ZEJULA
Niraparib tosylate

QUALITATIVE AND QUANTITATIVE COMPOSITION
ZEJULA 100 mg tablet is gray, oval-shaped (12 mm x 8 mm), 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.

Excipients with Known Effect
Each film-coated tablet contains 34.7 mg of lactose monohydrate (see section *Warnings and Precautions*). For the full list of excipients, see section *List of Excipients*.

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.

Dosage and Administration
Pharmaceutical form
Film coated tablets.

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

Posology
First-line ovarian cancer maintenance treatment
The recommended starting dose of *ZEJULA* is 200 mg (two 100-mg tablets), taken once daily. However, for those patients who weigh ≥77 kg and have baseline platelet count ≥150,000/µL, the recommended starting dose of *ZEJULA* is 300 mg (three 100-mg tablets), taken once daily (see section *Warnings and Precautions* and *Undesirable Effects*).

Recurrent ovarian cancer maintenance treatment
The dose is three 100 mg tablets once daily, equivalent to a total daily dose of 300 mg.

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

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

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

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

In general, it is recommended to first interrupt the treatment (but no longer than 28 consecutive days) to allow the patient to recover from the adverse reaction and then restart at the same dose. In the case that the adverse reaction recurs, it is recommended to interrupt the treatment and then resume at the lower dose. If adverse reactions persist beyond a 28-day dose interruption, it is recommended that *ZEJULA* be discontinued. If adverse reactions are not manageable with this strategy of dose interruption and reduction, it is recommended that *ZEJULA* be discontinued.

Table 1: Recommended Dose Modifications for Adverse Reactions

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

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

Table 2: Dose Modifications for Non-haematologic Adverse Reactions

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

*CTCAE=Common Terminology Criteria for Adverse Events

Table 3: Dose Modifications for Haematologic Adverse Reactions

Haematologic adverse reactions have been observed during the treatment with *ZEJULA* especially during the initial phase of the treatment. It is therefore recommended to monitor complete blood counts (CBCs) weekly during the first month of treatment and modify the dose as needed. After the first month, it is recommended to monitor CBCs monthly and periodically after this time (see section *Warnings and Precautions*). Based on individual laboratory values, weekly monitoring for the second month may be warranted.	
Haematologic adverse reaction requiring transfusion or haematopoietic growth factor support	• For patients with platelet count ≤10,000/µL, platelet transfusion should be considered. If there are other risk factors for bleeding such as co-administration of anticoagulation or antiplatelet medicinal products, consider interrupting these substances and/or transfusion at a higher platelet count. • Resume *ZEJULA* at a reduced dose.
Platelet count <100,000/µL	First occurrence: • Withhold *ZEJULA* for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100,000/µL. • Resume *ZEJULA* at same or reduced dose per Table 1 based on clinical evaluation. • If platelet count is <75,000/µL at any time, resume at a reduced dose per Table 1.

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

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

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

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

Hepatic impairment
No dose adjustment is needed in patients with mild hepatic impairment (either aspartate aminotransferase (AST) > upper limit of normal (ULN) and total bilirubin (TB) ≤ ULN or any AST and TB >1.0 x – 1,5 x ULN). For patients with moderate hepatic impairment (any AST and TB >1.5 x - 3 x ULN) the recommended starting dose of *ZEJULA* is 200 mg once daily. There are no data in patients with severe hepatic impairment (any AST and TB >3 x ULN); use with caution in these patients (see sections *Warnings and Precautions* and *Pharmacokinetic*).

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

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

Method of administration
ZEJULA is for oral use.

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

ZEJULA can be taken without regard to meals.

Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section *List of Excipients*.

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

Warnings and Precautions
Haematologic adverse reactions
Haematologic adverse reactions (thrombocytopenia, anaemia, neutropenia) have been reported in patients treated with *ZEJULA* (see section *Undesirable Effects*). Patients with lower body weight or lower baseline platelet count may be at increased risk of Grade 3+ thrombocytopenia (see section *Posology*). Testing complete blood counts weekly for the first month, followed by monthly monitoring for the next 10 months of treatment and periodically after this time is recommended to monitor for clinically significant changes in any haematologic parameter during treatment (see section *Posology*).

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

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

Myelodysplastic syndrome/acute myeloid leukaemia
Cases of myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), including cases with fatal outcome, have been observed in patients treated with *ZEJULA* monotherapy or combination therapy in clinical trials and post-marketing (see section *Undesirable Effects*).

In clinical trials, the duration of Zejula treatment in patients prior to developing MDS/AML varied from 0.5 months to >4.9 years. The cases were typical of secondary, cancer therapy-related MDS/AML. All patients had received platinum-containing chemotherapy regimens and many had also received other DNA damaging agents and radiotherapy. Some of the patients had a history of bone marrow suppression. In the NOVA trial, the incidence of MDS/AML was higher in the g*BRCA*mut cohort (7.4%) than in the non-g*BRCA*mut cohort (1.7%).

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

Hypertension, including hypertensive crisis
Hypertension, including hypertensive crisis, has been reported with the use of *ZEJULA* (see section *Undesirable Effects*). Pre-existing hypertension should be adequately controlled before starting *ZEJULA* treatment. Blood pressure should be monitored at least weekly for two months, monitored monthly afterwards for the first year and periodically thereafter during treatment with *ZEJULA*. Home blood pressure monitoring may be considered for appropriate patients with instruction to contact their health care provider in case of rise in blood pressure.

Hypertension should be medically managed with antihypertensive medicinal products as well as adjustment of the *ZEJULA* dose (see section *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 section *Posology*). *ZEJULA* should be discontinued in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy.

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

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

Pregnancy/contraception
ZEJULA should not be used during pregnancy or in women of childbearing potential not willing to use highly effective contraception during therapy and for 6 months after receiving the last dose of *ZEJULA* (see section *Pregnancy and Lactation*). A pregnancy test should be performed on all women of childbearing potential prior to treatment.

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

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

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

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

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

Niraparib as a substrate of efflux transporters (P-gp, BCRP, BSEP, MRP2, and MATE1/2)
Niraparib is a substrate of P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP). However, due to its high permeability and bioavailability, the risk of clinically relevant interactions with medicinal products that inhibit these transporters is unlikely. Therefore, no dose adjustment for *ZEJULA* is required when administered concomitantly with medicinal products known to inhibit P-gp (e.g. amiodarone, verapamil) or BCRP (e.g. osimertinib, velpatasvir, and eltrombopag).

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

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

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

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

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

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

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

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

Inhibition of efflux transporters (P-gp, BCRP, BSEP, MRP2, and MATE1/2)
Niraparib is not an inhibitor of BSEP or MRP2. *In vitro*, niraparib inhibits P-gp very weakly and BCRP with an IC_{50}=161 µM and 5.8 µM, respectively. Therefore, a clinically meaningful interaction related to an inhibition of these efflux transporters, although unlikely, cannot be excluded. Caution is then recommended when niraparib is combined with substrates of BCRP (irinotecan, rosuvastatin, simvastatin, atorvastatin, and methotrexate).

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

The major primary metabolite M1 does not appear to be an inhibitor of P-gp, BCRP, BSEP, MRP2 or MATE1/2.

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

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

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

All clinical studies have only been performed in adults.

Pregnancy and Lactation
Women of childbearing potential/Contraception in females
Women of childbearing potential should not become pregnant while on treatment and should not be pregnant at the beginning of treatment. A pregnancy test should be performed on all women of childbearing potential prior to treatment. Women of childbearing potential must use highly effective contraception during therapy and for 6 months after receiving the last dose of *ZEJULA*.

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

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

Fertility
There are no clinical data on fertility. A reversible reduction of spermatogenesis was observed in rats and dogs (see section *Non-Clinical Information*).

Effects on Ability to Drive and Use Machines
ZEJULA has moderate influence on the ability to drive or use machines. Patients who take *ZEJULA* may experience asthenia, fatigue, dizziness or difficulties concentrating. Patients who experience these symptoms should observe caution when driving or using machines.

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

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

Tabulated list of adverse reactions
The following adverse reactions have been identified based on clinical trials and post-marketing surveillance in patients receiving *ZEJULA* monotherapy (see Table 4). Frequencies of occurrence of undesirable effects are based on pooled adverse events data generated from the PRIMA and NOVA studies (fixed starting dose of 300 mg/day) where patient exposure is known and defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); and very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 4: Tabulated List of Adverse Reactions

System Organ Class	Frequency of All CTCAE* Grades	Frequency of CTCAE* Grade 3 or 4

Infections and infestations	**Very common** Urinary tract infection **Common** Bronchitis, conjunctivitis	**Uncommon** Urinary tract infection, bronchitis
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 **Uncommon** Pancytopenia, febrile neutropenia	**Very common** Thrombocytopenia, anaemia, neutropenia **Common** Leukopenia **Uncommon** Pancytopenia, febrile neutropenia
Immune system disorders	**Common** Hypersensitivity†	**Uncommon** Hypersensitivity
Metabolism and nutrition disorders	**Very common** Decreased appetite **Common** Hypokalemia	**Common** Hypokalemia **Uncommon** Decreased appetite
Psychiatric disorders	**Very common** Insomnia **Common** Anxiety, depression, cognitive impairment†† **Uncommon** Confusional state	**Uncommon** Insomnia, anxiety, depression, confusional state
Nervous system disorders	**Very common** Headache, dizziness **Common** Dysgeusia **Rare** Posterior Reversible Encephalopathy Syndrome (PRES)**	**Uncommon** Headache
Cardiac disorders	**Very common** Palpitations **Common** Tachycardia	
Vascular disorders	**Very common** Hypertension **Rare** Hypertensive crisis	**Common** Hypertension
Respiratory, thoracic and mediastinal disorders	**Very common**	**Uncommon**

	Dyspnoea, cough, nasopharyngitis **Common** Epistaxis **Uncommon** Pneumonitis	Dyspnoea, epistaxis, pneumonitis
Gastrointestinal disorders	**Very common** Nausea, constipation, vomiting, abdominal pain, diarrhoea, dyspepsia **Common** Dry mouth, abdominal distension, mucosal inflammation, stomatitis	**Common** Nausea, vomiting, abdominal pain **Uncommon** Diarrhoea, constipation, mucosal inflammation, stomatitis, dry mouth
Skin and subcutaneous tissue disorders	**Common** Photosensitivity, rash	**Uncommon** Photosensitivity, rash
Musculoskeletal and connective tissue disorders	**Very common** Back pain, arthralgia **Common** Myalgia	**Uncommon** Back pain, arthralgia, myalgia
General disorders and administration site conditions	**Very common** Fatigue, asthenia **Common** Oedema peripheral	**Common** Fatigue, asthenia
Investigations	**Common** Gamma-glutamyl transferase increased, AST increased, blood creatinine increased, ALT increased, blood alkaline phosphatase increased, weight decreased	**Common** Gamma-glutamyl transferase increased, ALT increased **Uncommon** AST increased, blood alkaline phosphatase increased

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

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

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

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

In the NOVA and PRIMA studies, patients eligible for *ZEJULA* therapy had the following baseline haematologic parameters: absolute neutrophil count (ANC) ≥1,500 cells/µL; platelets ≥100,000 cells/µL and haemoglobin ≥9 g/dL (NOVA) or ≥10 g/dL (PRIMA) prior to therapy. In the clinical programme, haematologic

adverse reactions were managed with laboratory monitoring and dose modifications (see section *Posology*).

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

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

In NOVA, approximately 60% of patients receiving *ZEJULA* experienced thrombocytopenia of any grade, and 34% of patients experienced Grade 3/4 thrombocytopenia. In patients with baseline platelet count less than 180 × 109/L, thrombocytopenia of any grade and Grade 3/4 occurred in 76% and 45% of the patients, respectively. The median time to onset of thrombocytopenia regardless of grade and Grade 3/4 thrombocytopenia was 22 and 23 days, respectively. The rate of new incidences of thrombocytopenia after intensive dose modifications were performed during the first two months of treatment from Cycle 4 was 1.2%. The median duration of thrombocytopenia events of any grade was 23 days, and the median duration of Grade 3/4 thrombocytopenia was 10 days. Patients treated with *ZEJULA* who develop thrombocytopenia might have an increased risk of haemorrhage. In the clinical programme, thrombocytopenia was managed with laboratory monitoring, dose modification and platelet transfusion where appropriate (see section *Posology*). Discontinuation due to thrombocytopenia events (thrombocytopenia and platelet count decreased) occurred in approximately 3% of the patients.

In the NOVA study, 48 of 367 (13%) of patients experienced bleeding with concurrent thrombocytopenia; all bleeding events concurrent with thrombocytopenia were Grade 1 or 2 in severity except for one event of Grade 3 petechiae and haematoma observed concurrently with a serious adverse reaction of pancytopenia. Thrombocytopenia occurred more commonly in patients whose baseline platelet count was less than 180 × 109/L. Approximately 76% of patients with lower baseline platelets (<180 × 109/L) who received *ZEJULA* experienced thrombocytopenia of any grade, and 45% of the patients experienced Grade 3/4 thrombocytopenia. Pancytopenia has been observed in <1% of patients receiving niraparib.

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

In NOVA, approximately 50% of patients experienced anaemia of any grade, and 25% experienced Grade 3/4 anaemia. The median time to onset of anaemia of any grade was 42 days, and 85 days for Grade 3/4 events. The median duration of anaemia of any grade was 63 days, and 8 days for Grade ¾ events. Anaemia of any grade might persist during *ZEJULA* treatment. In the clinical programme, anaemia was managed with laboratory monitoring, dose modification (see section *Posology*), and where appropriate with red blood cell transfusions. Discontinuation due to anaemia occurred in 1% of patients.

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

In NOVA, approximately 30% of patients receiving *ZEJULA* experienced neutropenia of any grade, and 20% of patients experienced Grade 3/4 neutropenia. The median time to onset of neutropenia of any grade was 27 days, and 29 days for Grade 3/4 events. The median duration of neutropenia of any grade was 26 days, and 13 days for Grade 3/4 events. In addition, Granulocyte-Colony Stimulating Factor (G-CSF) was administered to approximately 6% of patients treated with niraparib as concomitant therapy for neutropenia. Discontinuation due to neutropenia events occurred in 2% of patients.

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 g*BRCA*mut following 75 months survival follow-up. All patients had potential contributing factors for the development of MDS/AML, having received previous chemotherapy with platinum agents. Many had also received other DNA damaging agents and radiotherapy. The majority of reports were in g*BRCA*mut carriers. Some 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% 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 3.8% in patients receiving *ZEJULA* and 1.7% in patients receiving placebo at a follow-up of 75 months. In g*BRCA*mut and non-g*BRCA*mut cohorts, the incidence of MDS/AML was 7.4% and 1.7% in patients receiving *ZEJULA* and 3.1% and 0.9% in patients receiving placebo, respectively.

Hypertension
In PRIMA, Grade 3/4 hypertension occurred in 6% of *ZEJULA*-treated patients compared to 1% of placebo-treated patients with a median time from first dose to first onset of 50 days (range: 1 to 589 days) and with a median duration of 12 days (range: 1 to 61 days). 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 ¾ hypertension occurred in 8.2% of patients. Hypertension was readily managed with anti-hypertensive medicinal products. Discontinuation due to hypertension occurred in <1% of patients.

Paediatric population
No studies have been conducted in paediatric patients.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to GSK Indonesia via website https://gsk.public.reportum.com and Pusat Farmakovigilans/MESO Nasional Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor dan Zat Adiktif Badan Pengawas Obat dan Makanan.
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Website: https://e-meso.pom.go.id/ADR

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Pharmacotherapeutic group: antineoplastic agents, other antineoplastic agents, ATC code: L01XK02.

Mechanism of action and pharmacodynamic effects

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

Clinical efficacy and safety

First-line ovarian cancer maintenance treatment

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

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

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

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

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

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

Table 5: Efficacy Results – PRIMA (Determined by BICR)

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

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

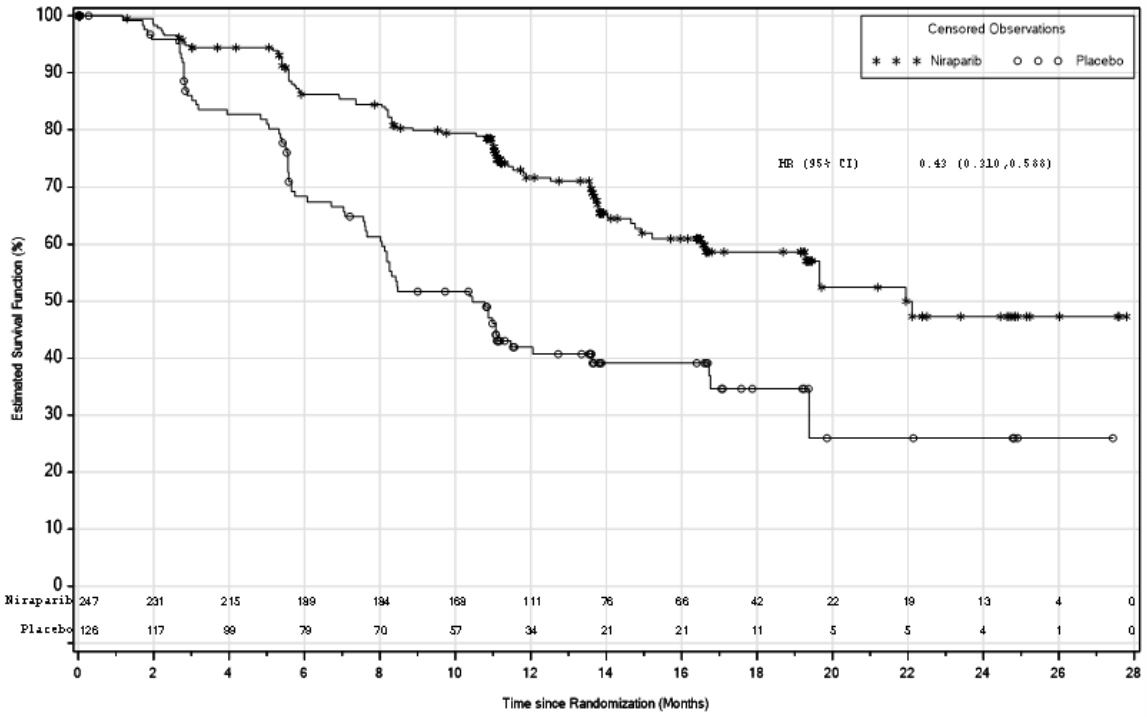
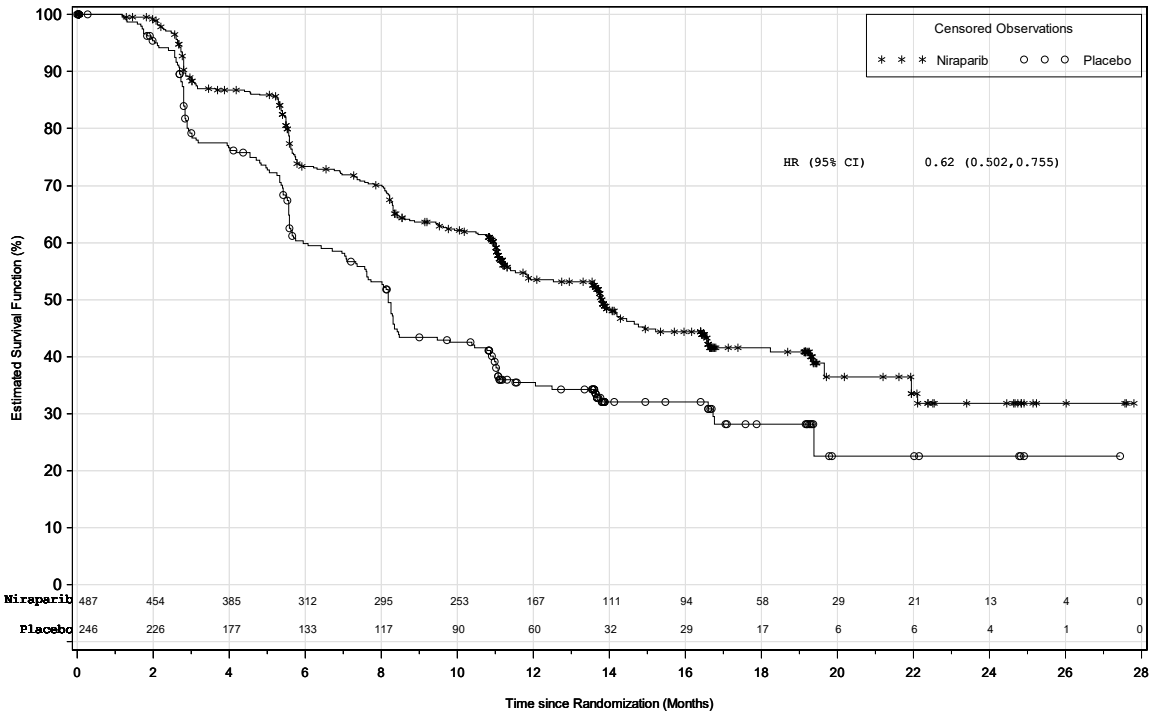


Figure 2: Progression-free Survival in The Overall Population - PRIMA (ITT Population, N=733)



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.

Platinum-sensitive recurrent ovarian cancer maintenance treatment
The safety and efficacy of niraparib as maintenance therapy was studied in a Phase 3 randomised, double-blind, placebo-controlled international trial (NOVA) in patients with relapsed predominantly high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who were platinum sensitive, defined by complete response (CR) or partial response (PR) for more than six months to their penultimate (next to last) platinum-based therapy. To be eligible for niraparib treatment, the patient should be in response (CR or PR) following completion of last platinum-based chemotherapy. The CA-125 levels should be normal (or a >90% decrease in CA-125 from baseline) following their last platinum treatment, and be stable for at least 7 days. Patients could not have received prior PARPi therapy, including *ZEJULA*. Eligible patients were assigned to one of two cohorts based on the results of a germline *BRCA* (g*BRCA*) mutation test. Within each cohort, patients were randomised using a 2:1 allocation of niraparib and placebo. Patients were assigned to the g*BRCA*mut cohort based on blood samples for g*BRCA* analysis that were taken prior to randomisation. Testing for tumour *BRCA* (t*BRCA*) mutation and HRD was performed using the HRD test on tumour tissue obtained at the time of initial diagnosis or at the time of recurrence.

Randomisation within each cohort was stratified by time to progression after the penultimate platinum therapy before study enrolment (6 to <12 months and ≥12 months); use or not of bevacizumab in conjunction with the penultimate or last platinum regimen; and best response during the most recent platinum regimen (complete response and partial response).

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

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

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

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

The primary efficacy analysis for PFS was determined by blinded central independent assessment and was prospectively defined and assessed for the g*BRCA*mut cohort and the non-g*BRCA*mut cohort separately. Overall survival (OS) analyses were secondary outcome measures.

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

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

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

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

The study met its primary objective of statistically significantly improved PFS for niraparib maintenance monotherapy compared with placebo in the g*BRCA*mut cohort as well as in the overall non-g*BRCA*mut cohort. Table 6 and Figures 3 and 4 show the results for the PFS primary endpoint for the primary efficacy populations (g*BRCA*mut cohort and the overall non-g*BRCA*mut cohort).

Table 6: Summary of Primary Objective Outcomes in The NOVA Study

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

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

Figure 3: Kaplan-Meier Plot for Progression-free Survival in The g*BRCA*mut Cohort Based on IRC Assessment - NOVA (ITT Population, N=203)

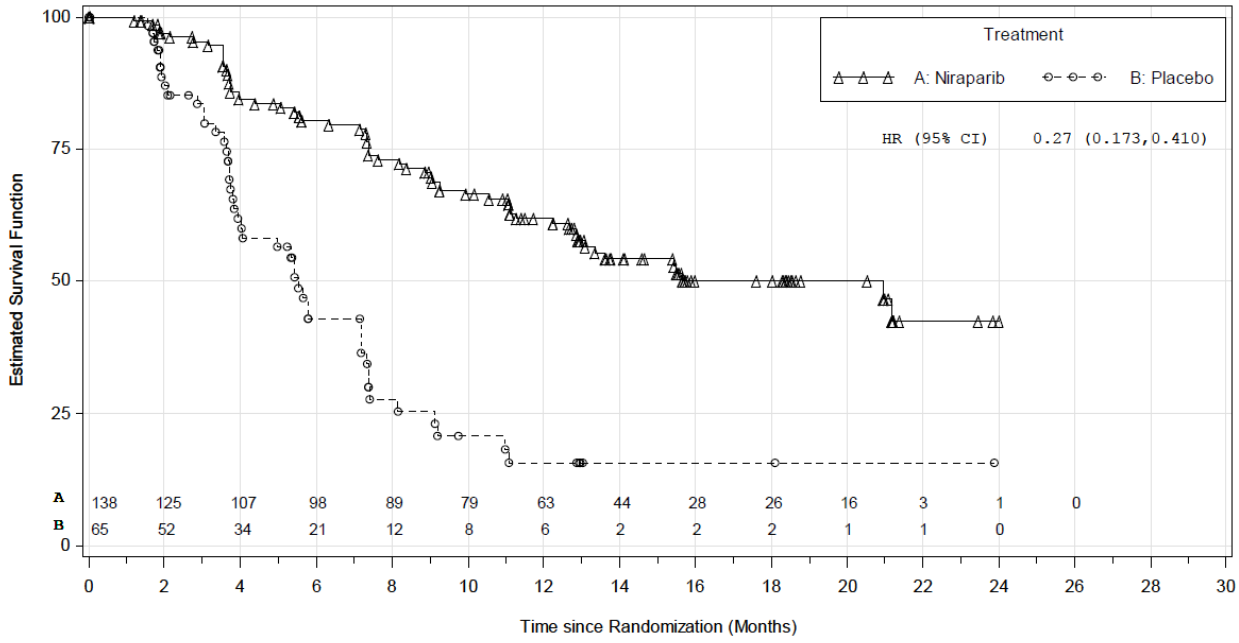
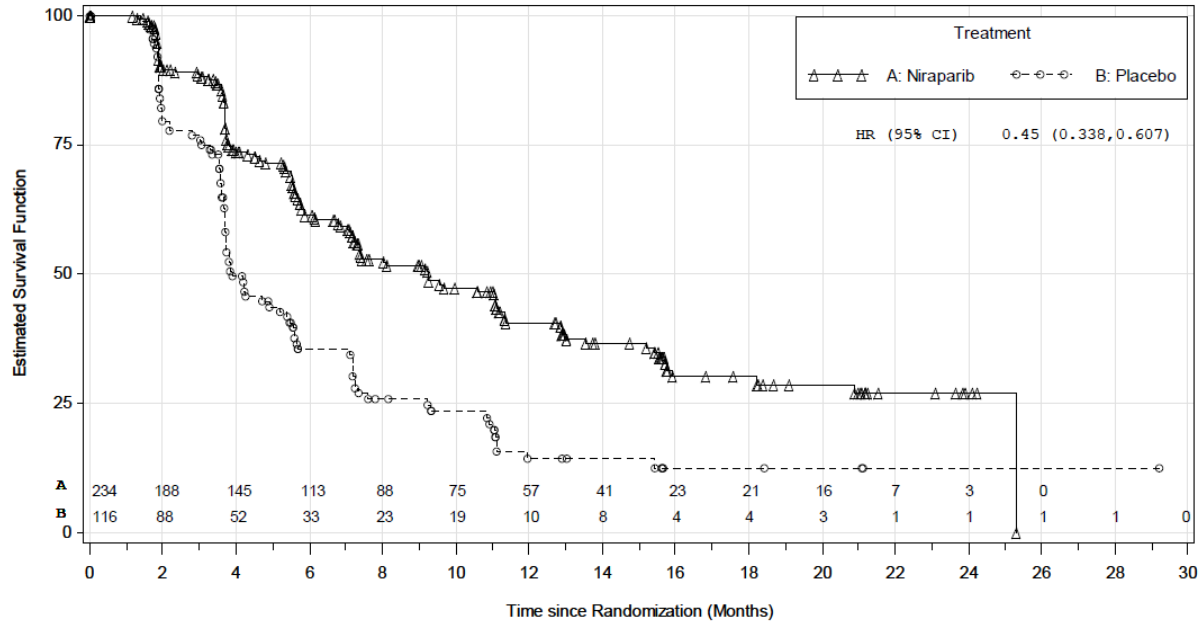


Figure 4: Kaplan-Meier Plot for Progression-free Survival in The Non-g*BRCA*mut Cohort /Overall Based on IRC Assessment – NOVA (ITT Population, N=350)



Secondary efficacy endpoints in NOVA

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

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

0.61, 1.20). The cohort maturity for the g*BRCA*mut cohort was 76%. The median the non-g*BRCA*mut cohort (n=350) was 31.0 months for patients treated with niraparib compared with 34.8 months for patients on placebo (HR=1.06; 95% CI: 0.81, 1.37). The cohort maturity for the non-g*BRCA*mut cohort was 79%.

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

Pharmacokinetics

Absorption

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

The systemic exposures (C_{max} and AUC) to niraparib increased in a dose-proportional manner when the dose of niraparib increased from 30 mg to 400 mg. The absolute bioavailability of niraparib is approximately 73%, indicating minimal first pass effect. In a population pharmacokinetic analysis of niraparib, the inter-individual variability in bioavailability was estimated to a coefficient of variation (CV) of 31%.

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.

Distribution

Niraparib was moderately protein bound in human plasma (83%), mainly with serum albumin. In a population pharmacokinetic analysis of niraparib, the apparent volume of distribution (V_d/F) was 1,311 L (based on a 70 kg patient) in cancer patients (CV 116%), indicating extensive tissue distribution of niraparib.

Biotransformation

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

Elimination

Following a single oral 300-mg dose of niraparib, the mean terminal half-life ($t_{½}$) of niraparib ranged from 48 to 51 hours (approximately 2 days). In a population pharmacokinetic analysis, the apparent total clearance (CL/F) of niraparib was 16.5 L/h in cancer patients (CV 23.4%).

Niraparib is eliminated primarily through the hepatobiliary and renal routes. Following an oral administration of a single 300-mg dose of [^{14}C]-niraparib, on average 86.2% (range 71% to 91%) of the dose was recovered in urine and faeces over 21 days. Radioactive recovery in the urine accounted for 47.5% (range 33.4% to 60.2%) and in the faeces for 38.8% (range 28.3% to 47%) of the dose. In pooled samples collected over 6 days, 40% of the dose was recovered in the urine primarily as metabolites and 31.6% of the dose was recovered in the faeces primarily as unchanged niraparib.

Special populations

<u>Renal impairment</u>

In the population pharmacokinetic analysis, patients with mild (creatinine clearance 60-90 mL/min) and moderate (30-60 mL/min) renal impairment had mildly reduced niraparib clearance compared to individuals with normal renal function (7-17% higher exposure in mild and 17-38% higher exposure in moderate renal impairment). The difference in exposure is not considered to warrant dose adjustment. No patients with pre-existing severe renal impairment or end-stage renal disease undergoing hemodialysis were identified in clinical studies (see section *Posology*).

<u>Hepatic impairment</u>

In the population pharmacokinetic analysis of data from clinical studies in patients, pre-existing mild hepatic impairment (n=155) did not influence the clearance of niraparib. In a clinical study of cancer patients using

NCI-ODWG criteria to classify the degree of hepatic impairment, niraparib AUC_{inf} in patients with moderate hepatic impairment (n=8) was 1.56 (90% CI: 1.06, 2.30) times the niraparib AUC_{inf} in patients with normal hepatic function (n=9) following administration of a single 300 mg dose. Niraparib dose adjustment is recommended for patients with moderate hepatic impairment (see section *Posology*). Moderate hepatic impairment did not have an effect on niraparib C_{max} or on niraparib protein binding. The pharmacokinetics of niraparib have not been assessed in patients with severe hepatic impairment (see sections *Posology* and *Warnings and Precautions*).

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

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

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

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

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

Repeat-dose toxicity
Decreased spermatogenesis was observed in rats and dogs at exposure levels below those seen clinically and was largely reversible within 4 weeks of cessation of dosing.

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

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

Carcinogenicity
Carcinogenicity studies have not been conducted with niraparib.

PHARMACEUTICAL INFORMATION
List of Excipients
Tablet core
Crospovidone
Lactose monohydrate
Magnesium stearate
Microcrystalline cellulose (E 460)
Povidone (E 1201)
Silica, colloidal hydrated

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

Shelf Life
The expiry date is indicated on the packaging.

Storage
Do not store above 30°C.

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

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

Incompatibilities
Not applicable.

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

Package Quantities and Reg. No.
ZEJULA 100 mg, 8 blisters @ 7 film-coated tablets Reg.No. XXXXXXXXXXXXXXX

HARUS DENGAN RESEP DOKTER

Manufactured by:
Catalent Greenville Inc.
Greenville, USA

Packaged by:
Millmount Healthcare Ltd.
Drogheda, Ireland

Released by:
Millmount Healthcare Ltd.
Stamullen, Ireland

Imported by:
PT Glaxo Wellcome Indonesia
Jakarta, Indonesia

Version number : 01
Reference : GDS07/IPI07 – First Registration
Date of local revision : 01 October 2025

INFORMASI UNTUK PASIEN

ZEJULA Tablet Salut Selaput
Niraparib tosylate

Baca keseluruhan brosur ini secara teliti sebelum Anda mulai menggunakan obat ini karena mengandung informasi penting untuk Anda.
- Simpan brosur ini. Anda mungkin perlu membacanya kembali.
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan pada dokter, perawat atau apoteker.
- Obat ini hanya diresepkan untuk Anda. Jangan diberikan kepada orang lain. Hal tersebut dapat membahayakan mereka, meskipun gejala penyakit mereka sama dengan gejala Anda.
- Jika Anda merasakan efek samping, konsultasikan dengan dokter, perawat atau apoteker. Hal ini termasuk kemungkinan efek samping lain yang tidak tertulis dalam brosur ini. *Lihat Bagian 4.*

Apa saja yang ada dalam brosur Ini:

1. Apa itu ZEJULA dan digunakan untuk apa

Apa itu ZEJULA dan bagaimana ZEJULA bekerja

ZEJULA mengandung bahan aktif niraparib. Niraparib adalah sejenis obat anti kanker penghambat PARP. Penghambat PARP memblokir enzim yang disebut poli [adenosin difosfat-ribosa] polimerase (PARP). PARP membantu sel memperbaiki DNA yang rusak, sehingga memblokirnya berarti DNA dari sel kanker tidak dapat diperbaiki. Hal ini menyebabkan kematian sel tumor dan membantu mengendalikan kanker.

ZEJULA digunakan untuk apa

ZEJULA digunakan pada wanita dewasa untuk pengobatan kanker ovarium, tuba falopi (bagian dari sistem reproduksi wanita yang menghubungkan ovarium ke rahim), atau peritoneum (selaput yang melapisi perut).

Zejula digunakan untuk kanker yang:
- memiliki respon pada pengobatan pertama dengan kemoterapi berbasis platinum, atau
- kembali (kambuh) setelah merespon pengobatan kanker sebelumnya dengan standar kemoterapi berbasis platinum.

2. Apa yang perlu Anda ketahui sebelum menggunakan ZEJULA

Jangan gunakan ZEJULA
- Jika Anda alergi terhadap niraparib atau salah satu bahan obat ini (*Lihat Bagian 6*).
- Jika Anda sedang menyusui.

Perhatian khusus dan pencegahan

Konsultasikan dengan dokter, apoteker atau perawat Anda sebelum atau saat menggunakan obat ini, jika Anda mengalami hal di bawah ini:
- Jumlah sel darah rendah
  ZEJULA menurunkan jumlah sel darah Anda, seperti jumlah sel darah merah (anemia), jumlah sel darah putih (neutropenia), atau jumlah trombosit darah (trombositopenia). Tanda dan gejala yang harus Anda waspadai yaitu termasuk demam atau infeksi, dan memar atau pendarahan yang tidak normal (lihat bagian 4 untuk informasi lebih lanjut). Dokter Anda akan melakukan uji darah pada Anda secara teratur selama pengobatan.

- Sindrom *myelodysplastic*/leukemia myeloid akut
  Walapun hal ini jarang terjadi, jumlah sel darah yang rendah mungkin merupakan tanda masalah yang lebih serius pada sumsum tulang seperti sindrom myelodysplastic' (MDS) atau leukemia myeloid akut

(AML). Dokter Anda mungkin akan melakukan uji pada sumsum tulang Anda untuk memeriksa masalah ini.

- Tekanan darah tinggi
  ZEJULA dapat menyebabkan tekanan darah tinggi, yang dalam beberapa kasus bisa parah. Dokter Anda akan mengukur tekanan darah Anda secara teratur selama perawatan Anda. Dokter juga mungkin akan memberikan obat untuk mengobati tekanan darah tinggi dan menyesuaikan dosis ZEJULA Anda, jika perlu. Dokter Anda mungkin akan menyarankan pemantauan tekanan darah di rumah dan instruksi kapan harus menghubunginya jika terjadi kenaikan tekanan darah.

- *Posterior Reversible Encephalopathy Syndrome* (PRES)
  Terdapat efek samping neurologis yang jarang terjadi, disebut PRES, yang dikaitkan dengan pengobatan ZEJULA. Jika Anda merasa sakit kepala, terdapat perubahan penglihatan, kebingungan atau kejang dengan atau tanpa tekanan darah tinggi, silakan hubungi dokter Anda.

Anak-anak dan remaja
Anak-anak di bawah usia 18 tahun tidak boleh diberikan ZEJULA. Belum ada studi terkait ZEJULA pada kelompok usia ini.

Obat-obatan lain dan ZEJULA
Beri tahu dokter atau apoteker Anda jika Anda sedang, baru saja, atau mungkin akan menggunakan obat lain.

Kehamilan
ZEJULA tidak boleh digunakan selama kehamilan karena dapat membahayakan bayi Anda. Jika Anda sedang hamil, curiga mungkin hamil atau berencana untuk hamil, mintalah saran dokter Anda sebelum menggunakan obat ini.

Jika Anda seorang wanita yang memiliki kemungkinan akan hamil, Anda harus menggunakan kontrasepsi yang sangat efektif saat menggunakan ZEJULA, dan Anda harus terus menggunakan kontrasepsi yang sangat efektif selama 6 bulan setelah penggunaan dosis terakhir Anda. Dokter Anda akan meminta Anda untuk memastikan bahwa Anda tidak hamil dengan tes kehamilan sebelum memulai pengobatan Anda. Hubungi dokter Anda segera jika Anda mengetahui bahwa Anda hamil saat sedang menggunakan ZEJULA.

Menyusui
ZEJULA tidak boleh digunakan jika Anda sedang menyusui karena saat ini tidak diketahui apakah obat dapat masuk ke dalam ASI. Jika Anda sedang menyusui, Anda harus berhenti sebelum mulai menggunakan ZEJULA dan Anda tidak boleh menyusui lagi sampai 1 bulan setelah menggunakan dosis terakhir Anda. Mintalah saran dokter Anda sebelum menggunakan obat ini.

Mengemudi dan menggunakan mesin
Ketika menggunakan ZEJULA, Anda mungkin akan merasa lemah, tidak fokus, lelah atau pusing sehingga mempengaruhi kemampuan Anda untuk mengemudi dan menggunakan mesin. Amati tanda-tanda dan selalu waspada saat mengemudi atau menggunakan mesin.

ZEJULA mengandung laktosa
Jika Anda telah diberitahu oleh dokter Anda bahwa Anda memiliki intoleransi terhadap beberapa jenis gula, hubungi dokter Anda sebelum menggunakan produk obat ini.

3. Cara menggunakan ZEJULA

Selalu gunakan obat ini sesuai saran dokter atau apoteker. Konsultasikan dengan dokter atau apoteker jika Anda tidak yakin.

Untuk kanker ovarium yang telah merespon pengobatan pertama dengan kemoterapi berbasis platinum
Dosis awal yang dianjurkan adalah 200 mg (dua tablet 100 mg), diminum bersamaan sekali sehari, dengan atau tanpa makanan. Jika berat badan Anda sebelum memulai pengobatan ≥77 kg dan jumlah platelet ≥150.000/µL, dosis awal yang dianjurkan adalah 300 mg (tiga tablet 100 mg), diminum bersamaan sekali sehari, dengan atau tanpa makanan.

Untuk kanker ovarium yang datang kembali (kambuh)
Dosis awal yang dianjurkan adalah 300 mg (tiga tablet 100 mg), diminum bersamaan sekali sehari, dengan atau tanpa makanan.

Gunakan ZEJULA pada waktu yang sama setiap hari. Penggunaan ZEJULA pada saat akan tidur dapat membantu Anda mengurangi mual.

Dokter Anda mungkin menyesuaikan dosis awal jika Anda memiliki masalah dengan hati Anda.

Dokter Anda mungkin merekomendasikan dosis yang lebih rendah jika Anda mengalami efek samping (seperti mual, kelelahan, perdarahan/memar yang tidak wajar, anemia).

Dokter Anda akan memeriksa Anda secara teratur, dan biasanya Anda akan terus menggunakan ZEJULA selama Anda merasakan manfaat, dan tidak menderita efek samping yang tidak dapat diterima.

Apabila Anda menggunakan ZEJULA lebih dari yang seharusnya
Jika Anda menggunakan lebih dari dosis normal, segera hubungi dokter.

Apabila Anda lupa menggunakan ZEJULA
Jangan menggunakan dosis tambahan jika Anda melewatkan satu dosis atau muntah setelah menggunakan ZEJULA. Gunakan dosis berikutnya di waktu yang dijadwalkan. Jangan menggunakan dosis ganda untuk mengganti dosis yang terlewatkan.

Jika Anda memiliki pertanyaan lebih lanjut tentang penggunaan obat ini, tanyakan kepada dokter, apoteker, atau perawat Anda.

4. Efek samping yang mungkin terjadi

Seperti semua obat lainnya, obat ini dapat menimbulkan efek samping, tapi tidak semua orang mungkin akan mengalaminya.

<u>Segera</u> hubungi dokter jika Anda merasakan salah satu efek samping SERIUS berikut – Anda mungkin membutuhkan perawatan medis segera:

Sangat umum (terjadi hingga lebih dari 1 dari 10 orang)
- Memar atau berdarah lebih lama dari biasanya jika Anda terluka - ini mungkin tanda jumlah keping darah rendah (trombositopenia).
- Sesak napas, merasa sangat lelah, kulit pucat, atau detak jantung cepat - ini mungkin tanda jumlah sel darah merah rendah (anemia).
- Demam atau infeksi - jumlah sel darah putih yang rendah (neutropenia) dapat meningkatkan risiko Anda terkena infeksi. Tanda-tandanya mungkin termasuk demam, menggigil, merasa lemah atau bingung, batuk, nyeri atau perasaan terbakar saat buang air kecil. Beberapa infeksi bisa menjadi serius dan dapat menyebabkan kematian.
- Pengurangan jumlah sel darah putih dalam darah (leukopenia)

Umum (terjadi hingga **1 dari 10 orang**)
- Reaksi alergi (termasuk reaksi alergi berat yang dapat mengancam jiwa). Ditandai dengan ruam yang timbul dan gatal (gatal-gatal) dan bengkak, kadang pada wajah atau mulut (angioedema), menyebabkan kesulitan bernapas, dan kolaps atau kehilangan kesadaran.
- Jumlah sel darah rendah karena masalah pada sumsum tulang atau kanker darah dari sumsum tulang 'sindrom *myelodysplastic*' (MDS) atau 'leukemia myeloid akut' (AML).

Jarang (terjadi pada hingga **1 dari 1.000 orang**)
- Peningkatan tekanan darah secara tiba-tiba, yang mungkin merupakan keadaan medis darurat yang dapat menyebabkan kerusakan organ atau dapat mengancam jiwa.
- Sebuah kondisi otak dengan gejala termasuk kejang, sakit kepala, kebingungan, dan perubahan dalam penglihatan (*Posterior Reversible Encephalopathy Syndrome* atau PRES), yang merupakan keadaan medis darurat yang dapat menyebabkan kerusakan organ atau dapat mengancam jiwa.

Hubungi dokter Anda jika Anda merasakan efek samping lain, termasuk berikut:

Sangat umum (terjadi hingga lebih dari 1 dari 10 orang)
- Merasa sakit (mual)
- Sensasi terbakar pada ulu hati (dispepsia)
- Penurunan jumlah sel darah putih dalam darah
- Penurunan jumlah trombosit dalam darah
- Penurunan jumlah sel darah merah dalam darah (anemia)
- Merasa lelah
- Merasa lemah
- Sembelit
- Muntah
- Sakit perut
- Ketidakmampuan untuk tidur
- Sakit kepala
- Nafsu makan berkurang
- Hidung berair atau tersumbat
- Diare
- Sesak napas
- Sakit punggung
- Nyeri sendi
- Tekanan darah tinggi
- Gangguan pencernaan
- Pusing
- Batuk
- Infeksi saluran kemih
- Palpitasi (merasa jantung Anda berdebar-debar atau berdetak lebih keras dari biasanya).

Umum (terjadi hingga **1 dari 10 orang**)
- Reaksi seperti terbakar sinar matahari setelah terpapar cahaya
- Pembengkakan pada kaki, pergelangan kaki, betis, dan/atau tangan
- Kadar kalium yang rendah dalam darah
- Peradangan atau pembengkakan saluran udara antara mulut dan hidung dan paru-paru, bronkitis
- Perut kembung
- Perasaan khawatir, gugup, atau gelisah
- Perasaan sedih, tertekan
- Pendarahan pada hidung
- Penurunan berat badan
- Nyeri otot
- Gangguan konsentrasi, pemahaman, ingatan dan pemikiran (gangguan kognitif)
- Mata kemerahan
- Detak jantung yang cepat dapat menyebabkan pusing, nyeri dada, atau sesak napas
- Mulut kering
- Radang pada mulut dan/atau saluran pencernaan
- Ruam
- Hasil tes darah meningkat
- Hasil tes darah abnormal
- Rasa tidak normal di mulut.

Tidak umum (terjadi hingga **1 dari 100 orang**)
- Pengurangan jumlah sel darah merah, sel darah putih dan trombosit
- Keadaan bingung
- Radang paru-paru yang dapat menyebabkan sesak napas dan kesulitan bernapas (radang paru-paru yang tidak menular).

Pelaporan efek samping
Jika efek samping menjadi serius, atau jika Anda melihat terdapat efek samping yang tidak tercantum dalam

brosur ini, segera konsultasikan pada dokter atau apoteker Anda.
Laporkan Kejadian Tidak Diinginkan (KTD) ke GSK Indonesia melalui situs web https://gsk.public.reportum.com.

5. Bagaimana cara penyimpanan ZEJULA

Jauhkan ZEJULA dari pandangan dan jangkauan anak-anak.

Jangan menggunakan obat setelah tanggal kedaluwarsa yang tertulis pada kemasan karton dan blister. Tanggal kedaluwarsa merujuk pada tanggal terakhir bulan tersebut.

Simpan ZEJULA pada suhu di bawah 30°C.

Simpan ZEJULA dalam kemasan aslinya untuk melindungi tablet dari penyerapan air pada kondisi kelembapan yang tinggi.

Jangan membuang obat apapun di air limbah atau limbah rumah tangga. Tanyakan pada apoteker bagaimana membuang obat yang tidak digunakan lagi. Tindakan ini akan membantu melindungi lingkungan.

6. Isi dari kemasan dan informasi lain

Kandungan pada ZEJULA

- Bahan aktif niraparib. Setiap tablet salut selaput mengandung *niraparib tosylate monohydrate* setara dengan 100 mg niraparib.
- ZEJULA tablet salut selaput juga mengandung bahan lainnya:
  Inti tablet: *crospovidone, lactose monohydrate, magnesium stearate, microcrystalline cellulose (E 460), povidone (E 1201), colloidal hydrated silica.*
  Salut tablet: *polyvinyl alcohol (E 1203), titanium dioxide (E 171), macrogol (E 1521), talc (E 553b), black iron oxide (E 172).*

Penampakan ZEJULA dan isi kemasan

ZEJULA tablet salut selaput 100 mg tersedia dalam blister *foil* berisi 8 x 7 tablet salut selaput. Tablet ini berwarna abu-abu, berbentuk oval ditandai dengan kode ‘100’ pada salah satu sisinya dan “Zejula” pada sisi lainnya.

HARUS DENGAN RESEP DOKTER

Dus, 8 blister @ 7 tablet salut selaput Reg. No. XXXXXXXXXXXXXX

Diproduksi oleh:
Catalent Greenville Inc.
Greenville, USA

Dikemas oleh:
Millmount Healthcare Ltd.
Drogheda, Ireland

Dirilis oleh:
Millmount Healthcare Ltd.
Stamullen, Ireland

Diimpor oleh:
PT Glaxo Wellcome Indonesia
Jakarta, Indonesia

Version number : 01
Reference : GDS07/IPI07
Date of local revision : 01 October 2025