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## **ZEJULA**

### **Niraparib**

## **QUALITATIVE AND QUANTITATIVE COMPOSITION**

### **Film-coated tablet**

*ZEJULA* 100 mg tablet is gray, oval-shaped, film-coated tablet debossed with “100” on one side and “Zejula” on the other.

*ZEJULA* 200 mg tablet is blue, oval-shaped, film-coated tablet debossed with “200” on one side and “Zejula” on the other.

*ZEJULA* 300 mg tablet is green, oval-shaped, film-coated tablet debossed with “300” on one side and “Zejula” on the other.

Each film-coated tablet contains niraparib tosylate monohydrate equivalent to 100 mg, 200 mg or 300 mg niraparib.

## **CLINICAL INFORMATION**

### **Indications**

*ZEJULA* is indicated:

- as monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.
- as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy. The overall survival benefit in patients without germline BRCA mutation ovarian cancer has not been demonstrated (see *Clinical Studies* section).

### **Dosage and Administration**

### **Pharmaceutical Form**

Tablet.

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## 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  $\geq 77$  kg and have baseline platelet count  $\geq 150,000/\mu\text{L}$ , the recommended starting dose of *ZEJULA* is 300 mg taken once daily.

For the maintenance treatment of advanced ovarian cancer, patients should start treatment with *ZEJULA* no later than 12 weeks after their most recent platinum-containing regimen.

### *Recurrent ovarian cancer maintenance treatment*

The dose is 300 mg once daily.

#### *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 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.

For the maintenance treatment of recurrent ovarian cancer, patients should start treatment with *ZEJULA* no later than 8 weeks after their most recent platinum-containing regimen.

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.

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**

<i>Starting dose</i>	200 mg/day	300 mg/day
First dose reduction	100 mg/day	200 mg/day
Second dose reduction	Discontinue medication.	100 mg/day <sup>a</sup>

<sup>a</sup>If further dose reduction below 100 mg/day is required, discontinue *ZEJULA*.

**Table 2: Dose modifications for non-haematological adverse reactions**

Non-haematological CTCAE <sup>a</sup> $\geq$ Grade 3 treatment-related adverse reaction where prophylaxis is not considered feasible or adverse reaction persists despite treatment	First occurrence: <ul style="list-style-type: none"> <li>Withhold <i>ZEJULA</i> for a maximum of 28 days or until resolution of adverse reaction.</li> <li>Resume <i>ZEJULA</i> at a reduced dose level per Table 1.</li> </ul>
	Second occurrence: <ul style="list-style-type: none"> <li>Withhold <i>ZEJULA</i> for a maximum of 28 days or until resolution of adverse reaction.</li> <li>Resume <i>ZEJULA</i> at a reduced dose or discontinue per Table 1.</li> </ul>
CTCAE $\geq$ Grade 3 treatment-related adverse reaction lasting more than 28 days while patient is administered <i>ZEJULA</i> 100 mg/day	Discontinue treatment.

<sup>a</sup>CTCAE=Common Terminology Criteria for Adverse Events

**Table 3: Dose modifications for haematological adverse reactions**

Haematological adverse reactions have been observed during the treatment with <i>ZEJULA</i> 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 <i>Warnings and Precautions</i> ). Based on individual laboratory values, weekly monitoring for the second month may be warranted.	
Haematological adverse reaction requiring transfusion or haematopoietic growth factor support	<ul style="list-style-type: none"> <li>For patients with platelet count <math>\leq 10,000/\mu\text{L}</math>, 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.</li> <li>Resume <i>ZEJULA</i> at a reduced dose.</li> </ul>
Platelet count $< 100,000/\mu\text{L}$	First occurrence: <ul style="list-style-type: none"> <li>Withhold <i>ZEJULA</i> for a maximum of 28 days and monitor blood counts weekly until platelet</li> </ul>

	counts return to $\geq 100,000/\mu\text{L}$ . <ul style="list-style-type: none"> <li>Resume <i>ZEJULA</i> at same or reduced dose per Table 1 based on clinical evaluation.</li> <li>If platelet count is <math>&lt; 75,000/\mu\text{L}</math> at any time, resume at a reduced dose per Table 1.</li> </ul>
	Second occurrence: <ul style="list-style-type: none"> <li>Withhold <i>ZEJULA</i> for a maximum of 28 days and monitor blood counts weekly until platelet counts return to <math>\geq 100,000/\mu\text{L}</math>.</li> <li>Resume <i>ZEJULA</i> at a reduced dose per Table 1.</li> <li>Discontinue <i>ZEJULA</i> 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.</li> </ul>
Neutrophil $< 1,000/\mu\text{L}$ or Haemoglobin $< 8 \text{ g/dL}$	<ul style="list-style-type: none"> <li>Withhold <i>ZEJULA</i> for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to <math>\geq 1,500/\mu\text{L}</math> or haemoglobin returns to <math>\geq 9 \text{ g/dL}</math>.</li> <li>Resume <i>ZEJULA</i> at a reduced dose per Table 1.</li> <li>Discontinue <i>ZEJULA</i> 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.</li> </ul>
Confirmed diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML)	<ul style="list-style-type: none"> <li>Permanently discontinue <i>ZEJULA</i>.</li> </ul>

## Method of Administration

Swallow tablets whole with water. Do not chew or crush tablets.

*ZEJULA* can be taken without regard to meals (*see Pharmacokinetics*).

## 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 ( $\geq 65$  years). There are limited clinical data in patients aged 75 years or over.

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## 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 *Pharmacokinetics*).

## 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)  $\leq$ ULN or any AST and TB > 1.0x – 1.5x ULN). For patients with moderate hepatic impairment (any AST and TB > 1.5x – 3x 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 > 3x ULN); use with caution in these patients (see *Pharmacokinetics*).

## Contraindications

Hypersensitivity to the niraparib or to any of the excipients listed in Excipients.

Breast-feeding (see *Pregnancy and Lactation*).

## Warnings and Precautions

### Haematological adverse reactions

Haematological adverse reactions (thrombocytopenia, anaemia, neutropenia) have been reported in patients treated with *ZEJULA* (see *Adverse Reactions*).

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 *Posology*).

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

### 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 *Adverse Reactions*).

In clinical trials, the duration of *ZEJULA* treatment in patients prior to developing

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MDS/AML varied from 0.5 months to >4.9 years. The cases were typical of secondary, cancer therapy-related MDS/AML. All patients had received platinum-containing chemotherapy regimens and many had also received other DNA damaging agents and radiotherapy. Some of the patients had a history of bone marrow 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 *Adverse Reactions*). 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 *Posology*), 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 *Posology*). *ZEJULA* should be discontinued in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy.

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.

#### 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 *Adverse Reactions*). 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 *Pregnancy*). A pregnancy test should be performed on all women of childbearing potential prior to treatment.

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## 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 other medicinal products on niraparib*

##### *Niraparib as a substrate of CYPs (CYP1A2 and CYP3A4)*

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

##### *Niraparib as a substrate of efflux transporters (P-gp, BCRP, BSEP, MRP2, and MATE1/2)*

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

Niraparib is not a substrate of bile salt export pump (BSEP), or multidrug resistance-associated protein 2 (MRP2). The major primary metabolite M1 is not a substrate of P-gp, BCRP, BSEP, or MRP2. Niraparib is not a substrate of multidrug and toxin extrusion (MATE)-1 or 2, while M1 is a substrate of both.

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

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

##### *Niraparib as a substrate of renal uptake transporters (OAT1, OAT3, and OCT2)*

Neither niraparib nor M1 is a substrate of organic anion transporter 1 (OAT1), 3 (OAT3), and organic cation transporter 2 (OCT2). No dose adjustment for *ZEJULA* is required when administered concomitantly with medicinal products known to inhibit OAT1 (e.g.

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probenecid) or OAT3 (e.g. probenecid, diclofenac), or OCT2 uptake transporters (e.g. cimetidine, quinidine).

#### Effect of niraparib on other medicinal products

##### *Inhibition of CYPs (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4)*

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

Even though inhibition of CYP3A4 in the liver is not expected, the potential to inhibit CYP3A4 at the intestinal level has not been established at relevant niraparib concentrations. Therefore, caution is recommended when *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).

##### *Inhibition of UDP-glucuronosyltransferases (UGTs)*

Niraparib did not exhibit inhibitory effect against the UGT isoforms (UGT1A1, UGT1A4, UGT1A9, and UGT2B7) up to 200  $\mu\text{M}$  *in vitro*. Therefore, the potential for a clinically relevant inhibition of UGTs by niraparib is minimal.

##### *Induction of CYPs (CYP1A2 and CYP3A4)*

Neither niraparib nor M1 is a CYP3A4 inducer *in vitro*. *In vitro*, niraparib weakly induces CYP1A2 at high concentrations and the clinical relevance of this effect could not be completely ruled out. M1 is not a CYP1A2 inducer. Therefore, caution is recommended when *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  $\text{IC}_{50} = 161 \mu\text{M}$  and  $5.8 \mu\text{M}$ , 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  $\text{IC}_{50}$  of  $0.18 \mu\text{M}$  and  $\leq 0.14 \mu\text{M}$ , 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)*

Neither niraparib nor M1 is an inhibitor of organic anion transport polypeptide 1B1 (OATP1B1) or 1B3 (OATP1B3).



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

*Inhibition of renal uptake transporters (OAT1, OAT3, and OCT2)*

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

## **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*.

### **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 *Animal toxicology and/or pharmacology*).

### **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.

### **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 *Contraindications*).

## **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.

## **Adverse Reactions**

### **Clinical trial data**

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### 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 ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  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<sup>a</sup>**

<b>System Organ Class</b>	<b>Frequency of all CTCAE<sup>b</sup> grades</b>	<b>Frequency of CTCAE<sup>b</sup> grade 3 or 4</b>
Infections and infestations	<b>Very common</b> Urinary tract infection <b>Common</b> Bronchitis, conjunctivitis	<b>Uncommon</b> Urinary tract infection, bronchitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	<b>Common</b> Myelodysplastic syndrome/acute myeloid leukaemia	<b>Common</b> Myelodysplastic syndrome/acute myeloid leukaemia
Blood and lymphatic system disorders	<b>Very common</b> Thrombocytopenia, anaemia, neutropenia, leukopenia <b>Common</b> Neutropenic infection <b>Uncommon</b> Febrile neutropenia, pancytopenia, neutropenic sepsis	<b>Very common</b> Thrombocytopenia, anaemia, neutropenia <b>Common</b> Leukopenia <b>Uncommon</b> Neutropenic infection, febrile neutropenia, neutropenic sepsis, pancytopenia
Immune system disorders	<b>Common</b> Hypersensitivity (including anaphylaxis)	<b>Uncommon</b> Hypersensitivity (including anaphylaxis)
Metabolism and nutrition disorders	<b>Very common</b> Decreased appetite <b>Common</b> Hypokalemia	<b>Common</b> Hypokalemia <b>Uncommon</b> Decreased appetite
Psychiatric disorders	<b>Very common</b> Insomnia <b>Common</b> Anxiety, depression, cognitive impairment (memory impairment, concentration impairment) <b>Uncommon</b> Confusional state/disorientation, hallucination	<b>Uncommon</b> Insomnia, anxiety, depression, confusional state/disorientation, hallucination

System Organ Class	Frequency of all CTCAE <sup>b</sup> grades	Frequency of CTCAE <sup>b</sup> grade 3 or 4
Nervous system disorders	<b>Very common</b> Headache, dizziness <b>Common</b> Dysgeusia <b>Rare</b> Posterior Reversible Encephalopathy Syndrome (PRES)	<b>Uncommon</b> Headache <b>Rare</b> Posterior Reversible Encephalopathy Syndrome (PRES)
Cardiac disorders	<b>Very common</b> Palpitations <b>Common</b> Tachycardia	
Vascular disorders	<b>Very common</b> Hypertension <b>Rare</b> Hypertensive crisis	<b>Common</b> Hypertension <b>Rare</b> Hypertensive crisis
Respiratory, thoracic and mediastinal disorders	<b>Very common</b> Dyspnoea, cough, nasopharyngitis <b>Common</b> Epistaxis <b>Uncommon</b> Non-infectious pneumonitis	<b>Uncommon</b> Dyspnoea, epistaxis, non-infectious pneumonitis
Gastrointestinal disorders	<b>Very common</b> Nausea, constipation, vomiting, abdominal pain, diarrhoea, dyspepsia <b>Common</b> Dry mouth, mucositis, stomatitis	<b>Common</b> Nausea, vomiting, abdominal pain <b>Uncommon</b> Diarrhoea, constipation, mucositis, stomatitis, dry mouth
Skin and subcutaneous tissue disorders	<b>Common</b> Photosensitivity, rash	<b>Uncommon</b> Photosensitivity, rash
Musculoskeletal and connective tissue disorders	<b>Very common</b> Back pain, arthralgia <b>Common</b> Myalgia	<b>Uncommon</b> Back pain, arthralgia, myalgia
General disorders and administration site conditions	<b>Very common</b> Fatigue, asthenia <b>Common</b> Oedema peripheral	<b>Common</b> Fatigue, asthenia
Investigations	<b>Common</b> Gamma-glutamyl transferase increased, AST increased, blood creatinine increased, ALT increased, blood alkaline phosphatase increased, weight decreased	<b>Common</b> Gamma-glutamyl transferase increased, ALT increased <b>Uncommon</b> AST increased, blood alkaline phosphatase increased

<sup>a</sup>. Frequency based on niraparib clinical trial data not limited to pivotal NOVA or PRIMA monotherapy studies.

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<sup>b</sup>. 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 Warnings and Precautions 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 *Posology*).

In the PRIMA study, patients eligible for *ZEJULA* therapy had the following baseline haematological parameters: absolute neutrophil count (ANC)  $\geq 1,500$  cells/ $\mu$ L; platelets  $\geq 100,000$  cells/ $\mu$ L and haemoglobin  $\geq 10$  g/dL prior to therapy. The overall incidence of Grade  $\geq 3$  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 niraparib based on baseline weight or platelet count, Grade  $\geq 3$  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)  $\geq 1,500$  cells/ $\mu$ L; platelets  $\geq 100,000$  cells/ $\mu$ L and haemoglobin  $\geq 9$  g/dL prior to therapy. Haematological adverse reactions (thrombocytopenia, anaemia, neutropenia) have been reported in patients treated with *ZEJULA*.

Grade  $\geq 3$  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.

#### *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

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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/ $\mu$ L, thrombocytopenia of any grade and Grade 3/4 occurred in 76 % and 45 % of the patients, respectively. The median time to onset of thrombocytopenia regardless of grade and Grade 3/4 thrombocytopenia was 22 and 23 days, respectively. The rate of new incidences of thrombocytopenia after intensive dose modifications were performed during the first two months of treatment from Cycle 4 was 1.2 %. The median duration of thrombocytopenia events of any grade was 23 days, and the median duration of Grade 3/4 thrombocytopenia was 10 days. Patients treated with *ZEJULA* who develop thrombocytopenia might have an increased risk of haemorrhage. 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/ $\mu$ L. Approximately 76 % of patients with lower baseline platelets (< 180,000 cells/ $\mu$ L) who received *ZEJULA* experienced thrombocytopenia of any grade, and 45 % of the patients experienced Grade 3/4 thrombocytopenia. Pancytopenia has been observed in < 1 % of patients receiving *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 *Posology*), 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

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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 *gBRCAmut* 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 *gBRCAmut* 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 *gBRCAmut* and non-*gBRCAmut* 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.

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## 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.

## PHARMACOLOGICAL PROPERTIES

### Pharmacodynamics

#### ATC code

L01XK02

#### 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.

### Pharmacodynamic effects

#### Cardiac Electrophysiology

The potential for QTc prolongation with niraparib was evaluated in a randomized, placebo-controlled trial in patients with cancer (367 patients on niraparib and 179 patients on placebo). No large changes in the mean QTc interval (>20 ms) were detected in the trial following the treatment of niraparib 300 mg once daily.

### Pharmacokinetics

#### Absorption

Following a single-dose administration of niraparib 300 mg 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.

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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 niraparib 300 mg hard capsule.

Following a high-fat meal in patients with solid tumours, the  $C_{\max}$  and  $AUC_{\text{inf}}$  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  $C_{\max}$ ,  $AUC_{\text{last}}$  and  $AUC_{\infty}$  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 ( $t_{1/2}$ ) 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 [ $^{14}\text{C}$ ]-niraparib, on average 86.2 % (range 71 % to 91 %) of the dose was recovered in urine and faeces over 21 days. Radioactive recovery in the urine accounted for 47.5 % (range 33.4 % to 60.2 %) and in the faeces for 38.8 % (range 28.3 % to 47.0 %) of the dose. In pooled samples collected over 6 days, 40.0 % of the dose was recovered in the urine primarily as metabolites and 31.6 % of the dose was recovered in the faeces primarily as unchanged niraparib.

## **Special patient populations**

### **Children**



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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 ( $\text{CLCr} < 90$  to  $\geq 60$  mL/min) and moderate ( $\text{CLCr} < 60$  to  $\geq 30$  mL/min) renal impairment had mildly reduced niraparib clearance compared to individuals with normal renal function (7- 17 % higher exposure in mild and 17-38 % higher exposure in moderate renal impairment). The difference in exposure is not considered to warrant dose adjustment. No patients with pre-existing severe renal impairment or end-stage renal disease undergoing hemodialysis were identified in clinical studies (see *Posology*).

### **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  $\text{AUC}_{\text{inf}}$  in patients with moderate hepatic impairment (n=8) was 1.56 (90 % CI: 1.06 to 2.30) times the niraparib  $\text{AUC}_{\text{inf}}$  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 *Posology*). Moderate hepatic impairment did not have an effect on niraparib  $\text{C}_{\text{max}}$  or on niraparib protein binding.

The pharmacokinetics of niraparib have not been assessed in patients with severe hepatic impairment (see *Posology*).

### **Age, weight, 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.

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

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

## **Clinical Studies**

### **First-line ovarian cancer maintenance treatment**

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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 *ZEJULA* capsules or matched placebo. PRIMA was initiated with a starting dose of 300 mg QD in 475 patients (whereof 317 was randomised to the niraparib arm vs. 158 in the placebo arm) in continuous 28-day cycles. The starting dose in PRIMA was changed with Amendment 2 of the Protocol. From that point forward, patients with a baseline body weight  $\geq 77$  kg and baseline platelet count  $\geq 150,000/\mu\text{L}$  were administered *ZEJULA* 300 mg (3 $\times$ 100 mg capsules) (n=34) or placebo (3 capsules) daily (n=21) while patients with a baseline body weight  $< 77$  kg or baseline platelet count  $< 150,000/\mu\text{L}$  were administered *ZEJULA* 200 mg (2 $\times$ 100 mg capsules) (n=122) or placebo (2 capsules) daily (n=61).

Patients were randomised post completion of first-line platinum-based chemotherapy plus/minus surgery. Subjects were randomized within 12 weeks of the first day of the last cycle of chemotherapy. Subjects had  $\geq 6$  and  $\leq 9$  cycles of platinum-based therapy. Following interval debulking surgery subjects had  $\geq 2$  post-operative cycles of platinum-based therapy. Patients who had received bevacizumab with chemotherapy but could not receive bevacizumab as maintenance therapy were not excluded from the study. Patients could not have received prior PARP inhibitor therapy, including *ZEJULA*. 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 *ZEJULA* 200 or 300 mg or matched placebo administered QD in continuous 28-day cycles. Clinic visits occurred each cycle (4 weeks  $\pm$  3 days).

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

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

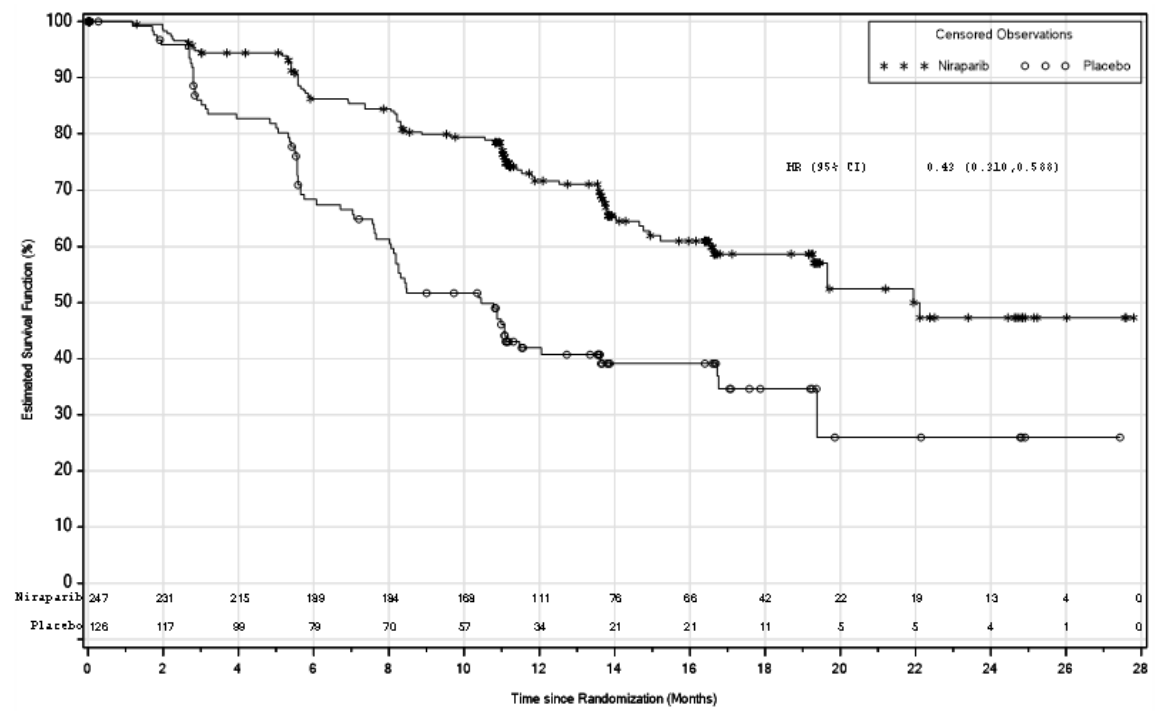
Secondary efficacy endpoints included PFS after the first subsequent therapy (PFS2) and OS (Table 5).

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

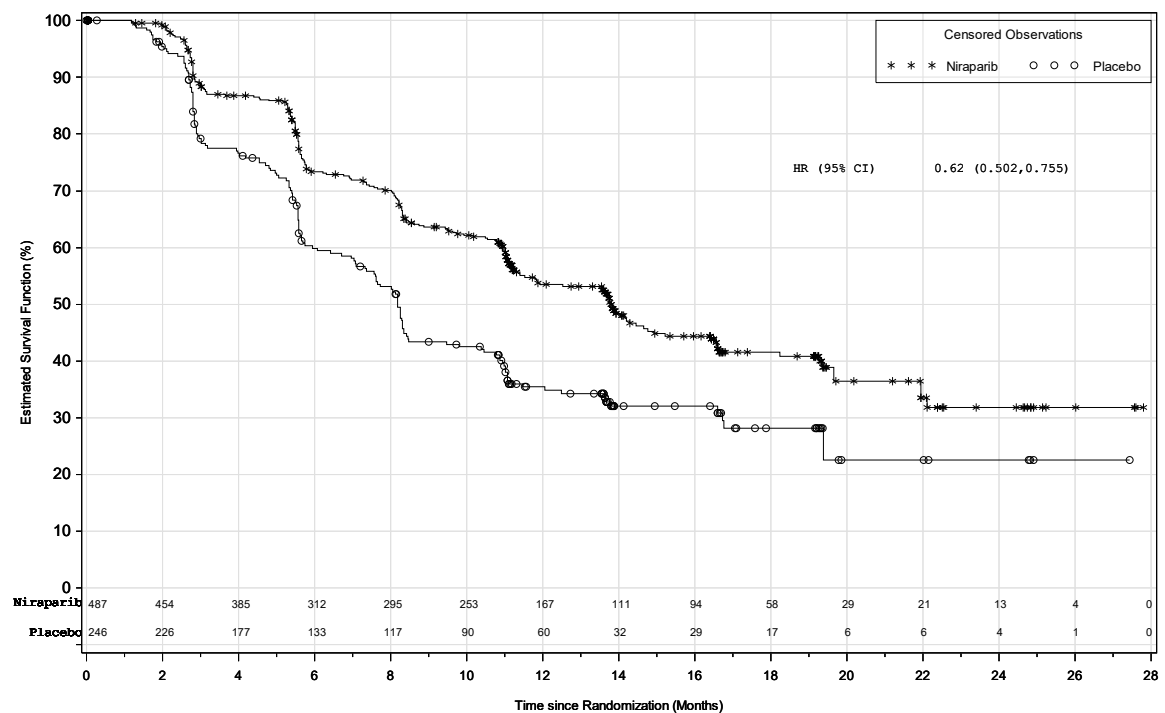
	HR deficient population		Overall population	
	niraparib (N=247)	placebo (N=126)	niraparib (N=487)	placebo (N=246)
<b>PFS median</b> (months; 95% CI)	21.9 (19.3, NE)	10.4 (8.1, 12.1)	13.8 (11.5, 14.9)	8.2 (7.3, 8.5)
Hazard ratio (HR) (95% CI)	0.43 (0.31, 0.59)		0.62 (0.50, 0.76)	
p-value	<0.0001		<0.0001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

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

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



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



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## Subgroup analyses

Within the HR deficient population, a hazard ratio of 0.40 (95 % CI: 0.27, 0.62) was observed in the subgroup of patients with *BRCA*mut ovarian cancer (n=223). In the subgroup of HR deficient patients without a *BRCA* mutation (n=150), a hazard ratio of 0.50 (95 % CI: 0.31, 0.83) was observed. In the HR proficient population (n=249), a hazard ratio of 0.68 (95 % CI: 0.49, 0.94) was observed.

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

## Recurrent ovarian cancer maintenance treatment

The safety and efficacy of *ZEJULA* capsule 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 (PARPi) therapy, including *ZEJULA*. Eligible patients were assigned to one of two cohorts based on the results of a germline *BRCA* (*gBRCA*) mutation test. Within each cohort, patients were randomised using a 2:1 allocation of *ZEJULA* 300 mg (3 x 100 mg capsules) or placebo (3 capsules) daily in continuous 28-day cycles. Patients were assigned to the *gBRCA*mut cohort based on blood samples for *gBRCA* analysis that were taken prior to randomisation. Testing for tumour *BRCA* (*tBRCA*) mutation and HRD was performed using the HRD test on tumour tissue obtained at the time of initial diagnosis or at the time of recurrence.

Randomisation within each cohort was stratified by time to progression after the penultimate platinum therapy before study enrolment (6 to < 12 months and ≥ 12 months); use 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.

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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*BRCAMut* cohort and the non-g*BRCAMut* cohort separately.

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

Demographics, baseline disease characteristics, and prior treatment history were generally well balanced between the *ZEJULA* and placebo arms in the g*BRCAMut* (n=203) and the non-g*BRCAMut* 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*BRCAMut* and non-g*BRCAMut* 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*BRCAMut* 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*BRCAMut* 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*BRCAMut* cohort (HR 0.27; 95 % CI: 0.173, 0.410;  $p < 0.0001$ ) as well as in the overall non-g*BRCAMut* 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*BRCAMut* cohort and the overall non-g*BRCAMut* cohort). A sensitivity analysis of investigator PFS showed the following results for the g*BRCAMut* cohort: HR 0.27 (95 % CI\*, 0.182, 0.401;  $p < 0.0001$ ); median PFS 14.8 months (95 % CI\*, 12.0, 16.6) for niraparib and median PFS 5.5 months (95 % CI\*, 4.9, 7.2) for placebo, and for the non-g*BRCAMut* cohort: HR 0.53 (95 % CI\*, 0.405, 0.683;  $p < 0.0001$ ); median PFS 8.7 months (95 % CI\*, 7.3, 10.0) for niraparib and median PFS 4.3 months (95 % CI\*, 3.7, 5.5) for placebo.

Table 6 shows the results for the secondary endpoints for time to first subsequent treatment (TFST), PFS after the first subsequent therapy (PFS2), and overall survival (OS) for the gBRCAmut cohort and the overall non-gBRCAmut cohort. The final OS analysis was confounded due to missing data and did not show improved OS in either the gBRCAmut cohort or the non-gBRCAmut cohort.

**Table 6: Efficacy results – NOVA**

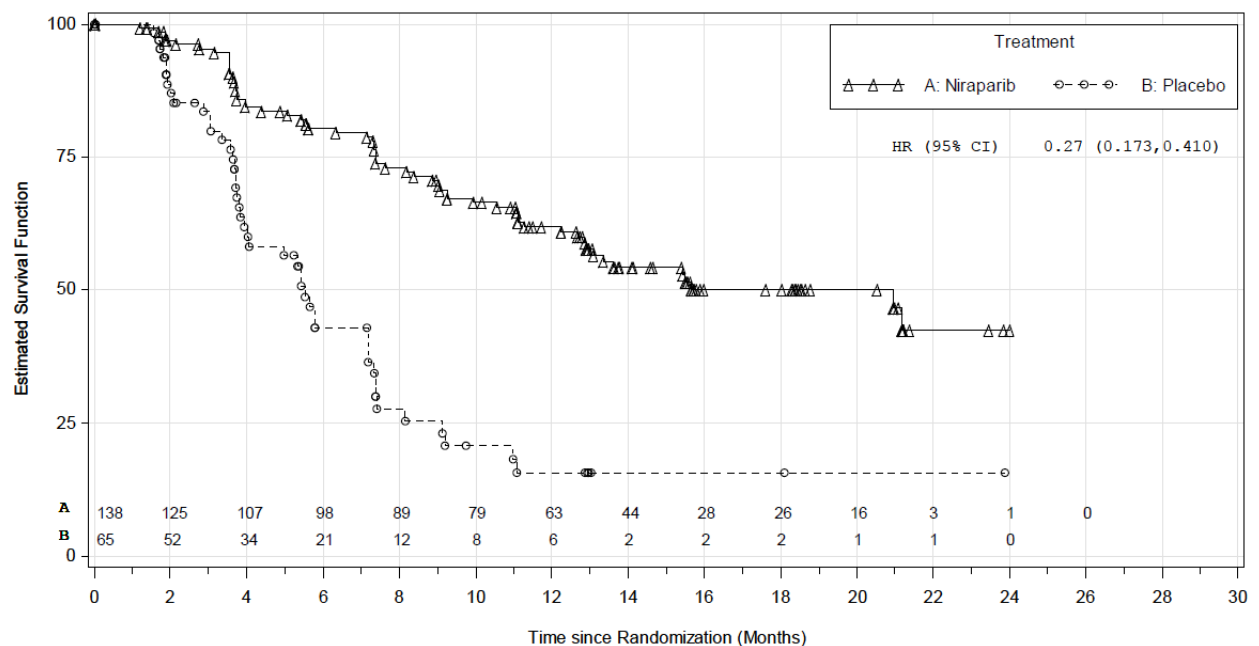
	gBRCAmut cohort		Non-gBRCAmut cohort	
	Niraparib (N = 138)	Placebo (N = 65)	Niraparib (N = 234)	Placebo (N = 116)
Primary Endpoint (determined by BICR)				
PFS median (months, 95% CI)	21.0 (12.9, NR)	5.5 (3.8, 7.2)	9.3 (7.2, 11.2)	3.9 (3.7, 5.5)
p-value	< 0.0001		< 0.0001	
Hazard ratio (HR) (95% CI)	0.27 (0.173, 0.410)		0.45 (0.338, 0.607)	
Secondary Endpoints**				
Time to first subsequent treatment median (months, 95% CI)	19.1 (14.6, 21.9)	8.6 (6.9, 12.2)	12.4 (10.9, 14.5)	7.4 (5.9, 8.7)
Hazard ratio (HR) (95% CI)	0.57 (0.41, 0.78)		0.58 (0.45, 0.74)	
Progression-free survival 2 median (months, 95% CI)	29.9 (24.8, 33.4)	22.7 (19.5, 25.9)	19.5 (17.1, 22.3)	16.1 (13.6, 22.8)
Hazard ratio (HR) (95% CI)	0.70 (0.50, 0.97)		0.80 (0.63, 1.02)	
Overall survival median (months, 95% CI)	40.9 (34.9, 52.9)	38.1 (27.6, 47.3)	31.0 (27.8, 35.6)	34.8 (27.9, 41.4)
Hazard ratio (HR) (95% CI)	0.85 (0.61, 1.20)		1.06 (0.81, 1.37)	

\*PFS=progression-free survival, CI=confidence interval, NE=Not Evaluable.

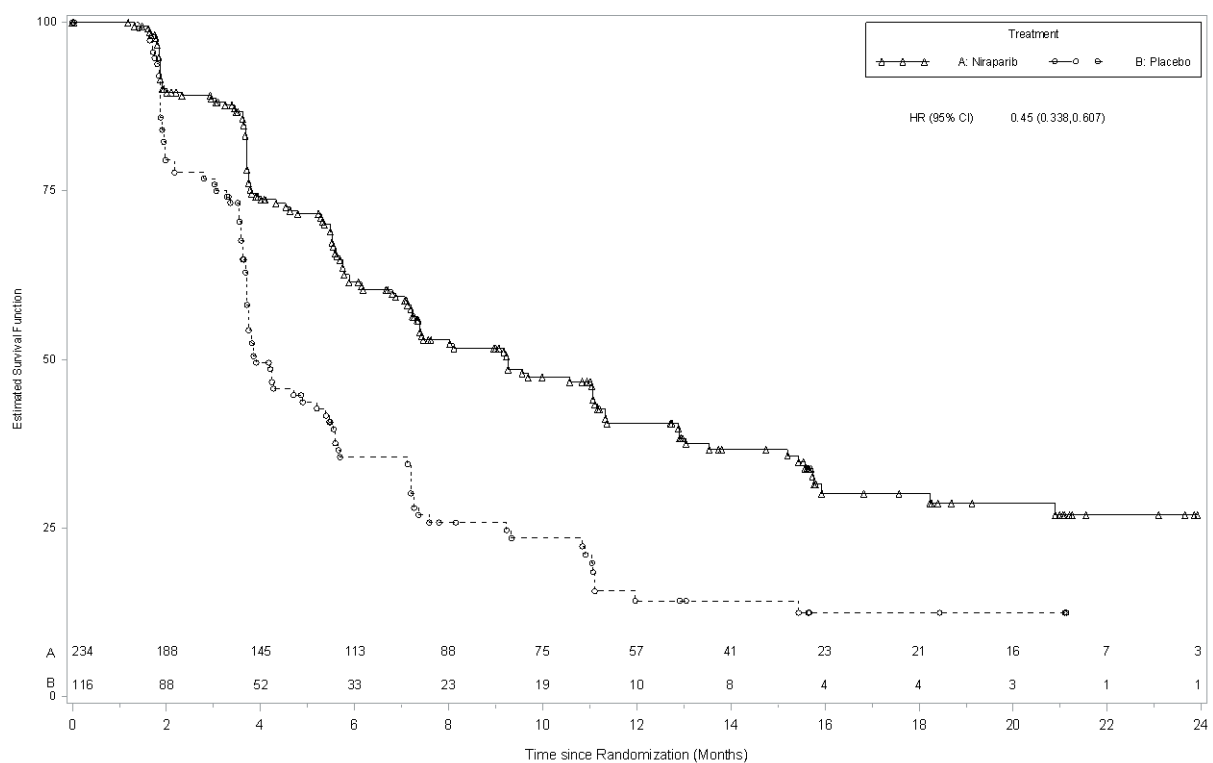
\*\* Due to the exploratory nature of the analyses and lack of alpha assignment, no definitive conclusions can be drawn from these data.

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

**Figure 3: Kaplan-Meier plot for progression-free survival in the *gBRCA*mut cohort based on IRC assessment – NOVA (ITT population, N = 203)**



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





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### *Secondary efficacy endpoints in NOVA*

At the final analysis, the median CFI in the gBRCAmut cohort was 20.0 months for patients treated with niraparib compared to 9.4 months for patients on placebo (HR=0.39; 95% CI: 0.27, 0.56). The median CFI in the non-gBRCAmut cohort was 13.4 months for patients treated with ZEPJULA compared to 8.7 months for patients on placebo (HR=0.56; 95% CI: 0.43, 0.73).

At the final analysis, the median TFST in the gBRCAmut cohort was 19.1 months for patients treated with ZEPJULA compared to 8.6 months for patients on placebo (HR=0.57; 95% CI: 0.41, 0.78). The median TFST in the non-gBRCAmut cohort was 12.4 months for patients treated with ZEPJULA compared to 7.4 months for patients on placebo (HR=0.58; 95% CI: 0.45, 0.74).

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

### *Overall survival analyses in NOVA*

Overall survival analyses were secondary outcome measures in the NOVA study. At the final analysis of overall survival, the median OS in the gBRCAmut cohort (n = 203) was 40.9 months for patients treated with ZEPJULA compared with 38.1 months for patients on placebo (HR=0.85; 95% CI: 0.61, 1.20). The cohort maturity for the gBRCAmut cohort was 76%.

The median OS in the non-gBRCAmut cohort (n = 350) was 31.0 months for patients treated with ZEPJULA compared with 34.8 months for patients on placebo (HR=1.06; 95% CI: 0.81, 1.37). The cohort maturity for the non-gBRCAmut cohort was 79%. The overall survival benefit in patients without germline BRCA mutation ovarian cancer has not been demonstrated.

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

## **Non-Clinical Information**

### **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

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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.

## **PHARMACEUTICAL INFORMATION**

### **List of Excipients**

#### Tablet Core

Crospovidone,  
Lactose monohydrate,  
Magnesium stearate,  
Microcrystalline cellulose,  
Povidone,  
Silicon dioxide.

#### Tablet Coat

Opadry II Gray (100 mg) – polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc and ferrousferic oxide

Opadry II Blue (200 mg) - polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc and FD&C Blue #2/Indigo carmine aluminium lake

Opadry II Green (300 mg) - polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, yellow iron oxide and FD&C Blue #1/Brilliant blue FCF aluminium lake

Purified water.

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## **Shelf Life**

The expiry date is indicated on the packaging.

## **Storage**

The storage conditions are detailed on the packaging.

## **Nature and Contents of Container**

*ZEJULA* film-coated tablets are available in OPA/aluminium/PVC/aluminium/vinyl/acrylic blister in cartons of 28, 56 and 84 tablets.

Not all presentations are available in every country.

## **Incompatibilities**

Not applicable.

## **Use and Handling**

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

## **Product Registrant**

GlaxoSmithKline Pte Ltd

23 Rochester Park, Singapore 139234

**Version number: GDS07/IPI06a(SI)**

**Date of issue: 14 November 2022**

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