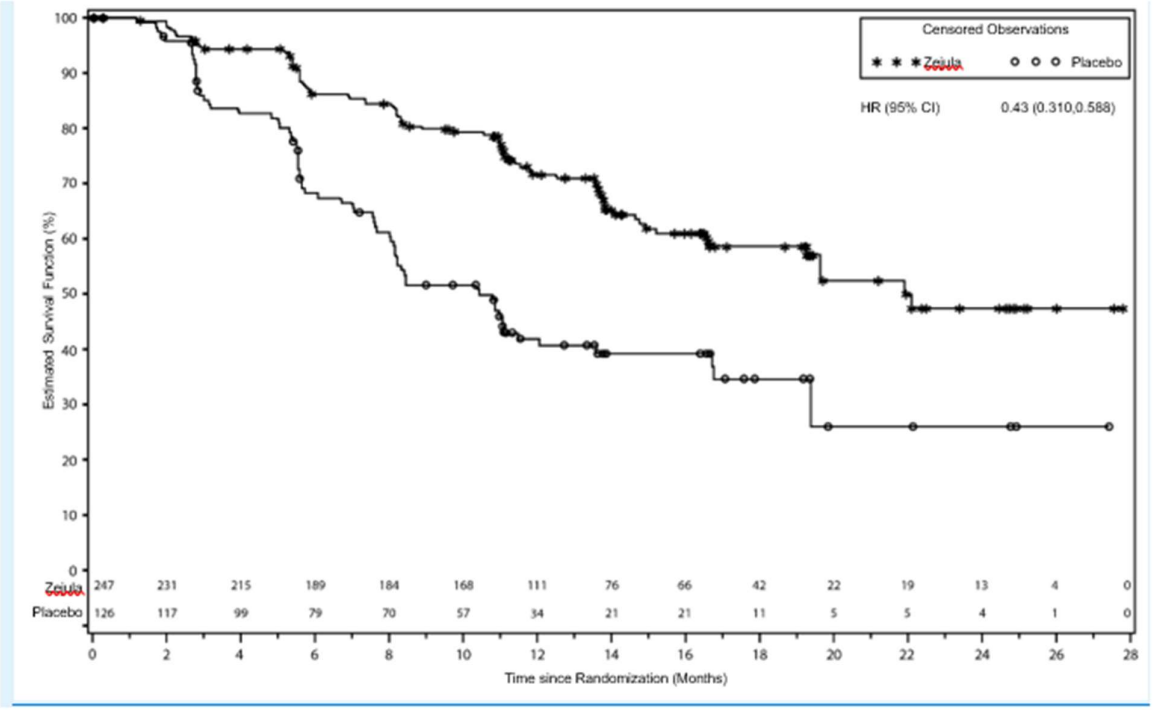
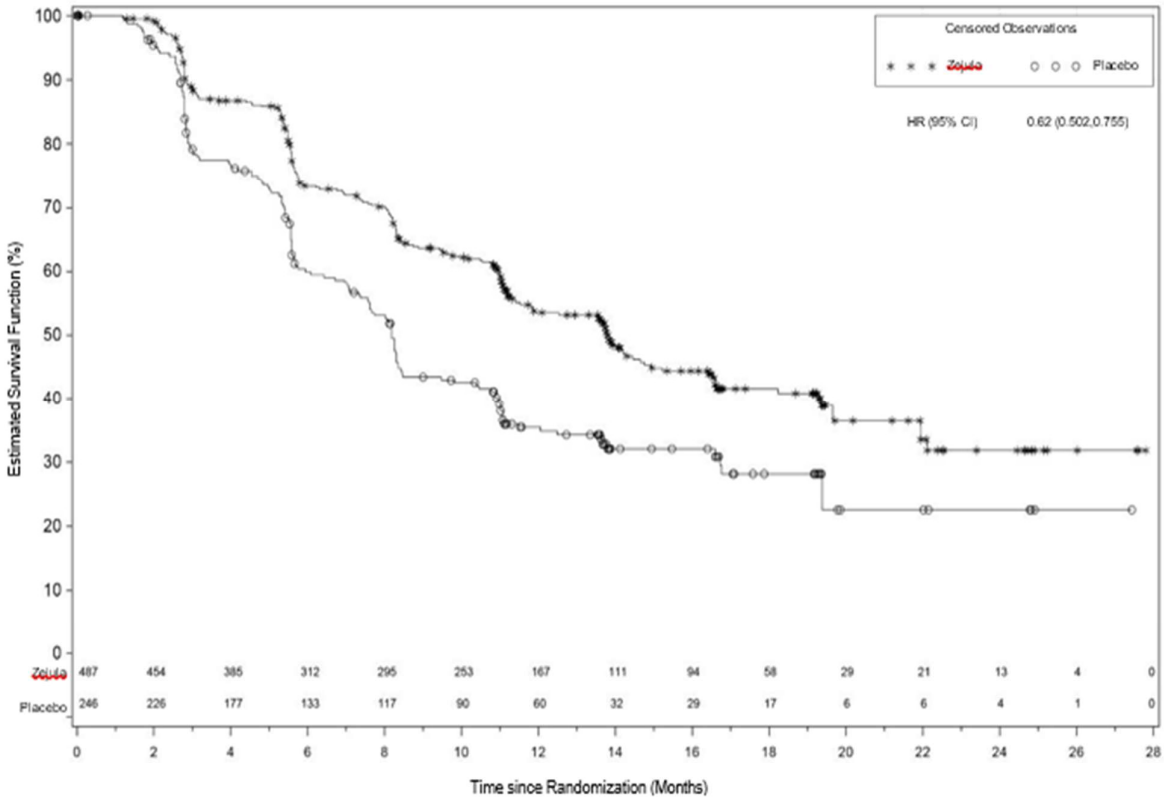


Figure 2: Progression-free survival in the overall population - PRIMA (ITT)



PFS subgroup analyses

Within the HR -deficient population, a PFS hazard ratio of 0.40 (95% CI: 0.27, 0.62) was observed in the subgroup of patients with *BRCA* mutation 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. The median PFS in the HR-proficient population (n = 249) was 8.1 months for patients randomised to Zejula compared with 5.4 months for placebo with a hazard ratio of 0.68 (95% CI: 0.49, 0.94).

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 PFS 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.

OS subgroup analyses

In the subgroup of HR-deficient patients with *BRCA* mutation ovarian cancer (n = 223), an OS hazard ratio of 0.94 (95% CI: 0.63, 1.41) was observed. In the subgroup of HR-deficient patients without a *BRCA* mutation (n = 149), a hazard ratio of 0.97 (95% CI: 0.62, 1.53) was observed.

The median OS in the HR-proficient population (n = 249) was 36.6 months for patients randomised to Zejula compared to 32.2 months in the placebo arm, with a hazard ratio of 0.93 (95% CI: 0.69, 1.26).

Platinum-sensitive 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 PARPi therapy, including Zejula. Eligible patients were assigned to one of two cohorts based on the results of a germline *BRCA* (g*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 tumour *BRCA* (t*BRCA*) 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 daily 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 (PFS) 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. Overall survival (OS) analyses were secondary outcome measures.

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

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 as well as in the overall non-g*BRCA*mut cohort. 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).

Table 6: Summary of primary objective outcomes in the NOVA study

	g*BRCA*mut cohort		**Non-g*BRCA*mut cohort**	
	Zejula(N = 138)	**Placebo (N = 65)**	**Zejula(N = 234)**	**Placebo (N = 116)**
PFS median (95% CI)	21.0 (12.9, NE)	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 (Zejula:placebo) (95% CI)	0.27 (0.173, 0.410)		0.45 (0.338, 0.607)	

PFS = progression-free survival; CI = confidence interval; NE = not evaluable.

Figure 3: **Progression-free survival in the g*BRCA*mut cohort based on IRC assessment - NOVA (ITT)**

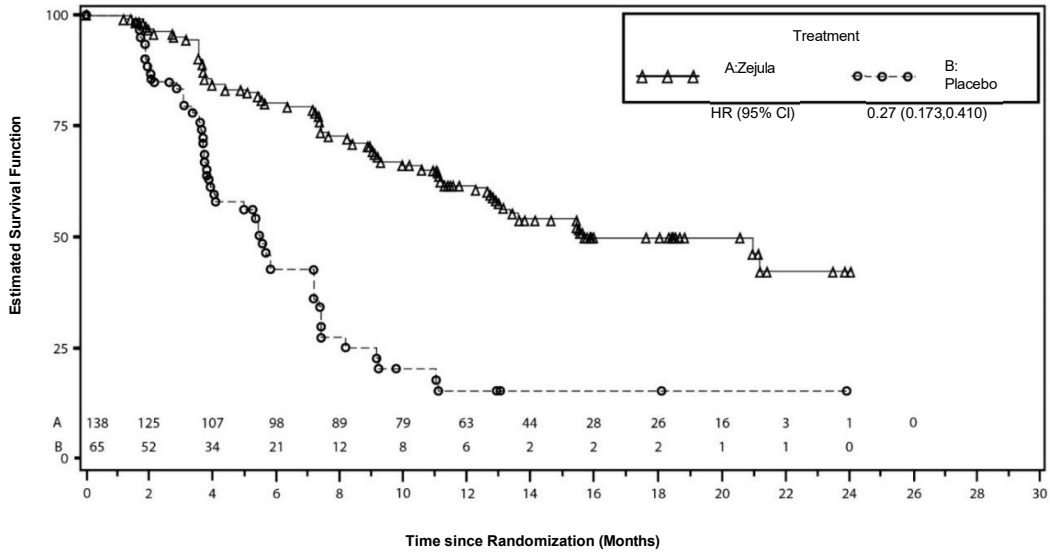
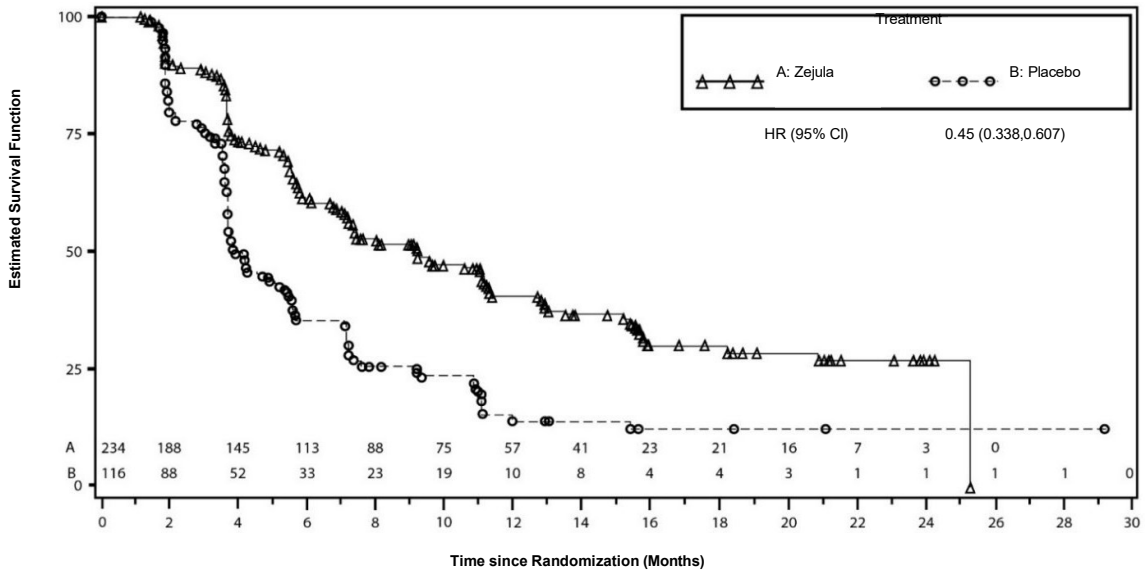


Figure 4: **Progression-free survival in the non-g*BRCA*mut cohort /overall based on IRC assessment – NOVA (ITT)**



Secondary efficacy endpoints in NOVA

At the final analysis, the median PFS2 in the g*BRCA*mut cohort was 29.9 months for patients treated with niraparib compared to 22.7 months for patients on placebo (HR = 0.70; 95% CI: 0.50, 0.97). The median PFS2 in the non-g*BRCA*mut cohort was 19.5 months for patients treated with niraparib compared to 16.1 months for patients on placebo (HR = 0.80; 95% CI: 0.63, 1.02).

At the final analysis of overall survival, the median OS in the g*BRCA*mut cohort (n = 203) was 40.9 months for patients treated with niraparib compared with 38.1 months for patients on placebo (HR = 0.85; 95% CI: 0.61, 1.20). The cohort maturity for the g*BRCA*mut cohort was 76%. The median

OS in the non-*gBRCA*mut cohort (n = 350) was 31.0 months for patients treated with niraparib compared with 34.8 months for patients on placebo (HR = 1.06; 95% CI: 0.81, 1.37). The cohort maturity for the non-g*BRCA*mut cohort was 79%.

Patient reported outcomes

Patient-reported outcome 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).

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 within 3 to 5 hours (ranged 508-875 ng/mL across studies). 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 33.8%.

Following a high-fat meal in patients with solid tumours, the C_{max} and AUC_{inf} of niraparib tablets increased by 11% and 28%, respectively, as compared with fasting conditions (see section 4.2).

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%), mainly with serum albumin. In a population pharmacokinetic analysis of niraparib, the apparent volume of distribution (V_d/F) was 1,206 L (based on a 70 kg patient) in cancer patients (CV 18.4%), 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 44 to 54 hours (approximately 2 days) across studies. In a population pharmacokinetic analysis, the apparent total clearance (CL/F) of niraparib was 15.9 L/h in cancer patients (CV 24.0%).

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%) of the dose. In pooled samples collected over 6 days, 40% 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.

In vitro studies

Niraparib is an inducer of CYP1A2 *in vitro* (see section 4.5).

Niraparib is a substrate of P-gp and BCRP. However, due to niraparib's high permeability and bioavailability, the risk of clinically relevant interactions with medicinal products that inhibit these transporters is unlikely.

Niraparib is an inhibitor of P-gp, BCRP, MATE1/2K and organic cation transporter 1 (OCT1) *in vitro* (see section 4.5).

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 . 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, 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.

Age (range 26 to 91 years) was not a significant factor on niraparib clearance or volume of distribution in the population pharmacokinetic analysis.

There are 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
Microcrystalline cellulose
Lactose monohydrate
Silicone dioxide
Povidone
Crospovidone
Magnesium stearate

Tablet coat
Polyvinyl alcohol
Titanium dioxide
Polyethylene glycol
Talc
Ferrosoferric oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

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 and 56 film-coated tablets, or OPA/aluminium/PVC/aluminium/vinyl/acrylic/paper child-resistant blisters in cartons of 84 and 56 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. MANUFACTURER

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

8. LICENSE HOLDER

Medison Pharma Ltd.
10 Hashiloach St.,
Israel

9. REGISTRATION NUMBER

176-54-37507-99

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