For the use only of Oncologists

ZEJULA

Niraparib Tablets 100mg

1. GENERIC NAME

Niraparib Tablets 100 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZEJULA 100 mg tablet is immediate release, gray, oval-shaped, film-coated tablet, debossed with "100" on one side and "Zejula" on the other side.

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

Colours: Ferrosoferric Oxide USP-NF and Titanium Dioxide IP

3. DOSAGE FORM AND STRENGTH

Film-coated tablets

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

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

ZEJULA is indicated:

- as monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO stage-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

Posology

First-line ovarian cancer maintenance treatment

The recommended starting dose of *ZEJULA* is 200 mg 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 taken once daily.

Recurrent ovarian cancer maintenance treatment

The dose is 300 mg once daily. For patients who weigh < 77 kg or have baseline platelet count < 150,000/μL, the recommended starting dose of *ZEJULA* is 200 mg taken orally once daily. 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. Treatment should be continued until disease progression or unacceptable toxicity.

Missing dose

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

Dose adjustments for adverse reactions

Recommendations for dose modifications for adverse reactions are provided in Tables 1, 2 and 3.

Table 1: Recommended dose modifications for adverse reactions

Starting dose	200 mg/day	300 mg/day
First dose reduction	100 mg/day	200 mg/day
Second dose reduction	Discontinue medication.	100 mg/day[a]

[a]If further dose reduction below 100 mg/day is required, discontinue *ZEJULA*.

Table 2: Dose modifications for non-haematological adverse reactions

Non-haematological CTCAE[a] ≥ Grade 3 treatment-related adverse reaction that persists despite treatment/prophylaxis[b]	*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.

a. CTCAE=Common Terminology Criteria for Adverse Events

b. Prophylaxis includes, but is not limited to, medications to prevent nausea, vomiting, diarrhoea, constipation, headache, back pain, myalgia, arthralgia, insomnia, decreased appetite, or dry mouth.

Table 3: Dose modifications for haematological adverse reactions

Haematological 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 Special Warnings and Precautions for Use*). Based on individual laboratory values, weekly monitoring for the second month may be warranted.	
Haematological 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 once 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 once daily.
Confirmed diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML)	• Permanently discontinue *ZEJULA*.

Method of Administration

Swallow tablets whole with water. Do not chew or crush tablets. *ZEJULA* can be taken without regard to meals. *(See section 5.3 Pharmacokinetic Properties)*

Children and Adolescents

The safety and efficacy of niraparib in children and adolescents below 18 years of age have not yet been established.

Elderly

No dose adjustment is necessary for elderly patients (≥ 65 years).

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 5.3 Pharmacokinetics*).

Hepatic impairment

No dose adjustment is needed in patients with mild hepatic impairment. For patients with moderate hepatic impairment, the recommended starting dose of *ZEJULA* is 200 mg once daily (*see Section 5.3 Pharmacokinetics*).

There are no data in patients with severe hepatic impairment; use with caution in these patients (*see Section 5.3 Pharmacokinetics*).

4.3 Contraindications

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

Breast-feeding (*see Section 4.6 Use in Special Populations*).

4.4 Special Warnings and Precautions for Use

Haematological adverse reactions

Haematological adverse reactions (thrombocytopenia, anaemia, neutropenia) have been reported in patients treated with *ZEJULA*. In the PRIMA study, patients eligible for *ZEJULA* therapy had the following baseline haematological parameters: absolute neutrophil count (ANC) ≥ 1,500 cells/μL; platelets ≥ 100,000 cells/μL and haemoglobin ≥ 10 g/dL prior to therapy. The overall incidence of Grade ≥3 thrombocytopenia, anaemia and neutropenia in clinical and/or laboratory findings were reported, respectively, in 39%, 31%, and 21% of patients receiving *ZEJULA*.

Discontinuation due to thrombocytopenia, anaemia, and neutropenia occurred, respectively, in 4%, 2%, and 2% of patients.

In patients who were administered a starting dose of *ZEJULA* based on baseline weight or platelet count, Grade ≥3 thrombocytopenia, anaemia and neutropenia were reported, respectively, in 22%, 23%, and 15% of patients receiving *ZEJULA*. Discontinuation due to thrombocytopenia, anaemia, and neutropenia occurred, respectively, in 3%, 3%, and 2% of patients.

In the NOVA study, patients eligible for *ZEJULA* therapy had the following baseline haematological parameters: absolute neutrophil count (ANC) ≥ 1,500 cells/μL; platelets ≥ 100,000 cells/μL and haemoglobin ≥ 9 g/dL prior to therapy.

Grade ≥3 thrombocytopenia, anaemia and neutropenia were reported, respectively, in 29%, 25%, and 20% of patients receiving *ZEJULA*. Discontinuation due to thrombocytopenia, anaemia, and neutropenia occurred, respectively, in 3%, 1%, and 2% of patients.

If a patient develops severe persistent haematological toxicity including pancytopenia that does not resolve within 28 days following interruption, *ZEJULA* should be discontinued.

Test complete blood counts weekly for the first month, followed by monthly monitoring for the next 10 months of treatment and periodically after this time to monitor for clinically significant changes in any haematological parameter during treatment *(see Section 4.2 Posology and Method of Administration)*.
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 Undesirable Effects)*.

Myelodysplastic syndrome/acute myeloid leukaemia
Myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML), including cases with fatal outcome, have been reported in patients who received *ZEJULA (see Section 4.8 Undesirable Effects)*.

In clinical trials, the duration of *ZEJULA* treatment in patients prior to developing MDS/AML varied from 1 month to > 4 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 suppression.

For suspected MDS/AML or prolonged haematological toxicities, the patient should be referred to a haematologist for further evaluation. If MDS/AML is confirmed, treatment with *ZEJULA* should be discontinued.

Hypertension, including hypertensive crisis
Hypertension, including hypertensive crisis, has been reported with the use of *ZEJULA (see Section 4.8 Undesirable Effects)*. Pre-existing hypertension should be adequately controlled before starting *ZEJULA* treatment. Blood pressure and heart rate should be monitored at least

weekly for the first two months, then monthly for the first year and periodically thereafter during treatment with *ZEJULA*.

Hypertension should be medically managed with antihypertensive medicinal products as well as adjustment of the *ZEJULA* dose *(see Section 4.2 Posology and Method of Administration)*, 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 Posology and Method of Administration)*. *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 rare reports (0.09% of clinical trial patients) of *ZEJULA* -treated patients developing signs and symptoms that are consistent with Posterior Reversible Encephalopathy Syndrome (PRES) *(see Section 4.8 Undesirable Effects)*. PRES is a rare neurologic disorder that can present with the following signs and 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 patients developing PRES, treatment of specific symptoms including control of hypertension is recommended, along with discontinuation of *ZEJULA*. 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 Use in Special Populations)*. A pregnancy test should be performed on all women of childbearing potential prior to treatment.

4.5 Drug Interactions

Pharmacodynamic interactions

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

The data on *ZEJULA* 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 niraparib on other medicinal products

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 *ZEJULA* is combined with active substances the metabolism of which is CYP3A4-dependent and, notably, those having a narrow therapeutic range (e.g. ciclosporin, tacrolimus, alfentanil, ergotamine, pimozide, quetiapine, and halofantrine).

Induction of CYPs (CYP1A2 and CYP3A4)

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

Inhibition of efflux transporters (P-gp, BCRP, BSEP, and MATE1/2)

Niraparib is not an inhibitor of BSEP. *In vitro*, niraparib inhibits P-gp very weakly and BCRP with an IC_{50} = 161 µM and 5.8 µM, respectively. Therefore, a clinically meaningful interaction related to an inhibition of these efflux transporters, although unlikely, cannot be excluded. Caution is then recommended when *ZEJULA* 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.

Inhibition of hepatic uptake transporters (OATP1B1, OATP1B3, and OCT1)

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

4.6 Use in Special Populations

Fertility

There are no clinical data on the effects of niraparib on fertility. A reversible reduction of spermatogenesis was observed in rats and dogs (*see Section 6 Nonclinical Properties*).

Pregnancy

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*.

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.

Lactation

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 Contraindications*).

4.7 Effects on Ability to Drive and Use Machines

ZEJULA may influence the ability to drive or use machines. Patients who take *ZEJULA* may experience asthenia, fatigue, difficulty concentrating, and dizziness. Patients who experience these symptoms should observe caution when driving or using machines.

4.8 Undesirable Effects

Clinical trial data

Tabulated list of adverse reactions

The following adverse reactions have been identified based on pooled data generated from the PRIMA and NOVA clinical trials in patients receiving *ZEJULA* monotherapy and during post-marketing experience (see Table 4).

Frequencies of occurrence of undesirable effects are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000);

very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 4: Tabulated list of adverse reactions[a]

System Organ Class	Frequency of all CTCAE[b] grades	Frequency of CTCAE[b] 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	**Common** Myelodysplastic syndrome/ acute myeloid leukaemia
Blood and lymphatic system disorders	**Very common** Thrombocytopenia, anaemia, neutropenia, leukopenia **Common** Neutropenic infection **Uncommon** Febrile neutropenia, pancytopenia, neutropenic sepsis	**Very common** Thrombocytopenia, anaemia, neutropenia **Common** Leukopenia **Uncommon** Neutropenic infection, febrile neutropenia, neutropenic sepsis, pancytopenia
Immune system disorders	**Common** Hypersensitivity (including anaphylaxis)	**Uncommon** Hypersensitivity (including anaphylaxis)
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 (memory impairment, concentration impairment)	**Uncommon** Insomnia, anxiety, depression, confusional state/disorientation, hallucination

System Organ Class	Frequency of all CTCAE[b] grades	Frequency of CTCAE[b] grade 3 or 4
	Uncommon Confusional state/disorientation, hallucination	
Nervous system disorders	**Very common** Headache, dizziness **Common** Dysgeusia **Rare** Posterior Reversible Encephalopathy Syndrome (PRES)	**Uncommon** Headache **Rare** Posterior Reversible Encephalopathy Syndrome (PRES)
Cardiac disorders	**Very common** Palpitations **Common** Tachycardia	
Vascular disorders	**Very common** Hypertension **Rare** Hypertensive crisis	**Common** Hypertension **Rare** Hypertensive crisis
Respiratory, thoracic and mediastinal disorders	**Very common** Dyspnoea, cough, nasopharyngitis **Common** Epistaxis **Uncommon** Non-infectious pneumonitis	**Uncommon** Dyspnoea, epistaxis, non-infectious pneumonitis
Gastrointestinal disorders	**Very common** Nausea, constipation, vomiting, abdominal pain, diarrhoea, dyspepsia **Common** Dry mouth, mucositis, stomatitis	**Common** Nausea, vomiting, abdominal pain **Uncommon** Diarrhoea, constipation, mucositis, stomatitis, dry mouth

System Organ Class	Frequency of all CTCAE[b] grades	Frequency of CTCAE[b] grade 3 or 4
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

[a.] Frequency based on niraparib clinical trial data not limited to pivotal NOVA or PRIMA monotherapy studies.

[b.] CTCAE=Common Terminology Criteria for Adverse Events version 4.02

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 300 mg (Table 4). *See Section 4.4 Special Warnings and Precautions for Use* for specific information regarding frequency of thrombocytopenia, anaemia and neutropenia.

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

Description of selected adverse reactions

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

In the clinical programme, haematological adverse reactions were managed with laboratory monitoring and dose modifications *(see Section 4.2 Posology and Method of Administration)*.

Thrombocytopenia

In the PRIMA study overall, 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 in the *ZEJULA* arm 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.

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 180,000 cells/µL, 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. 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 %) patients experienced bleeding with concurrent thrombocytopenia; all bleeding events concurrent with thrombocytopenia were Grade 1 or 2 in severity except for one event of Grade 3 petechiae and haematoma observed concurrently with a serious adverse event of pancytopenia. Thrombocytopenia occurred more commonly in patients whose baseline platelet count was less than 180,000 cells/µL. Approximately 76 % of patients with lower baseline platelets (< 180,000 cells/µL) 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 *ZEJULA*.

Anaemia

In the PRIMA study overall, 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 in the *ZEJULA* arm 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.

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 4.2 Posology and Method of Administration)*, and where appropriate with red blood cell transfusions. Discontinuation due to anaemia occurred in 1 % of patients.

Neutropenia

In the PRIMA study overall, 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 in the *ZEJULA* arm 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.

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 *ZEJULA* 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 5.6 years 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 of the patients had a history of previous cancer or of bone marrow suppression.

In the PRIMA study, the incidence of MDS/AML was 0.8% in patients receiving *ZEJULA* and 0.4% in patients received placebo.

In the NOVA study in patients with relapsed ovarian cancer who had received at least two prior lines of platinum chemotherapy, the overall incidence of MDS/AML was 3.5% in patients receiving *ZEJULA* and 1.7% in patients receiving placebo at a follow-up of 5.6 years. In

g*BRCA*mut and non-g*BRCA*mut cohorts, the incidence of MDS/AML was 6.6% 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 in the *ZEJULA* arm 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. Discontinuation due to hypertension occurred in < 1% of patients.

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 provide general supportive measures and should treat symptomatically.

5. PHARMACOLOGICAL PROPERTIES

5.1 Mechanism of Action

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.

5.2 Pharmacodynamic Properties

ATC code: L01XK02

Cardiac Electrophysiology

Niraparib demonstrated no clinically significant QTc prolongation in clinical trials. The potential for QTc prolongation with niraparib was evaluated in a randomised, placebo controlled trial in patients with ovarian cancer (NOVA). QTcF analysis was conducted on 58 subjects in total (53 on niraparib, 5 on placebo) derived from the main NOVA study and two sub-studies (open label Food Effect and open label QTc). No patient who underwent intensive ECG monitoring in the NOVA main or QTc sub-study had QTcF >480 ms or QTcF change from baseline >30 ms at any post-dose time point.

The study assessed the effects of niraparib on cardiac repolarisation following a single dose of niraparib (300 mg orally), and correlated changes from baseline in QTc with plasma concentrations of niraparib. In patients who underwent intensive ECG monitoring in the NOVA main or QTc sub-study, the largest increase observed in QTcF from baseline (ΔQTcF) was 4.3±8.8 ms (mean±SD) at 3 hours post-dose. The upper bound of the one-sided 95% CI of the ΔQTcF was 6.7 ms at 3 hours post-dose. The largest upper bound of the one-sided 95% CI of the mean change from baseline and placebo in QTcF interval (ΔΔQTcF) was 6.3 ms at 4 hours post-dose.

5.3 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 fold.

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

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

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. These changes in exposure were not clinically meaningful.

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 V_d/F was 1,074 L in cancer patients, indicating extensive tissue distribution of niraparib.

Metabolism

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

Elimination

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

Niraparib is eliminated primarily through the hepatobiliary and renal routes. Following oral administration of a single 300-mg dose of [14C]-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 patient populations

Children

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

Renal impairment

In the population pharmacokinetic analysis of data from clinical studies in patients, pre-existing mild (CLCr < 90 - ≥ 60 ml/min) and moderate (CLCr < 60 - ≥ 30 mL/min) renal impairment did not influence the clearance of niraparib. No patients with pre-existing severe

renal impairment or end-stage renal disease undergoing hemodialysis were identified in clinical studies *(see Section 4.2 Posology and Method of Administration).*

Hepatic impairment

In the population pharmacokinetic analysis of data from clinical studies in patients, pre-existing mild hepatic impairment 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. *ZEJULA* dose adjustment is recommended for patients with moderate hepatic impairment *(see Section 4.2 Posology and Method of Administration)*. 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 Section 4.2 Posology and Method of Administration)*.

Age, weight and race

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

5.4 Clinical studies

First-line ovarian cancer maintenance treatment

PRIMA was a double-blind, placebo-controlled trial in which patients (n=733) in complete or partial response to first-line platinum-based chemotherapy were randomized 2:1 to niraparib or matched placebo. The study included a starting dose of 200 mg or 300 mg depending on baseline body weight or platelet count. The study also included patients receiving a starting dose of 300 mg once daily, regardless of body weight or platelet count.

Patients were randomised post-completion of first-line platinum-based chemotherapy plus/minus surgery. Bevacizumab was allowed with chemotherapy. Patients who had neoadjuvant chemotherapy followed by interval debulking surgery could have visible residual or no residual disease. 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 vs negative or

not determined]. Testing for HRD was performed using the HRD test on tumour tissue obtained at the time of initial diagnosis.

Patients began treatment on Cycle 1/Day 1 (C1/D1) with *ZEJULA* 200 or 300 mg or matched placebo administered once daily in continuous 28-day cycles. Clinic visits occurred each cycle (4 weeks ± 3 days). In the PRIMA study, 52 % of patients had a dose interruption in Cycle 1, 9% of patients in Cycle 1 and 47% of patients in Cycle 2 had a dose reduction.

PRIMA was initiated with a starting dose of 300 mg once daily in continuous 28-day cycles (henceforth referred to as a fixed starting dose or FSD). Based on retrospective analyses of the NOVA trial, 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 *ZEJULA* 300 mg (3×100 mg capsules) or placebo (3 capsules) daily and patients with a baseline body weight <77 kg or baseline platelet count <150,000/μL were administered *ZEJULA* 200 mg (2×100 mg capsules) or placebo (2 capsules) daily (henceforth referred to as an individualized starting dose or ISD).

Overall, the median dose intensity in subjects who received *ZEJULA* was 181.3 mg/day and the median relative dose intensity was 63% in subjects who received *ZEJULA*. In patients who received the individualised starting dose, the median dose intensity was 178.6 mg/day and the median relative dose intensity was 66%. In patients who received the fixed starting dose, the median dose intensity was 181.8 mg/day and the median relative dose intensity was 61%.

The major efficacy outcome measure, progression-free survival (PFS), was 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 was 62 and ranged from 32 to 85 years among patients randomised to *ZEJULA* and 33 to 88 years among patients randomised to placebo. Eighty-nine percent of all patients were white.

Sixty-nine percent of patients randomised with *ZEJULA* and 71% of patients randomized 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. Sixty-seven percent of the patients received NACT. Sixty-nine percent of the patients had a complete response to the first-line platinum-based chemotherapy.

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

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

	HR deficient population		**Overall population**	
	niraparib (N=247)	**placebo (N=126)**	**niraparib (N=487)**	**placebo (N=246)**
PFS median months (95% CI)[b]	21.9 (19.3, NE)	10.4 (8.1, 12.1)	13.8 (11.5, 14.9)	8.2 (7.3, 8.5)
P value[b]	<0.0001		<0.0001	
Hazard ratio (HR)[c] (95% CI)	0.43 (0.31, 0.59)		0.62 (0.50, 0.76)	

[a] efficacy analysis was based on blinded independent central review (BICR).
[b] based on a stratified log-rank test
[c] based on a stratified Cox proportional hazards model
NE=Not Evaluable

In patients who were administered 200 or 300 mg dose of *ZEJULA* based on baseline weight or platelet count, comparable efficacy was observed with a hazard ratio of 0.39 (95% CI [0.22, 0.72]) in the HR deficient population, and with a hazard ratio of 0.69 (95% CI [0.48, 0.98]) in the overall population.

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

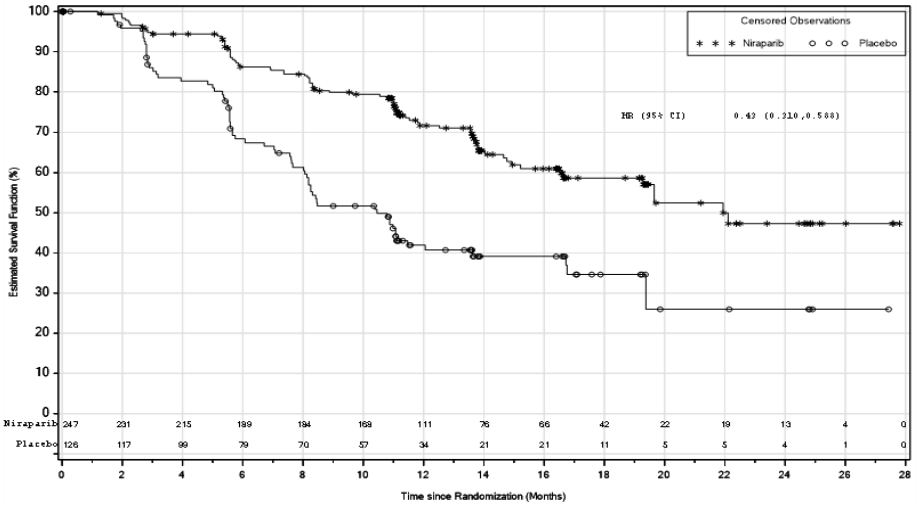
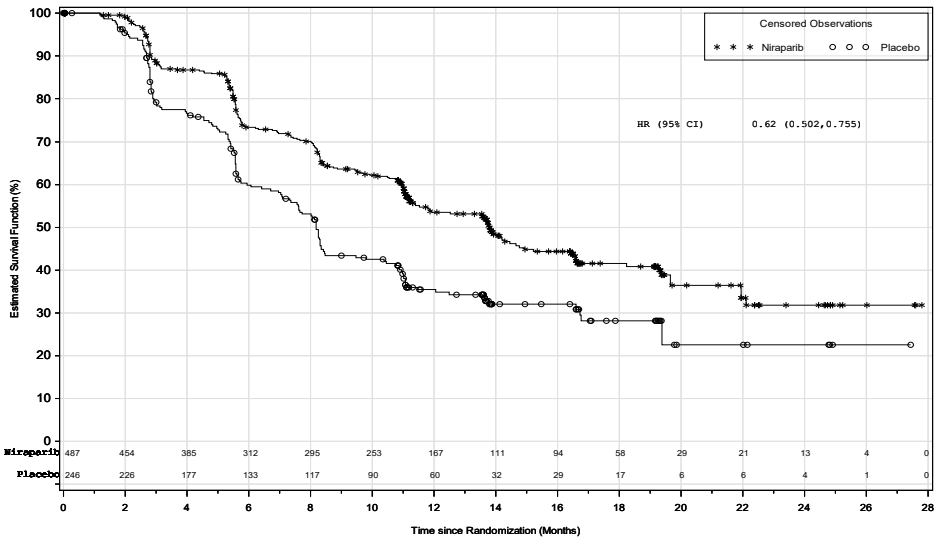


Figure 2: Progression-free survival in the overall population (ITT population, N=733)



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 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 (HRD negative) population (N= 249), a hazard ratio of 0.68 (95% CI [0.49, 0.94]) was observed.

At the time of the primary PFS analysis, the interim analysis of OS demonstrated a hazard ratio of 0.70 (95% CI [0.44, 1.11]) with an estimated survival at two years after randomisation of 84% for patients receiving *ZEJULA*, as compared to 77% for patients receiving placebo. For the HR deficient population, the hazard ratio was 0.61 (95% CI [0.265, 1.388]) and for the HR proficient population, the hazard ratio was 0.51 (95% CI [0.271, 0.973]).
No statistically significant differences were observed between *ZEJULA* and placebo in patient reported symptoms or HRQoL as measured by improvement and worsening rates in FOSI, EQ-5D-5L, and EORTC-QLQ.

Recurrent ovarian cancer maintenance treatment

The safety and efficacy of *ZEJULA* 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 *ZEJULA* 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 *ZEJULA* 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 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 *ZEJULA* 300 mg or matched placebo administered once 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 *ZEJULA* -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.

Demographics, baseline disease characteristics, and prior treatment history were generally well balanced between the *ZEJULA* 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 *ZEJULA* 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 *ZEJULA* arm than the placebo arm (14 and 7 cycles, respectively). More patients in the *ZEJULA* 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 *ZEJULA* arm than in the placebo arm (8 and 5 cycles, respectively). More patients in the *ZEJULA* 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 *ZEJULA* 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).

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 (months, 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) (95 % CI)	0.27 (0.173, 0.410)		0.45 (0.338, 0.607)	

CI = confidence interval.

Prior to unblinding of the study, tumours of patients were tested for the presence of HRD using an experimental HRD test, which evaluates three indirect measures of tumour genome instability: loss of heterozygosity, telomeric allelic imbalance (TAI), and large-scale state transitions. In the HRDpos group, the hazard ratio was 0.38 (95% CI, 0.243, 0.586; $p < 0.0001$). In the HRDneg group, the hazard ratio was 0.58 (95% CI, 0.361, 0.922;

p = 0.0226). The experimental test was not able to discriminate which patients would or would not benefit from *ZEJULA* 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)

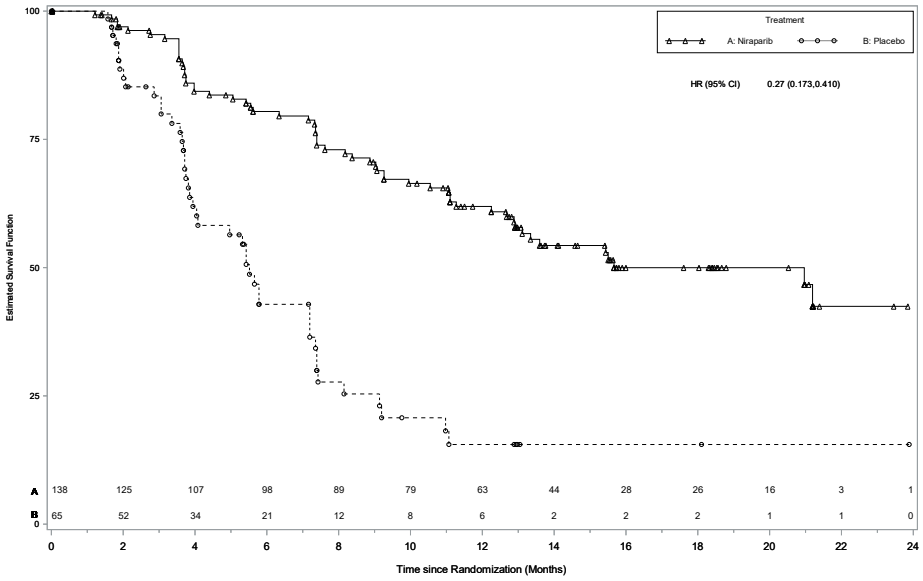
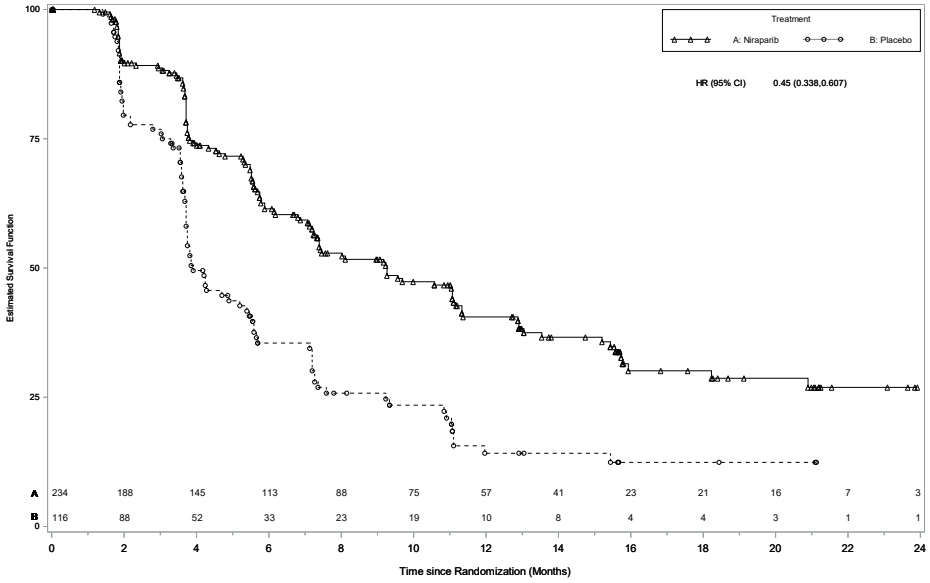


Figure 4: Kaplan-Meier plot for progression-free survival in the non-g*BRCA*mut cohort overall based on IRC assessment (ITT population, N = 350)



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

Data to support ISD in recurrent ovarian cancer maintenance treatment population

NORA was a randomised, double-blind, placebo-controlled clinical phase III study (n= 265) conducted in China to evaluate the efficacy and safety of niraparib as maintenance therapy in patients with platinum-sensitive recurrent ovarian cancer. After the first 16 patients were enrolled on a fixed starting dose of 300 mg, the study was amended to include an individualised starting dose of 200 mg or 300 mg depending on baseline body weight or platelet count (henceforth referred to as an individualised starting dose or ISD).

The PFS for all patients in the study (n=265) and for patients with an ISD (n=249) was 18.3 months in the niraparib group and 5.4 months in the placebo group. Comparable efficacy was observed with a hazard ratio of 0.32 (95% CI: 0.23, 0.46) for all patients in the study, and a hazard ratio of 0.30 (95% CI 0.21, 0.43) in the patients with an ISD.

Patients receiving a starting dose of niraparib 200 mg accounted for 87.5% (155 of 177 cases) of the pooled patients receiving niraparib, and had a median PFS consistent with the pooled niraparib group (18.3 months), indicating a therapeutic effect in the patients receiving an ISD regimen and no reduction in the therapeutic effect compared with the overall population of NORA or the patient population of NOVA study.

6. NONCLINICAL PROPERTIES

6.1 Animal Toxicology or Pharmacology

Carcinogenesis/mutagenesis

Carcinogenicity studies have not been conducted with niraparib.

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.

Animal toxicology and/or 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.

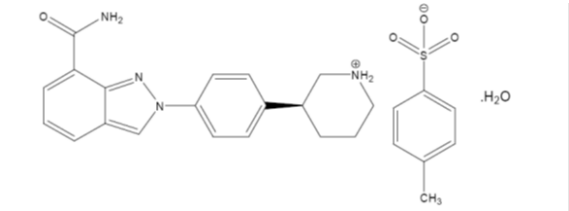
In repeat-dose oral toxicity studies, niraparib was administered daily for up to 3 months' duration in rats and dogs. The major primary target organ for toxicity in both species was the bone marrow, with associated changes in peripheral haematology parameters.

Additionally, decreased spermatogenesis was seen in both species. These findings occurred at exposure levels below those seen clinically and were largely reversible within 4 weeks of cessation of dosing.

7. DESCRIPTION

Niraparib is an orally available poly(ADP-ribose) polymerase (PARP) inhibitor.

The chemical name for niraparib tosylate monohydrate is 2-{4-[(3S)-piperidin-3-yl]phenyl}-2H-indazole 7-carboxamide 4-methylbenzenesulfonate hydrate (1:1:1). The molecular formula is $C_{26}H_{30}N_4O_5S$ and it has a molecular weight of 510.61 amu. The molecular structure is shown below:



Niraparib tosylate monohydrate is a white to off-white, non-hygroscopic crystalline solid. Niraparib solubility is pH independent below the pKa of 9.95, with an aqueous free base solubility of 0.7 mg/mL to 1.1 mg/mL across the physiological pH range.

List of Excipients

Tablet Core: Microcrystalline Cellulose, Lactose monohydrate, Povidone, Crospovidone, Silicon Dioxide, Magnesium Stearate

Tablet Coat: Opadry® II Gray

Ingredients of Opadry® II Gray are Polyvinyl alcohol, Titanium dioxide (E171), Polyethylene glycol, Talc, Ferrosoferric oxide (E172)

8. PHARMACEUTICAL PARTICULARS

8.1 Incompatibilities

Not applicable

8.2 Shelf Life

36 months

The expiry date is indicated on the label and packaging.

8.3 Packaging Information

ZEJULA Film-coated tablets are available in oPA/aluminium/PVC/aluminium/vinyl/acrylic blisters in cartons.

Pack sizes: 28, 56 and 84 tablets in a pack

Not all presentations are available in India.

8.4 Storage and Handling Instructions

Do not store above 30°C. Keep out of the sight and reach of children.

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

9. PATIENT COUNSELLING INFORMATION

Oncologists may counsel their patients (and/or their patients' caregiver as applicable) about the special warnings and precautions for use, drug interactions, undesirable effects, and any relevant contraindications of *ZEJULA*. Patients (and/or patients' caregiver) may also be informed about posology, method of administration and storage/handling information as applicable.

10. DETAILS OF MANUFACTURER

Manufactured by:

Catalent Greenville, Inc.

1240 Sugg Parkway

Greenville, North Carolina (NC) 27834

United States (USA)

Registered Office

GSK Pharma India Private Limited

1, Battery House,

Bhulabhai Desai Road, Mumbai 400026

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Import permission no. IMP/ND/25/2023 dated 1-May-2023

12. DATE OF REVISION

1-May-2023

Version: ZEJ/PI/IN/2023/02 dated 15 June 2023

Adapted from Niraparib GDS version 05 / IPI version 04 dated 15 June 2022