NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Zejula (niraparib) 100 mg capsules

Zejula (niraparib) 100 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains niraparib tosilate monohydrate equivalent to 100 mg niraparib. Excipients with known effect: lactose monohydrate (present in the capsule), tartrazine (colouring agent present in the capsule shell).

Each film coated tablet contains niraparib tosilate monohydrate equivalent to 100 mg niraparib. Excipients with known effect: lactose monohydrate (present in the tablet).

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

3. PHARMACEUTICAL FORM

Capsule

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

Tablet

Grey oval shaped film-coated tablet debossed with “100” on one side and “Zejula” on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zejula is indicated:

- for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube or primary peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.
- for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy.

Efficacy in the proposed indications varies by patient HRD/gBRCAm status. See section 5.1 Pharmacodynamic properties for details.

4.2 Dose and method of administration

Dose

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

First-line ovarian cancer maintenance treatment

The recommended starting dose of niraparib is 200 mg taken once daily. For patients who weigh ≥ 77 kg and have baseline platelet count ≥ 150,000/µL, the recommended starting dose of niraparib is 300 mg taken once daily.

Recurrent ovarian cancer maintenance treatment

The recommended starting dose is 300 mg (three 100 mg capsules or tablets) 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 or tablets should be swallowed whole with water. The capsules or tablets 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 Tables 1, 2 and 3.

Table 1: Recommended dose modifications for adverse reactions		
Starting dose	200 mg/day	300 mg/day
First dose reduction	100 mg/day	200 mg/day
Second dose reduction	Discontinue medication.	100 mg/day*

*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 that persists despite treatment/prophylaxis**	First occurrence: • Withhold Zejula for a maximum of 28 days or until resolution of adverse reaction. • Resume Zejula at a reduced dose per Table 1. Second occurrence: • Withhold niraparib for a maximum of 28 days or until resolution of adverse reaction. • Resume niraparib 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 Zejula.

‡CTCAE=Common Terminology Criteria for Adverse Events

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

Table 3: Dose modifications for 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 ≤ 10,000/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 products and/or transfusion at a higher platelet count. • Resume Zejula at a reduced dose per Table 1.
Platelet count <100,000 μL	First occurrence: • Withhold Zejula for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥ 100,000/μL. • Resume Zejula at same or reduced dose based on clinical evaluation. • If platelet count is < 75,000/μL at any time, resume at a reduced dose per Table 1.
	Second occurrence: • Withhold Zejula for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥ 100,000/μL. • Resume Zejula at a reduced dose per Table 1. • Discontinue Zejula if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg once daily.

Table 3: Dose modifications for haematologic adverse reactions	
Neutrophil < 1,000/μL or Haemoglobin < 8 g/dL	• Withhold Zejula for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥ 1,500/μL or haemoglobin returns to ≥ 9 g/dL. • Resume Zejula at a reduced dose per Table 1. • Discontinue Zejula if neutrophils and/or haemoglobin have not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg once daily.
Confirmed diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML)	• Permanently discontinue Zejula.

Special Populations

Elderly

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

Renal impairment

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

Hepatic impairment

No dose adjustment is needed in patients with mild hepatic impairment.

For patients with moderate hepatic impairment, the recommended starting dose of niraparib is 200 mg once daily (see Section 5.2 Pharmacokinetic Properties.).

There are no data in patients with severe hepatic impairment; use with caution in these patients, see Section 5.2 Pharmacokinetic Properties.

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.

Method of administration

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

Zejula can be taken without regard to meals (see section 5.2 Pharmacokinetic Properties).

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

Haematologic adverse reactions (thrombocytopenia, anaemia, neutropenia) have been reported in patients treated with Zejula. In the PRIMA study, patients eligible for niraparib therapy had the following baseline haematological parameters: absolute neutrophil count (ANC) ≥ 1,500 cells/μL; platelets ≥ 100,000 cells/μL and haemoglobin ≥ 10 g/dL prior to therapy. The overall incidence of Grade ≥3 thrombocytopenia, anaemia and neutropenia in clinical and/or laboratory findings were reported, respectively, in 39%, 31%, and 21% of patients receiving Zejula. Discontinuation due to thrombocytopenia, anaemia, and neutropenia occurred, respectively, in 4%, 2%, and 2% of patients.

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

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

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

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

Test complete blood counts weekly for the first month, followed by monthly monitoring for the next 10 months of treatment and periodically after this time to monitor for clinically significant changes in any 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 patients who received Zejula (see Section 4.8 Undesirable effects).

In clinical trials, the duration of Zejula treatment in patients prior to developing MDS/AML varied from 1 month to > 4 years. The cases were typical of secondary, cancer therapy-related MDS/AML. All patients had received platinum-containing chemotherapy regimens and many had also received other DNA damaging agents and radiotherapy. Some of the patients had a history of bone marrow suppression.

For suspected MDS/AML or prolonged haematological toxicities, the patient should be referred to a haematologist for further evaluation. If MDS/AML is confirmed, treatment with Zejula should be discontinued 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 and heart rate should be monitored at least weekly for the first two months, then monthly for the first year and periodically thereafter during treatment with Zejula.

Hypertension should be medically managed with antihypertensive medicinal products as well as adjustment of the Zejula dose (see Section 4.2 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.

Posterior Reversible Encephalopathy Syndrome (PRES)

There have been rare reports (0.09% of clinical trial patients) of Zejula-treated patients developing signs and symptoms that are consistent with Posterior Reversible Encephalopathy Syndrome (PRES) (see 4.8 Adverse Reactions). PRES is a rare neurologic disorder that can present with the following signs and symptoms including seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended, along with discontinuation of niraparib. The safety of reinitiating niraparib therapy in patients previously experiencing PRES is not known.

Pregnancy/contraception

Zejula should not be used during pregnancy or in women of childbearing potential not willing to use highly effective contraception during therapy and for 6 months after receiving the last dose of Zejula (see Section 4.6 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 Interaction with other medicines and other forms of interaction

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 niraparib on other medicinal products

Even though inhibition of CYP3A4 in the liver is not expected, the potential to inhibit CYP3A4 at the intestinal level has not been established at relevant niraparib concentrations. Therefore, caution is recommended when 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 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, and MATE1/2)

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

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

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

Breast-feeding

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

Fertility

There are no clinical data on the effects of niraparib on fertility. A reversible reduction of spermatogenesis was observed in rats and dogs (see Animal toxicology and/or pharmacology).

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, difficulty concentrating and dizziness. Patients who experience these symptoms should observe caution when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

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

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

Tabulated list of adverse reactions

Table 4: Tabulated list of adverse reactions[a]

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

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

System Organ Class	Frequency of all CTCAE[b] grades	Frequency of CTCAE[b] grade 3 or 4
	Common Dry mouth, mucositis, stomatitis	Diarrhoea, mucositis, 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

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

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

The adverse reactions noted in the group of patients who were administered a 200-mg starting dose of Zejula based on baseline weight or platelet count were of similar or lesser frequency compared to the group administered 300 mg (Table 4). See 4.4 Special Warnings and Precautions For Use 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 Zejula treatment with the incidence decreasing over time.

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

Thrombocytopenia

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

In NOVA, approximately 60% of patients receiving Zejula experienced thrombocytopenia of any grade, and 34% of patients experienced Grade 3/4 thrombocytopenia. In patients with baseline platelet count less than 180,000 cells/μL, thrombocytopenia of any grade and Grade 3/4 occurred in 76% and 45% of the patients, respectively. The median time to onset of thrombocytopenia regardless of grade, and Grade 3/4 thrombocytopenia was 22 and 23 days, respectively. The rate of new incidences of thrombocytopenia after intensive dose modifications were performed during the first two months of treatment from Cycle 4 was 1.2%. The median duration of thrombocytopenia events of any grade was 23 days, and the median duration of Grade 3/4 thrombocytopenia was 10 days. Patients treated with Zejula who develop thrombocytopenia might have an increased risk of haemorrhage. Discontinuation due to thrombocytopenia events (thrombocytopenia and platelet count decreased) occurred in approximately 3% of the patients.

In the NOVA study, 48 of 367 (13%) 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 180,000 cells/μL. Approximately 76% of patients with lower baseline platelets (< 180,000 cells/μL) who received Zejula experienced thrombocytopenia of any grade, and 45% of the patients experienced Grade 3/4 thrombocytopenia. Pancytopenia has been observed in < 1% of patients receiving Zejula.

Anaemia

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

In NOVA, approximately 50% of patients experienced anaemia of any grade, and 25% experienced Grade 3/4 anaemia. The median time to onset of anaemia of any grade was 42 days, and 85 days for Grade 3/4 events. The median duration of anaemia of any grade was 63 days, and 8 days for Grade 3/4 events. Anaemia of any grade might persist during Zejula treatment. In the clinical programme, anaemia was managed with laboratory monitoring, dose modification (see 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

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

In NOVA, approximately 30% of patients receiving Zejula experienced neutropenia of any grade, and 20% of patients experienced Grade 3/4 neutropenia. The median time to onset of neutropenia of any grade was 27 days, and 29 days for Grade 3/4 events. The median duration of neutropenia of any grade was 26 days, and 13 days for Grade 3/4 events. In 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.

Myelodysplastic syndrome/Acute myeloid leukaemia

In clinical studies, MDS/AML occurred in 1% patients treated with niraparib, with 41% of cases having a fatal outcome. The incidence was higher in patients with relapsed ovarian cancer who had received 2 or more lines of prior platinum chemotherapy and with *gBRCAmut* following 5.6 years survival follow-up. All patients had potential contributing factors for the development of MDS/AML, having received previous chemotherapy with platinum agents. Many had also received other DNA damaging agents and radiotherapy. The majority of reports were in *gBRCAmut* carriers. Some of the patients had a history of previous cancer or of bone marrow suppression.

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

In the NOVA study in patients with relapsed ovarian cancer who had received at least two prior lines of platinum chemotherapy, the overall incidence of MDS/AML was 3.5% in patients receiving niraparib and 1.7% in patients receiving placebo at a follow-up of 5.6 years. In *gBRCAmut* and non-*gBRCAmut* cohorts, the incidence of MDS/AML was 6.6% and 1.7% in patients receiving niraparib and 3.1% and 0.9% in patients receiving placebo, respectively.

Hypertension

In PRIMA, Grade 3-4 hypertension occurred in 6% of Zejula-treated patients compared to 1% of placebo-treated patients with a median time from first dose to first onset in the Zejula arm of 50 days (range: 1 to 589 days) and with a median duration of 12 days (range: 1 to 61 days). Discontinuation due to hypertension occurred in 0% of patients.

In NOVA, hypertension of any grade occurred in 19.3% of patients treated with Zejula. Grade 3/4 hypertension occurred in 8.2% of patients. Discontinuation due to hypertension occurred in < 1% of patients.

Paediatric population

There are no clinical study data with Zejula in the paediatric population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via: https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: other neoplastic agents, ATC code: L01XK02

Mechanism of action

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

Pharmacodynamic effects

The pharmacodynamic response of niraparib has not been characterized.

Clinical efficacy and safety

First-line ovarian cancer maintenance treatment

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

Patients were randomised post-completion of first-line platinum-based chemotherapy plus/minus surgery. Bevacizumab was allowed with chemotherapy. Patients who had neoadjuvant chemotherapy followed by interval debulking surgery could have visible residual or no residual disease. Randomisation was stratified by best response during the front-line platinum regimen (complete response vs partial response), neoadjuvant

chemotherapy (NACT) (Yes vs No), and homologous recombination deficiency (HR) status [positive vs negative or not determined]. Testing for HRD was performed using the HRD test on tumour tissue obtained at the time of initial diagnosis.

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

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

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

The major efficacy outcome measure, progression-free survival (PFS), was determined by blinded independent central review (BICR) per RECIST, version 1.1. Overall survival (OS) was a key secondary objective. PFS testing was performed hierarchically: first in the HR deficient population, then in the overall population. The median age was 62 and ranged from 32 to 85 years among patients randomised to niraparib and 33 to 88 years among patients randomised to placebo. Eighty-nine percent of all patients were white. Sixty-nine percent of patients randomised with 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. Sixty-seven percent of the patients received NACT. Sixty-nine percent of the patients had a complete response to the first-line platinum-based chemotherapy.

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

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

	HR deficient population		Overall population	
	Zejula (N=247)	placebo (N=126)	niraparib (N=487)	placebo (N=246)
PFS median	21.9 (19.3, NE)	10.4 (8.1, 12.1)	13.8 (11.5, 14.9)	8.2 (7.3, 8.5)

(months; 95% CI)[b]				
p-value[b]	<0.0001		<0.0001	
Hazard ratio (HR)[c] (95% CI)	0.43 (0.31, 0.59)		0.62 (0.50, 0.76)	

[a] Efficacy analysis was based on blinded independent central review (BICR).

[b] Based on a stratified log-rank test

[c] Based on a stratified Cox proportional hazards model

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

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

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

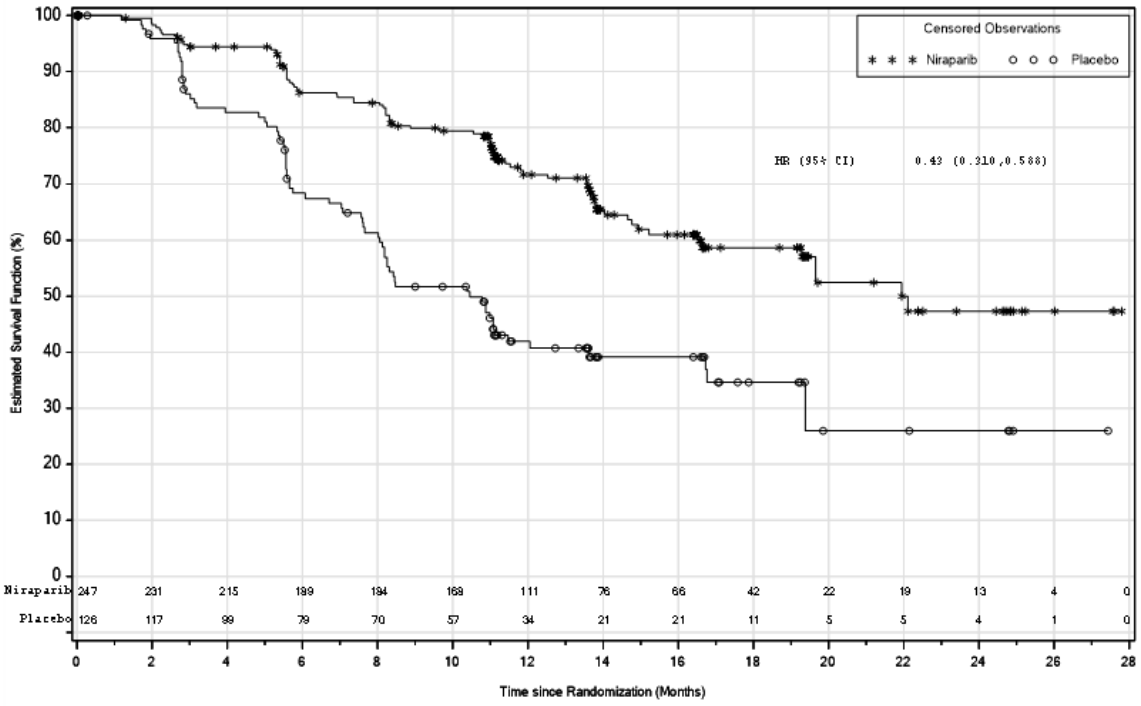
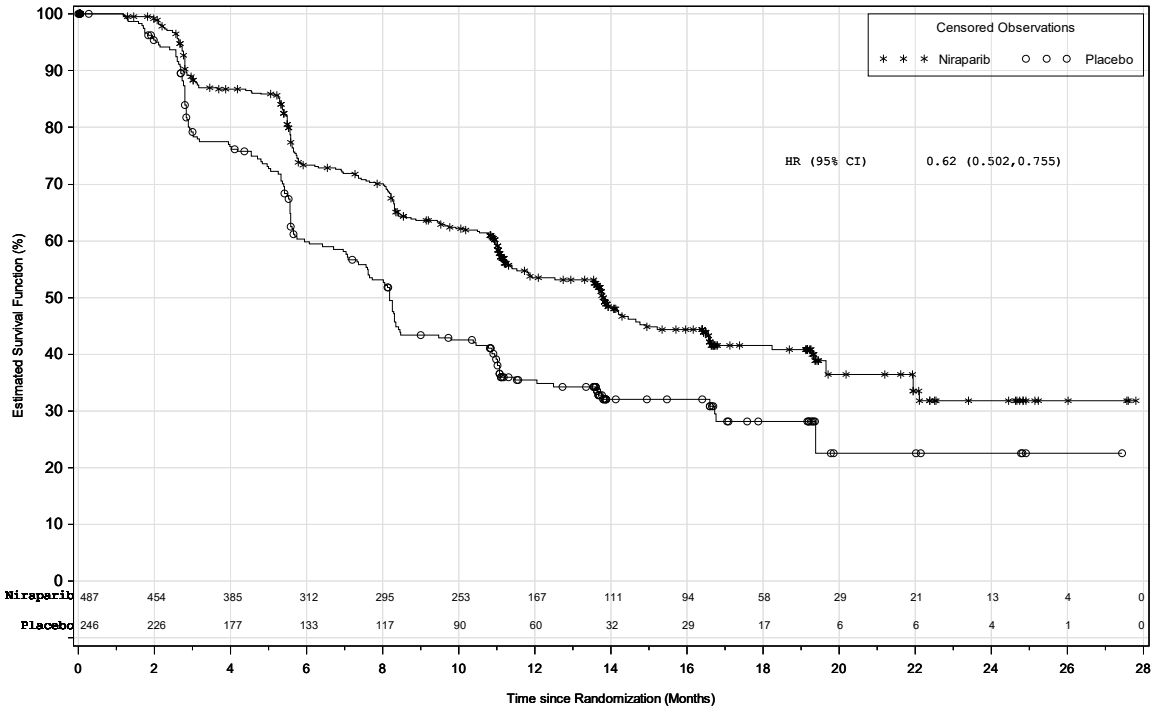


Figure 2: Progression-free survival in the overall population- PRIMA (ITT population, N=733)



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

At the time of the primary PFS analysis, the interim analysis of OS demonstrated a hazard ratio of 0.70 (95% CI: 0.44, 1.11) with an estimated survival at two years after randomisation of 84% for patients receiving Zejula, as compared to 77% for patients receiving placebo. For the HR deficient population, the hazard ratio was 0.61 (95% CI: 0.265, 1.388) and for the HR proficient population, the hazard ratio was 0.51 (95% CI:0.271, 0.973).

No statistically significant differences were observed between niraparib and placebo in patient reported symptoms or HRQoL as measured by improvement and worsening rates in FOSI, EQ-5D-5L, and EORTC-QLQ.

Recurrent ovarian cancer maintenance treatment

The safety and efficacy of Zejula as maintenance therapy was studied in a Phase 3 randomised, double-blind, placebo-controlled international trial (NOVA) in patients with relapsed predominantly high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who were platinum sensitive, defined by complete response (CR) or partial response (PR) for more than six months to their penultimate (next to last) platinum-based therapy. To be eligible for Zejula treatment, the patient 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 (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 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 g*BRCA* mutation and HRD was performed using the HRD test on tumour tissue obtained at the time of initial diagnosis or at the time of recurrence.

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

Patients began treatment on Cycle 1/Day 1 (C1/D1) with Zejula 300 mg or matched placebo administered 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 6 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 6: Summary of primary objective outcomes in the NOVA study

	g*BRCA*mut cohort		**Non-g*BRCA*mut cohort**	
	Zejula (N = 138)	**placebo (N = 65)**	**Zejula (N = 234)**	**placebo (N = 116)**
PFS median in months (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 (HR) (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.

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

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

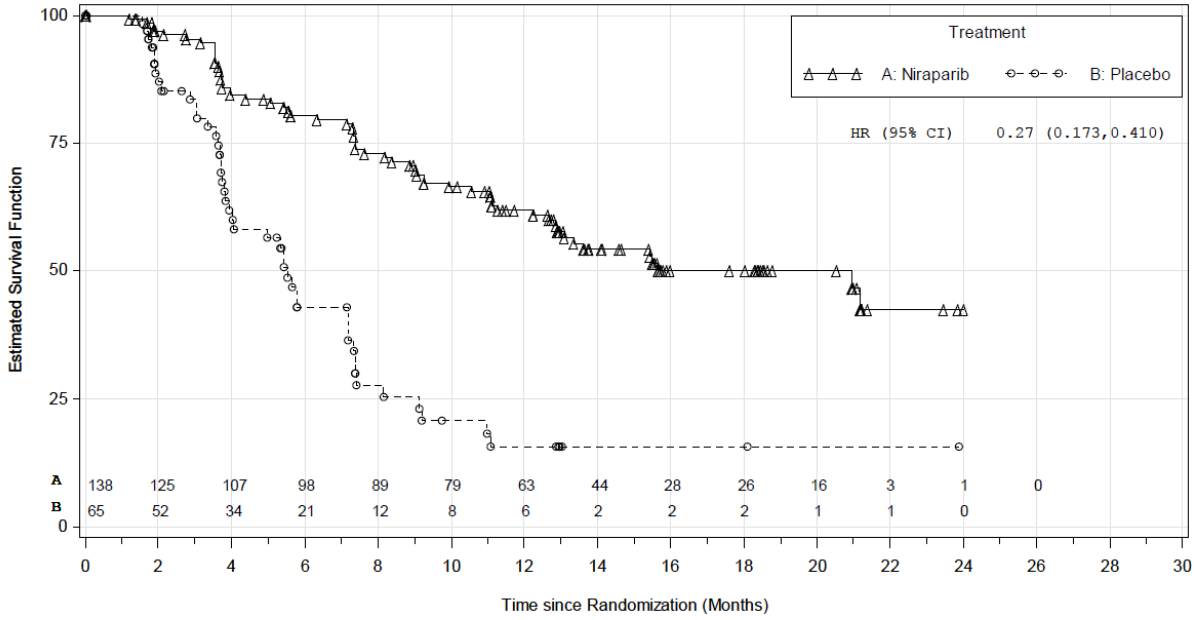
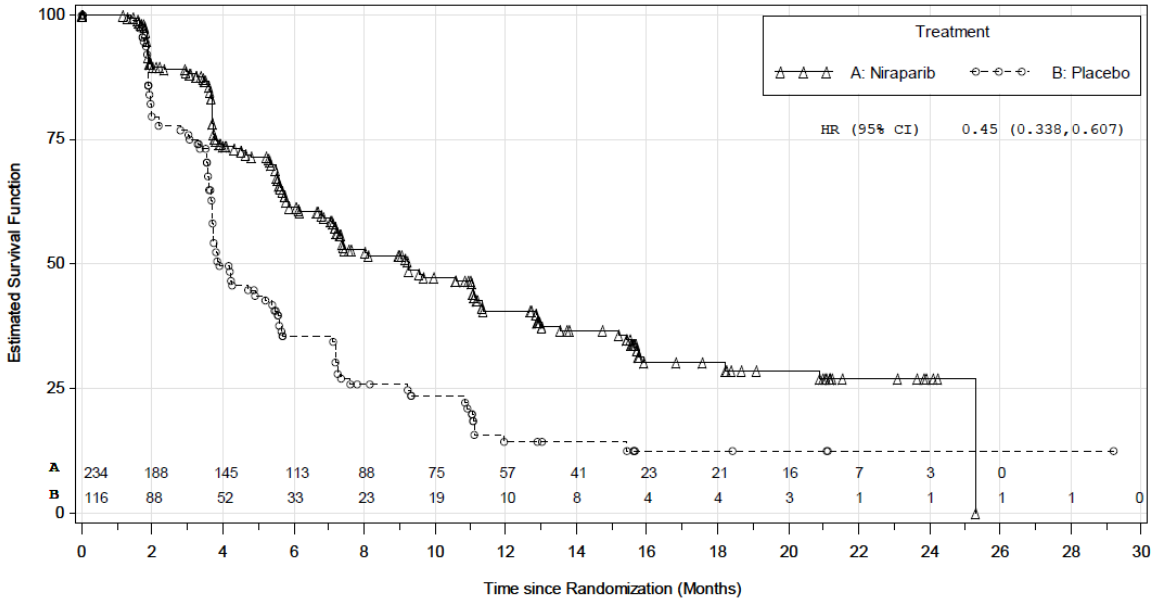


Figure 4: Kaplan-Meier plot for progression-free survival in the non-g*BRCA*mut cohort overall based on IRC assessment- NOVA (ITT population, N = 350)



Secondary efficacy endpoints in NOVA

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

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

At the final analysis, the median PFS2 in the 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).

Overall survival analyses in NOVA

Overall survival analyses were secondary outcome measures in the NOVA study. At the final analysis of overall survival, the median OS in the g*BRCA*mut cohort (n = 203) was 40.9 months for patients treated with niraparib compared with 38.1 months for patients on placebo (HR=0.85; 95% CI: 0.61, 1.20). The cohort maturity for the g*BRCA*mut cohort was 76%. The median OS in the non-*gBRCA*mut cohort (n = 350) was 31.0 months for patients treated with niraparib compared with 34.8 months for patients on placebo (HR=1.06; 95% CI: 0.81, 1.37). The cohort maturity for the non-g*BRCA*mut cohort was 79%.

Overall survival analyses in NORA

The overall survival results of NOVA are supported by an OS analyses from a Phase 3 regional registrational study. NORA was a randomised, double-blind, placebo-controlled clinical study (n = 265) conducted in China to evaluate the efficacy and safety of niraparib as maintenance therapy in patients with platinum-sensitive recurrent ovarian cancer.

Based on an analysis of preliminary OS events from the NORA study, a potential favourable OS trend was observed in the niraparib maintenance treatment arm, compared with placebo in ITT (44% maturity), g*BRCA*mut (36% maturity) and non-g*BRCA*mut (47% maturity), despite considerable numbers of patients in the placebo arm receiving PARPi in subsequent therapy.

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

Data to support ISD in recurrent ovarian cancer maintenance treatment population

After the first 16 patients were enrolled on a fixed starting dose of 300 mg, the study was amended to include an individualised starting dose of 200 mg or 300 mg depending on baseline body weight or platelet count (henceforth referred to as an individualised starting dose or ISD).

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

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

Paediatric population

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

5.2 Pharmacokinetic properties

Absorption

Following a single-dose administration of 300 mg niraparib under fasting conditions, niraparib was measurable in plasma within 30 minutes and the mean peak plasma concentration (C_{max}) for niraparib was reached 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 capsules) with a high-fat high-calorie meal may result in a slight decrease in Cmax (~20%) relative to administration of Zejula (3 x 100 mg) under fasted conditions. Food did not significantly affect the overall exposure of niraparib (AUCT and AUC_{∞}).

The tablet and capsule formulations have been demonstrated to be bioequivalent. Following administration of either one 300 mg tablet or three 100 mg capsules of niraparib in 108 patients with solid tumours under fasting conditions, the 90% confidence intervals of the geometric mean ratios for the tablet compared to the capsules for C_{max}, AUC_{last} and AUC_{∞} fell within the limits of bioequivalence (0.80 and 1.25).

Following a high-fat meal in patients with solid tumours, the C_{max} and AUC_{inf} of niraparib tablets increased by 11% and 28% respectively, as compared with fasting conditions. These changes in exposure were not clinically meaningful.

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.

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 16.2 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 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).

In a clinical study of cancer patients using NCI-ODWG criteria to classify the degree of hepatic impairment, niraparib AUCinf in patients with moderate hepatic impairment (n=8) was 1.56 (90% CI: 1.06 to 2.30) times the niraparib AUCinf in patients with normal hepatic function (n=9) following administration of a single 300 mg dose. Niraparib dose adjustment is recommended for patients with moderate hepatic impairment (see section 4.2 Dose and method of administration). Moderate hepatic impairment did not have an effect on niraparib Cmax or on niraparib protein binding.

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

Capsules

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).

Tablets

Tablet core: microcrystalline cellulose, lactose monohydrate, povidone, crospovidone, silicone dioxide, magnesium stearate

Film coating: polyvinyl alcohol, titanium dioxide, polyethylene glycol, purified talc, ferrosoferric oxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Capsules

Store below 25ºC.

Tablets

Store below 30ºC.

6.5 Nature and contents of container

Capsules

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

Tablets

oPA/aluminium/PVC/aluminium/vinyl/acrylic blisters in cartons of 56 and 84 tablets.

Not all pack sizes or container types may be distributed in New Zealand.

6.6 Special precautions for disposal

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

GlaxoSmithKline NZ Limited
Private Bag 106600
Downtown
Auckland
New Zealand

Phone: (09) 367 2900
Facsimile: (09) 367 2910

9. DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to distribute the medicine:

17 March 2022

10. DATE OF REVISION OF THE TEXT

18 June 2024

SUMMARY TABLE OF CHANGES

Section changed	**Summary of new information**
1, 2, 3, 5.2, 6.1, 6.4, 6.5	Registration of 100 mg film-coated tablets
5.1	Update to ATC code

Version 5.0