▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

ZEJULA® (NIRAPARIB)

1 NAME OF THE MEDICINE

ZEJULA (niraparib)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains niraparib tosilate monohydrate equivalent to 100 mg niraparib. Excipients with known effect: Each capsule contains lactose monohydrate. Each capsule shell also contains the colouring agent tartrazine.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Capsule with a white body with “100 mg” printed in black ink and purple cap with “Niraparib” printed in white ink.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

ZEJULA is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

The recommended starting dose is 300 mg (three 100 mg capsules) taken orally once daily.

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

The capsules should be swallowed whole with water. The capsules should not be chewed or crushed. ZEJULA can be taken without regard to meals.

It is recommended that 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

To manage adverse reactions, consider interruption of treatment, dose reduction, or dose discontinuation. The recommended dose modifications for adverse reactions are listed in Table 1, Table 2 and Table 3.

Table 1: Recommended dose modifications for adverse reactions

Dose level	Dose
Starting dose	300 mg/day (three 100 mg capsules)
First dose reduction	200 mg/day (two 100 mg capsules)
Second dose reduction	100 mg/day* (one 100 mg capsule)

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

Table 2: Dose modifications for non-haematologic adverse reactions

Non-haematologic CTCAE* ≥ Grade 3 adverse reaction where prophylaxis is not considered feasible or adverse reaction persists despite treatment	• Withhold ZEJULA for a maximum of 28 days or until resolution of adverse reaction. • Resume ZEJULA at a reduced dose per Table 1. Up to 2 dose reductions are permitted.
CTCAE ≥ Grade 3 treatment-related adverse reaction lasting more than 28 days while patient is administered ZEJULA 100 mg/day	• Discontinue ZEJULA.

*CTCAE=Common Terminology Criteria for Adverse Events

Table 3: Dose modifications for haematologic adverse reactions

Haematologic adverse reactions have been observed during treatment with Zejula especially during the initial phase of the treatment. It is therefore recommended to monitor complete blood counts (CBCs) weekly during the first month of treatment and modify the dose as needed. After the first month, it is recommended to monitor CBCs monthly and periodically after this time (see Section 4.4 Special Warnings and Precautions for Use). Based on individual laboratory values, weekly monitoring for the second month may be warranted.	
Haematologic adverse reaction requiring transfusion or haematopoietic growth factor support	• For patients with platelet count ≤ 10 x 10^9/L, 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

Table 3: Dose modifications for haematologic adverse reactions	
	products and/or transfusion at a higher platelet count. • Resume ZEJULA at a reduced dose per Table 1.
Platelet count <100 x 10^9/L	First occurrence: • Withhold ZEJULA for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥100 x 10^9/L. • Resume Zejula at same or reduced dose based on clinical evaluation. • If platelet count is < 75 x 10^9/L 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 x 10^9/L. • Resume ZEJULA at a reduced dose per Table 1. • Discontinue ZEJULA if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg once daily.
Neutrophil <1 x 10^9/L or Haemoglobin <80 g/L	• Withhold ZEJULA for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥1.5 x 10^9/L or haemoglobin returns to ≥90 g/L. • Resume ZEJULA at a reduced dose per Table 1. • Discontinue ZEJULA if neutrophils and/or haemoglobin have not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg once daily.
Confirmed diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML)	• Discontinue ZEJULA.

Elderly

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

Renal impairment

No dose adjustment is necessary for patients with mild to moderate renal impairment. There are no data in patients with severe renal impairment or end stage renal disease undergoing haemodialysis; use with caution in these patients, see Section 5.2 Pharmacokinetic Properties.

Hepatic impairment

No dose adjustment is needed in patients with mild to moderate hepatic impairment. There are no data in patients with severe hepatic impairment; use with caution in these patients, see Section 5.2 Pharmacokinetic Properties.

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 ZEJULA in children and adolescents below 18 years of age have not yet been established. No data are available.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 List of Excipients.

Breast-feeding (see Section 4.6 Fertility, Pregnancy and Lactation).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Haematologic adverse reactions

In the NOVA study, patients eligible for ZEJULA therapy had the following baseline haematologic parameters: absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L; platelets ≥ 100 x 10^9/L and haemoglobin ≥ 90 g/L prior to therapy. Haematologic adverse reactions (thrombocytopenia, anaemia, neutropenia) have been reported in patients treated with ZEJULA. 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 event of pancytopenia. Thrombocytopenia occurred more commonly in patients whose baseline platelet count was less than 180 × 10^9/L. Approximately 76% of patients with lower baseline platelets (< 180 × 10^9/L) who received ZEJULA experienced thrombocytopenia of any grade, and 45% of the patients experienced Grade 3/4 thrombocytopenia. Pancytopenia has been observed in < 1% of patients receiving ZEJULA. If a patient develops severe persistent haematologic toxicity including pancytopenia that does not resolve within 28 days following interruption, ZEJULA should be discontinued.

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

Testing complete blood counts weekly for the first month, followed by monthly monitoring for the next 10 months of treatment and periodically after this time is recommended to monitor for clinically significant changes in any haematologic parameter during treatment, see Section 4.2 Dose and Method of Administration.

Due to the risk of thrombocytopenia, anticoagulants and medicinal products known to reduce the thrombocyte count should be used with caution, see Section 4.8 Adverse Effects (Undesirable Effects).

Myelodysplastic syndrome/acute myeloid leukaemia

Myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML), including cases with fatal outcome, have been reported in a small number of patients who received ZEJULA or placebo. In the NOVA trial, the incidence of MDS/AML in patients who received ZEJULA (1.4%) was similar to that in patients who received placebo (1.1%). Overall, MDS/AML has been reported in 7 out of 751 (0.9%) patients treated with ZEJULA in clinical studies.

The duration of ZEJULA treatment in patients prior to developing MDS/AML varied from 1 month to > 2 years. The cases were typical of secondary, cancer therapy-related MDS/AML. All patients had received multiple platinum-containing chemotherapy regimens and many had also received other DNA damaging agents and radiotherapy. Some of the patients had a history of bone marrow dysplasia.

If MDS and/or AML are confirmed while on treatment with ZEJULA, treatment should be discontinued and the patient treated appropriately.

Hypertension, including hypertensive crisis

Hypertension, including hypertensive crisis, has been reported with the use of ZEJULA. Pre-existing hypertension should be adequately controlled before starting ZEJULA treatment. Blood pressure should be monitored monthly for the first year and periodically thereafter during treatment with ZEJULA.

Hypertension should be medically managed with antihypertensive medicinal products as well as adjustment of the ZEJULA dose (see Section 4.2 Dose and Method of Administration), if necessary. In the clinical programme, blood pressure measurements were obtained on Day 1 of each 28-day cycle while the patient remained on ZEJULA. In most cases, hypertension was controlled adequately using standard antihypertensive treatment with or without ZEJULA dose adjustment, see Section 4.2 Dose and Method of Administration. ZEJULA should be discontinued in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy.

Pregnancy/contraception

ZEJULA should not be used during pregnancy or in women of childbearing potential not willing to use reliable contraception during therapy and for 1 month after receiving the last dose of ZEJULA (see Section 4.6 Fertility, Pregnancy and Lactation). A pregnancy test should be performed on all women of childbearing potential prior to treatment.

Lactose

ZEJULA capsules contain lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Tartrazine

This medicinal product contains tartrazine, which may cause allergic reactions.

Use in the elderly

See Section 4.2 Dose and Method of Administration.

Paediatric use

See Section 4.2 Dose and Method of Administration.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF 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 ZEJULA 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, 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). The major primary metabolite M1 is not a substrate of P-gp, BCRP, or BSEP. Niraparib is not a substrate of 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 (e.g. cimetidine, quinidine) uptake transporters.

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).

Induction of CYPs (CYP1A2 and CYP3A4)

Neither niraparib nor M1 is a CYP3A4 inducer i*n vitro*. *In vitro*, niraparib weakly induces CYP1A2 at high concentrations and the clinical relevance of this effect cannot 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, and MATE1/2)

Niraparib is not an inhibitor of BSEP. *In vitro*, niraparib inhibits P-gp very weakly and BCRP with an IC_{50} = 161 µM and 5.8 µM, respectively. Therefore, a clinically meaningful interaction related to an inhibition of these efflux transporters although unlikely, cannot be excluded. Caution is thus 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, or MATE1/2.

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

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

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

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

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

All clinical studies have only been performed in adults.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

There are no clinical data on fertility. While no direct fertility studies were conducted in animals, repeat-dose toxicity studies in rats and dogs showed decreased spermatogenesis, small testes and germ cell depletion in the testes and epididymides at niraparib doses of 20 mg/kg/day and 6 mg/kg/day (0.74- and 0.05-times clinical exposure based on AUC, respectively). There was a trend towards reversibility of these findings 2-4 weeks after dosing was stopped.

Use in pregnancy (Category D)

There are no or limited amount of data from the use of ZEJULA 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 fetal harm, including embryo-lethal and teratogenic effects, when administered to a pregnant woman. ZEJULA should not be used during pregnancy.

Women of childbearing potential should not become pregnant while on treatment and should not be pregnant at the beginning of treatment. A pregnancy test should be performed on all women of childbearing potential prior to treatment. Women of childbearing potential must use effective contraception during therapy and for 1 month after receiving the last dose of ZEJULA.

Use in lactation

It is unknown whether niraparib or its metabolites are excreted in human milk. Breast-feeding is contraindicated during administration of ZEJULA and for 1 month after receiving the last dose (see Section 4.3 Contraindications).

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

In the pivotal NOVA study, adverse reactions (ADRs) occurring ≥10% of patients receiving ZEJULA monotherapy were nausea, thrombocytopenia, fatigue/asthenia, anaemia, constipation, vomiting, abdominal pain, neutropenia, insomnia, headache, decreased appetite, nasopharyngitis, diarrhoea, dyspnea, hypertension, dyspepsia, back pain, dizziness, cough, urinary tract infection, arthralgia, palpitations, and dysgeusia.

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 in the NOVA study in patients receiving ZEJULA monotherapy (see Table 4).

Frequencies of occurrence of undesirable effects are defined as: very common ≥1/10); common ≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 4: Adverse drug reactions: frequencies based on all-causality adverse events*

System Organ Class	Frequency of all CTCAE grades	Frequency of CTCAE grade 3 or 4
Infections and infestations	**Very common** Urinary tract infection **Common** Bronchitis, conjunctivitis	**Uncommon** Urinary tract infection, bronchitis
Blood and lymphatic system disorders	**Very common** Thrombocytopenia, anaemia, neutropenia **Common** Leukopenia **Uncommon** Pancytopenia, febrile neutropenia	**Very common** Thrombocytopenia, anaemia, neutropenia **Common** Leukopenia **Uncommon** Pancytopenia, febrile neutropenia
Metabolism and nutrition disorders	**Very common** Decreased appetite **Common** Hypokalemia	**Common** Hypokalemia **Uncommon** Decreased appetite
Psychiatric disorders	**Very common** Insomnia **Common** Anxiety, depression	**Uncommon** Insomnia, anxiety, depression
Nervous system disorders	**Very common** Headache, dizziness, dysgeusia	**Uncommon** Headache
Cardiac disorders	**Very common** Palpitations **Common** Tachycardia	
Vascular disorders	**Very common** Hypertension	**Common** Hypertension
Respiratory, thoracic and mediastinal disorders	**Very common** Dyspnea, cough, nasopharyngitis **Common** Epistaxis	**Common** Dyspnea
Gastrointestinal disorders	**Very common** Nausea, constipation, vomiting, abdominal pain, diarrhoea,	**Common** Nausea, vomiting, abdominal pain

System Organ Class	Frequency of all CTCAE grades	Frequency of CTCAE grade 3 or 4
	dyspepsia **Common** Dry mouth, abdominal distension, mucosal inflammation (including mucositis), stomatitis	**Uncommon** Diarrhoea, constipation, mucosal inflammation (including mucositis), stomatitis, dry mouth
Skin and subcutaneous tissue disorders	**Common** Rash	**Uncommon** 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	**Uncommon** AST increased, ALT increased, blood alkaline phosphatase increased **Common** Gamma-glutamyl transferase increased

* Frequencies are based on percent of patients using all-causality adverse events.

Description of selected adverse reactions

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

Thrombocytopenia

Approximately 60% of patients receiving ZEJULA experienced thrombocytopenia of any grade, and 34% of patients experienced Grade 3/4 thrombocytopenia. In patients with baseline platelet count less than 180 × 10^9/L, thrombocytopenia of any grade and Grade 3/4 occurred in 76% and 45% of the patients, respectively. The median time to onset of thrombocytopenia regardless of grade, and Grade 3/4 thrombocytopenia was 22 and 23 days, respectively. The rate of new incidences of thrombocytopenia after intensive dose modifications were performed during the first two months of treatment from Cycle 4 was 1.2%. The median duration of thrombocytopenia events of any grade was 23 days, and the median

duration of Grade 3/4 thrombocytopenia was 10 days. Patients treated with ZEJULA who develop thrombocytopenia might have an increased risk of haemorrhage. In the clinical programme, thrombocytopenia was managed with laboratory monitoring, dose modification and platelet transfusion where appropriate (see Section 4.2 Dose and Method of Administration). Discontinuation due to thrombocytopenia events (thrombocytopenia and platelet count decreased) occurred in approximately 3% of the patients.

Anaemia

Approximately 50% of patients experienced anaemia of any grade, and 25% experienced Grade 3/4 anaemia. The median time to onset of anaemia of any grade was 42 days, and 85 days for Grade 3/4 events. The median duration of anaemia of any grade was 63 days, and 8 days for Grade 3/4 events. Anaemia of any grade might persist during ZEJULA treatment. In the clinical programme, anaemia was managed with laboratory monitoring, dose modification (see Section 4.2 Dose and Method of Administration), and, where appropriate, with red blood cell transfusions. Discontinuation due to anaemia occurred in 1% of patients.

Neutropenia

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 the clinical programme, neutropenia was managed with laboratory monitoring and dose modifications (see Section 4.2 Dose and Method of Administration). 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.

Hypertension

Hypertension, including hypertensive crisis, has been reported with ZEJULA therapy. Hypertension of any grade occurred in 19.3% of patients treated with ZEJULA. Grade 3/4 hypertension occurred in 8.2% of patients. In the clinical programme, 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 suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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.

Clinical trials

The safety and efficacy of ZEJULA as maintenance therapy was studied in a Phase 3 randomised, double-blind, placebo-controlled international trial (ENGOT-OV16 / 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 was required to be in response (CR or PR) following completion of last platinum based chemotherapy. The CA-125 levels were required to 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 should not have received prior PARP inhibitor therapy, including ZEJULA. Eligible patients were assigned to one of two cohorts based on the results of the BRACAnalysis mutation test. Within each cohort, patients were randomised using a 2:1 allocation of ZEJULA and placebo. Patients were assigned to the g*BRCA*mut cohort based on blood samples for g*BRCA* analysis that were taken prior to randomisation. Testing for t*BRCA* mutation and homologous recombination deficiency (HRD) was performed using the HRD test on tumour tissue obtained at the time of initial diagnosis or at the time of recurrence.

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

Patients began treatment on Cycle 1/Day 1 (C1/D1) with ZEJULA 300 mg or matched placebo administered 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 ZEJULA-treated patients in the NOVA study was 200 mg.

Progression-free survival was determined per RECIST (Response Evaluation Criteria in Solid Tumors, version 1.1) or clinical signs and symptoms and increased CA-125. PFS was measured from the time

of randomisation (which occurred up to 8 weeks after completion of the chemotherapy regimen) to disease progression or death.

The primary efficacy analysis for PFS was determined by blinded central independent assessment and was prospectively defined and assessed for the g*BRCA*mut cohort and the non-g*BRCA*mut cohort separately.

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

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

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

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

The study met its primary objective of statistically significantly improved PFS for ZEJULA maintenance monotherapy compared with placebo in the g*BRCA*mut cohort (HR 0.27; 95% CI* 0.173, 0.410; p < 0.0001) as well as in the overall non-g*BRCA*mut cohort (HR 0.45; 95% CI* 0.338, 0.607; p < 0.0001). Table 5 shows 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 5: Summary of primary objective outcomes in the ENGOT-OV16 study

	g*BRCA*mut cohort		**Non-g*BRCA*mut cohort**	
	ZEJULA (N = 138)	**placebo (N = 65)**	**ZEJULA (N = 234)**	**placebo (N = 116)**
PFS median in 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) (Nir:plac) (95% CI*)	**0.27** (0.173, 0.410)		**0.45** (0.338, 0.607)	

* CI denotes confidence interval.

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

was 0.58 (95% CI, 0.361, 0.922; p = 0.0226). The experimental test was not able to discriminate which patients would or would not benefit from ZEJULA maintenance therapy.

Figure 1: Kaplan-Meier plot for progression-free survival in the g*BRCA*mut cohort based on IRC assessment (ITT population, N = 203)

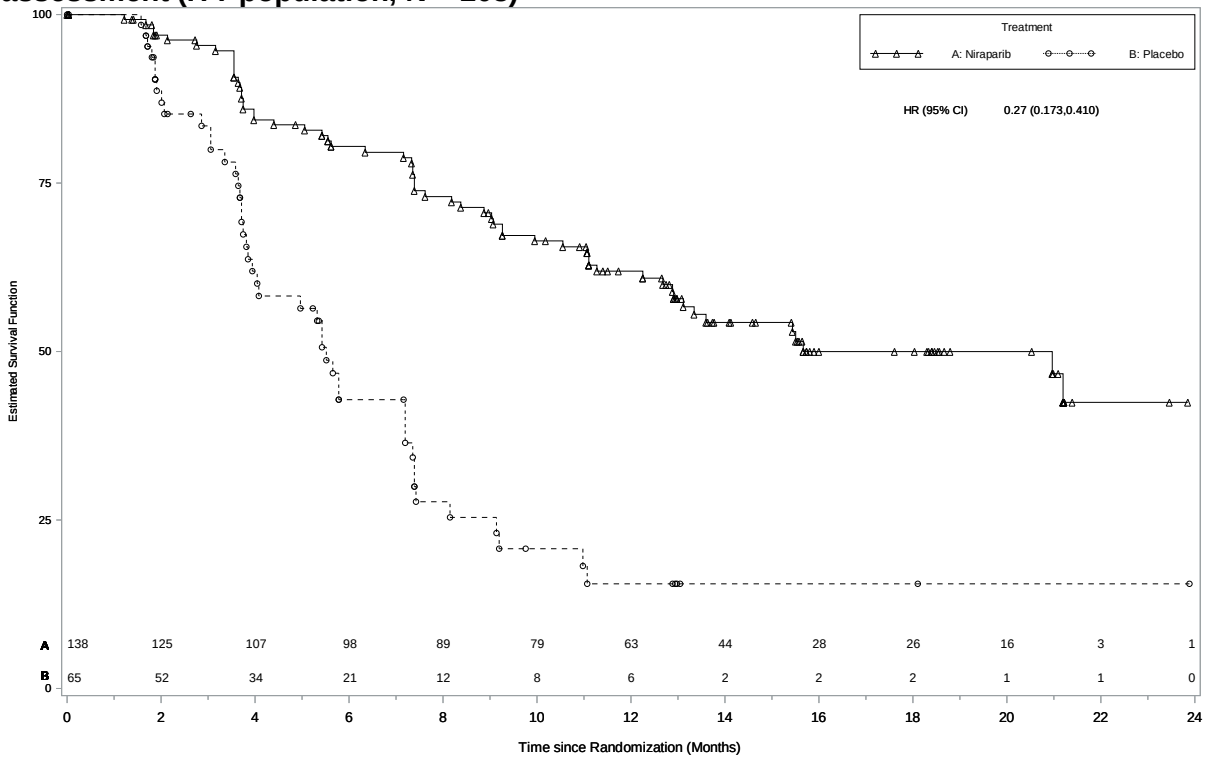
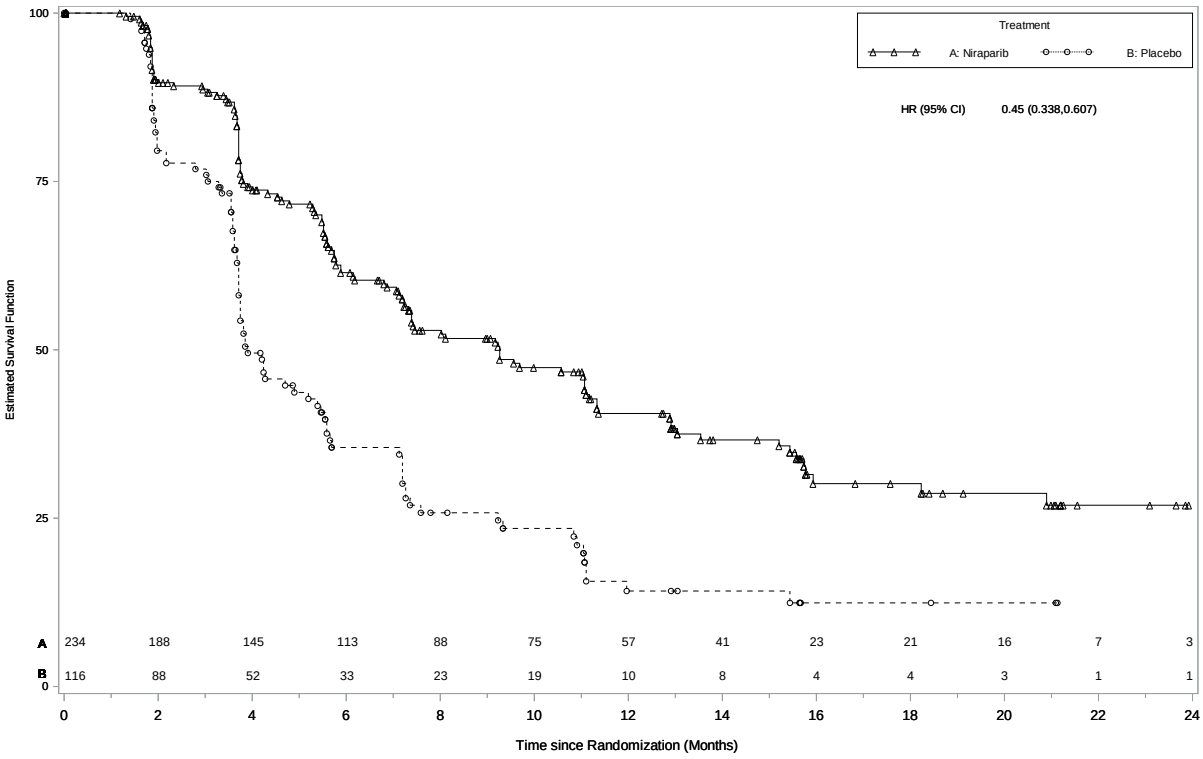


Figure 2: Kaplan-Meier plot for progression-free survival in the non-g*BRCA*mut cohort overall based on IRC assessment (ITT population, N = 350)



The secondary endpoints CFI, TFST, and PFS2 demonstrated a statistically significant and persistent treatment effect in favour of the ZEJULA treatment arm in the g*BRCA*mut cohort and the overall non-g*BRCA*mut cohort (Table 6).

Table 6: Secondary endpoints*

	g*BRCA*mut		non-g*BRCA*mut	
Endpoint	**ZEJULA N = 138**	**Placebo N = 65**	**ZEJULA N= 234**	**Placebo N = 116**
Chemotherapy-free interval				
Median (95% CI) – months	22.8 (17.9-NR)	9.4 (7.9-10.6)	12.7 (11.0-14.7)	8.6 (6.9-10.0)
P value	< 0.001		< 0.001	
Hazard ratio (95% CI)	0.26 (0.17-0.41)		0.50 (0.37-0.67)	
Time to first subsequent treatment				
Median (95% CI) – months	21.0 (17.5-NR)	8.4 (6.6-10.6)	11.8 (9.7-13.1)	7.2 (5.7-8.5)
P value	< 0.001		< 0.001	
Hazard ratio (95% CI)	0.31 (0.21-0.48)		0.55 (0.41-0.72)	

Progression-free survival 2				
Median (95% CI) – months	25.8 (20.3-NR)	19.5 (13.3-NR)	18.6 (16.2-21.7)	15.6 (13.2-20.9)
P value	0.006		0.03	
Hazard ratio (95% CI)	0.48 (0.28-0.82)		0.69 (0.49-0.96)	

*CI denotes confidence interval, g*BRCA*mut germline *BRCA* mutation, and NR not reached

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

At the time of the PFS analysis, limited overall survival data were available with 17% deaths across the two cohorts.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following a single-dose administration of 300 mg niraparib under fasting conditions, niraparib was measurable in plasma within 30 minutes and the mean peak plasma concentration (Cmax) 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.

Administration of Zejula (3 x 100 mg) with a high-fat high-calorie meal may result in a slight decrease in C_{max} (~20%) relative to administration of Zejula (3 x 100 mg) under fasted conditions. Food did not significantly affect the overall exposure of niraparib (AUC_T and AUC_∞).

Distribution

Niraparib was moderately protein bound in human plasma (83.0%), mainly with serum albumin. In a population pharmacokinetic analysis of niraparib, the Vd/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.

Excretion

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

Niraparib is eliminated primarily through the hepatobiliary and renal routes. Following an oral administration of a single 300-mg dose of [14C]-niraparib, on average 86.2% (range 71% to 91%) of the

dose was recovered in urine and faeces over 21 days. Radioactive recovery in the urine accounted for 47.5% (range 33.4% to 60.2%) and in the faeces for 38.8% (range 28.3% to 47.0%) of the dose. In pooled samples collected over 6 days, 40.0% of the dose was recovered in the urine primarily as metabolites and 31.6% of the dose was recovered in the faeces primarily as unchanged niraparib.

Special populations

Renal impairment

In the population pharmacokinetic analysis of data from clinical studies in patients, pre-existing mild (CLCr < 90 - ≥ 60 ml/min) and moderate (CLCr < 60 - ≥ 30 mL/min) renal impairment did not influence the clearance of niraparib. No patients with pre-existing severe renal impairment or end-stage renal disease undergoing hemodialysis were identified in clinical studies (see Section 4.2 Dose and Method of Administration).

Hepatic impairment

In the population pharmacokinetic analysis of data from clinical studies in patients, pre-existing mild and moderate hepatic impairment did not influence the clearance of niraparib. The pharmacokinetics of niraparib have not been assessed in patients with severe hepatic impairment (see Section 4.2 Dose and Method of Administration).

Age, weight and race

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

Paediatric population

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

5.3 PRECLINICAL SAFETY DATA

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.

Carcinogenicity

Carcinogenicity studies have not been conducted with niraparib.

Animal pharmacology and toxicology

In vitro, niraparib inhibited dopamine (DAT) and norepinephrine (NET) transporters at concentration levels below anticipated human exposure levels (based on unbound C_{max}). In mice, single doses of niraparib increased intracellular levels of dopamine and metabolites in the cortex. Reduced locomotor activity was seen in one of two single dose studies in mice. The clinical relevance of these findings is not known but effects on blood pressure and pulse rate that may be related to inhibition of these transporters have occurred in patients.

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 in dogs but not rats.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Capsule content:

lactose monohydrate, magnesium stearate

Capsule shell:

titanium dioxide, gelatin, brilliant blue FCF, erythrosine, tartrazine

Printing inks:

Black Ink; SW-9040 (PI:12418). White Ink; TekPrint SB-0007P White Ink (PI 2216).

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Aclar/PVC/aluminium foil perforated unit dose blisters in cartons of 28, 56, and 84 capsules.

HDPE bottles with a polypropylene (PP) child-resistant closure containing 90 capsules.

Not all presentations may be marketed.

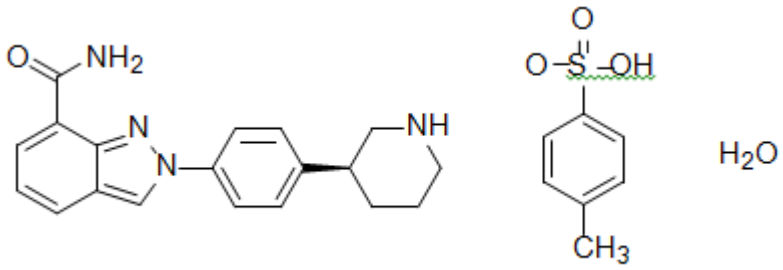
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name for niraparib tosilate monohydrate is (3S)-3-{4-[7-(aminocarbonyl)-2H-indazol-2-yl]phenyl}piperidinium 4-methylbenzenesulfonate monohydrate. The molecular formula is $C_{19}H_{20}N_4 \bullet OC_7H_8O_3S \bullet H_2O$ which corresponds to a formula weight of 510.61 g/mol. Niraparib tosilate monohydrate has one chiral centre of the S configuration. The chemical structure is shown below:



Niraparib tosilate monohydrate is a white to pale brown powder.

CAS number

1038915-60-4 (niraparib)
1613220-15-7 (niraparib tosilate monohydrate)

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (Schedule 4)

8 SPONSOR

Takeda Pharmaceuticals Australia Pty Ltd
Level 5
2 Chifley Square
Sydney NSW 2000
Ph: 1800 675 957

9 DATE OF FIRST APPROVAL

28 June 2019

10 DATE OF REVISION

<Not Applicable.>

Summary table of changes

Section changed	Summary of new information