ZEJULA Dosing Guide

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 a complete or partial response to platinum-based chemotherapy
- for the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with three or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either:
  - a deleterious or suspected deleterious *BRCA* mutation, or
  - genomic instability and who have progressed more than six months after response to the last platinum-based chemotherapy

  Select patients for therapy based on an FDA-approved companion diagnostic for ZEJULA.

Important Safety Information

Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), including some fatal cases, was reported in 15 patients (0.8%) out of 1,785 patients treated with ZEJULA monotherapy in clinical trials. The duration of therapy in patients who developed secondary MDS/cancer therapy-related AML varied from 0.5 months to 4.9 years. These patients had received prior chemotherapy with platinum agents and/or other DNA-damaging agents including radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

Please see additional Important Safety Information throughout, as well as the Prescribing Information.

RECOMMENDED ZEJULA STARTING DOSE BY INDICATION[1]

1L maintenance treatment for newly diagnosed advanced ovarian cancer*	2L+ maintenance treatment for recurrent ovarian cancer† and 4L+ late-line treatment following 3 prior lines of chemotherapy‡
200 mg taken orally once daily for: • Patients weighing <170 lb **OR** • Platelet count of <150,000/µL **300 mg taken orally once daily for:** • Patients weighing ≥170 lb **AND** • Platelet count of ≥150,000/µL	**300 mg taken orally once daily**

*Patients should start maintenance treatment with ZEJULA no later than 12 weeks after their most recent platinum-containing regimen.

†Patients should start maintenance treatment with ZEJULA no later than 8 weeks after their most recent platinum-containing regimen.

‡Treated with 3 or more prior chemotherapy regimens.

For patients with moderate hepatic impairment, reduce the starting dosage of ZEJULA to 200 mg once daily. Monitor patients for hematologic toxicity and reduce the dose further, if needed.[1]

Important Safety Information (continued)

Hematologic adverse reactions (thrombocytopenia, anemia, neutropenia, and/or pancytopenia) have been reported in patients receiving ZEJULA. The overall incidence of Grade ≥3 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 39%, 31%, and 21% of patients receiving ZEJULA in PRIMA; 29%, 25%, and 20% of patients receiving ZEJULA in NOVA; and 28%, 27%, and 13% of patients receiving ZEJULA in QUADRA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 4%, 2%, and 2% of patients in PRIMA; 3%, 1%, and 2% of patients in NOVA; and 4%, 2%, and 1% of patients in QUADRA. In patients who were administered a starting dose of ZEJULA based on baseline weight or platelet count in PRIMA, Grade ≥3 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 22%, 23%, and 15% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 3%, and 2% of patients. Do not start ZEJULA until patients have recovered from hematological toxicity caused by prior chemotherapy (≤Grade 1). Monitor complete blood counts weekly for the first month, monthly for the next 11 months, and periodically thereafter. If hematological toxicities do not resolve within 28 days following interruption, discontinue ZEJULA, and refer the patient to a hematologist for further investigations.

Hypertension and hypertensive crisis have been reported in patients receiving ZEJULA. Grade 3-4 hypertension occurred in 6% of patients receiving ZEJULA vs 1% of patients receiving placebo in PRIMA, with no reported discontinuations. Grade 3-4 hypertension occurred in 9% of patients receiving ZEJULA vs 2% of patients receiving placebo in NOVA, with discontinuation occurring in <1% of patients. Grade 3-4 hypertension occurred in 5% of ZEJULA-treated patients in QUADRA, with discontinuation occurring in <0.2% of patients. Monitor blood pressure and heart rate at least weekly for the first two months, then monthly for the first year, and periodically thereafter during treatment with ZEJULA. Closely monitor patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Manage hypertension with antihypertensive medications and adjustment of the ZEJULA dose if necessary.

1L MAINTENANCE TREATMENT FOR ADVANCED OVARIAN CANCER

1 DAILY DOSE

Zejula niraparib capsules 100 mg

MEDIAN PFS IN THE OVERALL POPULATION[1,2]

13.8 months ZEJULA **vs** **8.2** months Placebo

HR, 0.62 (95% CI, 0.50-0.76) *P*<0.0001

MEDIAN PFS IN THE HRd POPULATION[1,2]

21.9 months ZEJULA **vs** **10.4** months Placebo

HR, 0.43 (95% CI, 0.31-0.59) *P*<0.0001

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.

Study Design: PRIMA, a randomized, double-blind, placebo-controlled phase 3 trial, evaluated the safety and efficacy of ZEJULA in women (N=733) with newly diagnosed advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer following CR or PR to 1L platinum-based chemotherapy. Patients were randomized 2:1 to receive ZEJULA or placebo once daily. The primary endpoint was PFS in patients who had tumors that were HRd and then in the overall population, as determined on hierarchical testing. PFS was measured from time of randomization to time of disease progression or death.[1,2]

At the time of the PFS analysis, limited overall survival data were available with 11% deaths in the overall population.[1]

Important Safety Information (continued)

Posterior reversible encephalopathy syndrome (PRES) occurred in 0.1% of 2,165 patients treated with ZEJULA in clinical trials and has also been described in postmarketing reports. Monitor all patients for signs and symptoms of PRES, which include seizure, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Diagnosis requires confirmation by brain imaging. If suspected, promptly discontinue ZEJULA and administer appropriate treatment. The safety of reinitiating ZEJULA is unknown.

Embryo-fetal toxicity and lactation: Based on its mechanism of action, ZEJULA can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months after receiving their final dose of ZEJULA. Because of the potential for serious adverse reactions from ZEJULA in breastfed infants, advise lactating women to not breastfeed during treatment with ZEJULA and for 1 month after receiving the final dose.

Please see additional Important Safety Information throughout, as well as the Prescribing Information.

1L = first-line; 2L = second-line; 4L = fourth-line; CI = confidence interval; CR = complete response; HR = hazard ratio; HRd = homologous recombination deficient; PFS = progression-free survival; PR = partial response.

The approved starting dose for 1L maintenance is based on baseline weight and platelet count[1]

The only once-daily PARP inhibitor with an individualized starting dose[1-4]

If baseline weight: <170 lb OR platelets: <150,000/µL	STARTING DOSE:	FIRST DOSE REDUCTION:	SECOND DOSE REDUCTION:
	200 mg/day	100 mg/day	discontinue

If baseline weight: ≥170 lb AND platelets: ≥150,000/µL	STARTING DOSE:	FIRST DOSE REDUCTION:	SECOND DOSE REDUCTION:	THIRD DOSE REDUCTION:
	300 mg/day	200 mg/day	100 mg/day	discontinue

For patients with moderate hepatic impairment, reduce the starting dosage of ZEJULA to 200 mg once daily. Monitor patients for hematologic toxicity and reduce the dose further, if needed.[1]

Important Safety Information (continued)

Allergic reactions to FD&C Yellow No. 5 (tartrazine): ZEJULA capsules contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

First-line Maintenance Advanced Ovarian Cancer

Most common adverse reactions (Grades 1-4) in ≥10% of all patients who received ZEJULA in PRIMA were thrombocytopenia (66%), anemia (64%), nausea (57%), fatigue (51%), neutropenia (42%), constipation (40%), musculoskeletal pain (39%), leukopenia (28%), headache (26%), insomnia (25%), vomiting (22%), dyspnea (22%), decreased appetite (19%), dizziness (19%), cough (18%), hypertension (18%), AST/ALT elevation (14%), and acute kidney injury (12%).

Common lab abnormalities (Grades 1-4) in ≥25% of all patients who received ZEJULA in PRIMA included: decreased hemoglobin (87%), decreased platelets (74%), decreased leukocytes (71%), increased glucose (66%), decreased neutrophils (66%), decreased lymphocytes (51%), increased alkaline phosphatase (46%), increased creatinine (40%), decreased magnesium (36%), increased AST (35%) and increased ALT (29%).

Maintenance Recurrent Ovarian Cancer

Most common adverse reactions (Grades 1-4) in ≥10% of patients who received ZEJULA in NOVA were nausea (74%), thrombocytopenia (61%), fatigue/asthenia (57%), anemia (50%), constipation (40%), vomiting (34%), neutropenia (30%), insomnia (27%), headache (26%), decreased appetite (25%), nasopharyngitis (23%), rash (21%), hypertension (20%), dyspnea (20%), mucositis/stomatitis (20%), dizziness (18%), back pain (18%), dyspepsia (18%), leukopenia (17%), cough (16%), urinary tract infection (13%), anxiety (11%), dry mouth (10%), AST/ALT elevation (10%), dysgeusia (10%), palpitations (10%).

Please see additional Important Safety Information throughout, as well as the Prescribing Information.

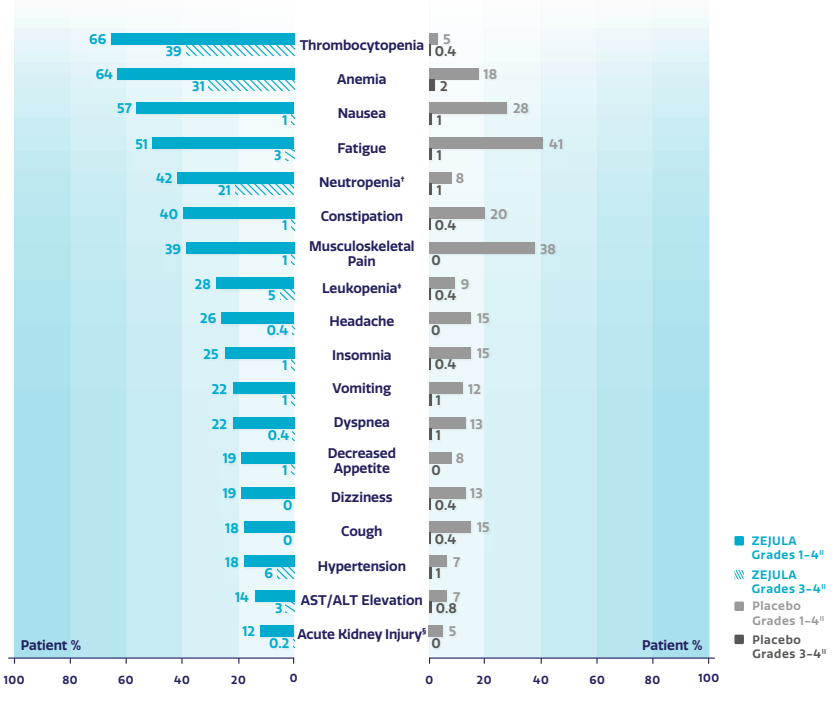
An established safety and tolerability profile, consistent with previous clinical trial experience[1,2]

1 DAILY DOSE
Zejula niraparib capsules 100 mg

12% of patients discontinued treatment with ZEJULA due to adverse events[2,5]

Adverse events resulting in discontinuation of ZEJULA in >1% of patients included thrombocytopenia (3.7%), anemia (1.9%), and nausea and neutropenia (1.2% each)[1]

Adverse Reactions Reported in ≥10% of All Patients Receiving ZEJULA in PRIMA[1]*



*All adverse reactions consist of grouped preferred terms except for nausea, vomiting, decreased appetite, headache, and insomnia, which are single preferred terms.

†Includes neutropenia, neutropenic infection, neutropenic sepsis, febrile neutropenia.

‡Includes leukopenia, lymphocyte count decreased, lymphopenia, white blood cell count decreased.

§Includes blood creatinine increased, blood urea increased, acute kidney injury, renal failure, blood creatine increased.

‖CTCAE = Common Terminology Criteria for Adverse Events version 4.02.

Side effects of ZEJULA may be managed with dose interruption and modification[1,2]

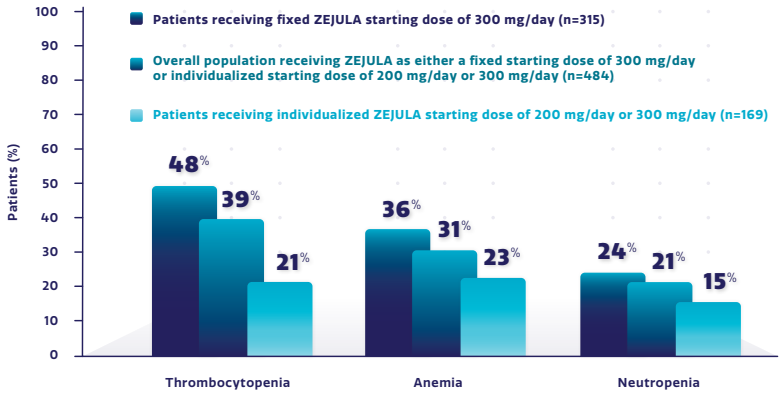
- In PRIMA, adverse events led to dose reduction or interruption in 80% of patients, most frequently from thrombocytopenia (56%), anemia (33%), and neutropenia (20%)[1]

1L = first-line; ALT = alanine transaminase; AST = aspartate transaminase; PARP = poly (ADP-ribose) polymerase.

Lower rates of select hematologic adverse reactions and similar efficacy were observed with an individualized starting dose[1,6,7*]

PRIMA prospectively evaluated the safety and efficacy of an individualized starting dose of either 200 mg or 300 mg, selected based on baseline weight and platelet count, as well as a fixed starting dose of 300 mg[1*]

Rates of Select Grade 3–4 Hematologic Adverse Reactions[1,6]



In PRIMA, patients in the overall and individualized populations experienced the same rates of grade 3-4 leukopenia.[1]

The individualized starting dose was shown to be effective in exploratory subgroup analyses* and is the approved starting dose for ZEJULA in first-line maintenance[1]

HR, 0.68 (95% CI, 0.48-0.97) in the overall population (n=258)
HR, 0.39 (95% CI, 0.22-0.72) in the HRd population (n=130)

In the *BRCA*m population (n=53)[7*]
HR, 0.29 (95% CI, 0.128-0.667)

*These analyses are exploratory in nature, do not control for type 1 error, and are not powered to determine treatment effect in any subgroup.

Important Safety Information (continued)

Common lab abnormalities (Grades 1-4) in ≥25% of patients who received ZEJULA in NOVA included: decrease in hemoglobin (85%), decrease in platelet count (72%), decrease in white blood cell count (66%), decrease in absolute neutrophil count (53%), increase in AST (36%), and increase in ALT (28%).

1 DAILY DOSE
Zejula
niraparib
capsules 100 mg

RESPOND WITH ZEJULA, A CONVENIENT ONCE-DAILY MAINTENANCE TREATMENT[1]

ONCE-DAILY ORAL MONOTHERAPY

TAKEN WITH OR WITHOUT FOOD

TAKEN ANY TIME OF THE DAY

ZEJULA should be taken at approximately the same time each day.[1]

No specific drug-drug interactions have been reported with ZEJULA†

†No clinical drug interaction studies have been performed with ZEJULA.

Important Safety Information (continued)

Treatment of Advanced HRD+ Ovarian Cancer

Most common adverse reactions (Grades 1-4) in ≥10% of patients who received ZEJULA in QUADRA were nausea (67%), fatigue (56%), thrombocytopenia (52%), anemia (51%), vomiting (44%), constipation (36%), abdominal pain (34%), musculoskeletal pain (29%), decreased appetite (27%), dyspnea (22%), insomnia (21%), neutropenia (20%), headache (19%), diarrhea (17%), acute kidney injury (17%), urinary tract infection (15%), hypertension (14%), cough (13%), dizziness (11%), AST/ALT elevation (11%), blood alkaline phosphatase increased (11%).

Common lab abnormalities (Grades 1-4) in ≥25% of patients who received ZEJULA in QUADRA included: decreased hemoglobin (83%), increased glucose (66%), decreased platelets (60%), decreased lymphocytes (57%), decreased leukocytes (53%), decreased magnesium (46%), increased alkaline phosphatase (40%), increased gamma glutamyl transferase (40%), increased creatinine (36%), decreased sodium (34%), decreased neutrophils (34%), increased aspartate aminotransferase (29%), and decreased albumin (27%).

Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), including some fatal cases, was reported in 15 patients (0.8%) out of 1785 patients treated with ZEJULA monotherapy in clinical trials. The duration of therapy in patients who developed secondary MDS/cancer therapy-related AML varied from 0.5 months to 4.9 years. These patients had received prior chemotherapy with platinum agents and/or other DNA-damaging agents including radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

Please see additional Important Safety Information throughout, as well as the Prescribing Information.

1L = first-line; *BRCA* = breast cancer susceptibility gene; *BRCA*m = *BRCA*-mutated; CI = confidence interval; HR = hazard ratio; HRd = homologous recombination deficient; PARP = poly (ADP-ribose) polymerase.

ZEJULA (niraparib) IS THE ONLY ONCE-DAILY PARP INHIBITOR INDICATED FOR RECURRENT OVARIAN CANCER[1,3,4]

Important Safety Information (continued)

Hematologic adverse reactions (thrombocytopenia, anemia, neutropenia, and/or pancytopenia) have been reported in patients receiving ZEJULA. The overall incidence of Grade ≥3 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 39%, 31%, and 21% of patients receiving ZEJULA in PRIMA; 29%, 25%, and 20% of patients receiving ZEJULA in NOVA; and 28%, 27%, and 13% of patients receiving ZEJULA in QUADRA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 4%, 2%, and 2% of patients in PRIMA; 3%, 1%, and 2% of patients in NOVA; and 4%, 2%, and 1% of patients in QUADRA. In patients who were administered a starting dose of ZEJULA based on baseline weight or platelet count in PRIMA, Grade ≥3 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 22%, 23%, and 15% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 3%, and 2% of patients. Do not start ZEJULA until patients have recovered from hematological toxicity caused by prior chemotherapy (≤Grade 1). Monitor complete blood counts weekly for the first month, monthly for the next 11 months, and periodically thereafter. If hematological toxicities do not resolve within 28 days following interruption, discontinue ZEJULA, and refer the patient to a hematologist for further investigations.

Hypertension and hypertensive crisis have been reported in patients receiving ZEJULA. Grade 3-4 hypertension occurred in 6% of patients receiving ZEJULA vs 1% of patients receiving placebo in PRIMA, with no reported discontinuations. Grade 3-4 hypertension occurred in 9% of patients receiving ZEJULA vs 2% of patients receiving placebo in NOVA, with discontinuation occurring in <1% of patients. Grade 3-4 hypertension occurred in 5% of ZEJULA-treated patients in QUADRA, with discontinuation occurring in <0.2% of patients. Monitor blood pressure and heart rate at least weekly for the first two months, then monthly for the first year, and periodically thereafter during treatment with ZEJULA. Closely monitor patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Manage hypertension with antihypertensive medications and adjustment of the ZEJULA dose if necessary.

Posterior reversible encephalopathy syndrome (PRES) occurred in 0.1% of 2,165 patients treated with ZEJULA in clinical trials and has also been described in postmarketing reports. Monitor all patients for signs and symptoms of PRES, which include seizure, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Diagnosis requires confirmation by brain imaging. If suspected, promptly discontinue ZEJULA and administer appropriate treatment. The safety of reinitiating ZEJULA is unknown.

Embryo-fetal toxicity and lactation: Based on its mechanism of action, ZEJULA can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months after receiving their final dose of ZEJULA. Because of the potential for serious adverse reactions from ZEJULA in breastfed infants, advise lactating women to not breastfeed during treatment with ZEJULA and for 1 month after receiving the final dose.

Allergic reactions to FD&C Yellow No. 5 (tartrazine): ZEJULA capsules contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

2L+ MAINTENANCE TREATMENT FOR RECURRENT OVARIAN CANCER

1 DAILY DOSE

Zejula niraparib capsules 100 mg

MEDIAN PFS IN THE g*BRCA*m POPULATION[1]

21 months ZEJULA **VS** **5.5** months Placebo

HR, 0.26 (95% CI, 0.17-0.41) *P*<0.0001

MEDIAN PFS IN THE non-g*BRCA*m POPULATION[1]

9.3 months ZEJULA **VS** **3.9** months Placebo

HR, 0.45 (95% CI, 0.34-0.61) *P*<0.0001

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

Study Design: NOVA, a phase 3, double-blind, placebo-controlled trial, evaluated the safety and efficacy of ZEJULA in women (N=553) with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer following CR or PR to second-line or later platinum-based chemotherapy. Patients were randomized to receive ZEJULA or placebo once daily. The primary endpoint was PFS, as assessed by an independent review. NOVA separately evaluated PFS in both the g*BRCA*m and non-g*BRCA*m cohorts. PFS was measured from time of randomization to time of disease progression or death. At the time of the PFS analysis, limited overall survival data were available, with 17% of survival events occurring in the study.[1,8,9]

Important Safety Information (continued)

First-line Maintenance Advanced Ovarian Cancer

Most common adverse reactions (Grades 1-4) in ≥10% of all patients who received ZEJULA in PRIMA were thrombocytopenia (66%), anemia (64%), nausea (57%), fatigue (51%), neutropenia (42%), constipation (40%), musculoskeletal pain (39%), leukopenia (28%), headache (26%), insomnia (25%), vomiting (22%), dyspnea (22%), decreased appetite (19%), dizziness (19%), cough (18%), hypertension (18%), AST/ALT elevation (14%), and acute kidney injury (12%).

Common lab abnormalities (Grades 1-4) in ≥25% of all patients who received ZEJULA in PRIMA included: decreased hemoglobin (87%), decreased platelets (74%), decreased leukocytes (71%), increased glucose (66%), decreased neutrophils (66%), decreased lymphocytes (51%), increased alkaline phosphatase (46%), increased creatinine (40%), decreased magnesium (36%), increased AST (35%) and increased ALT (29%).

Please see additional Important Safety Information throughout, as well as the Prescribing Information.

2L = second-line; *BRCA* = breast cancer susceptibility gene; CI = confidence interval; CR = complete response; g*BRCA*m = germline *BRCA*-mutated; non-g*BRCA*m = not germline *BRCA*-mutated; HR = hazard ratio; PARP = poly (ADP-ribose) polymerase; PFS = progression-free survival; PR = partial response.

ZEJULA is the only once-daily PARP inhibitor for ovarian cancer[1,3,4]

The approved starting dose of ZEJULA for 2L+ maintenance is 300 mg once daily[1]

ZEJULA Recommended Dose Modifications for Adverse Reactions[1]

STARTING DOSE:	FIRST DOSE REDUCTION:	SECOND DOSE REDUCTION:	THIRD DOSE REDUCTION:
300 mg/day	200 mg/day	100 mg/day	discontinue

For patients with moderate hepatic impairment, reduce the starting dosage of ZEJULA to 200 mg once daily. Monitor patients for hematologic toxicity and reduce the dose further, if needed.[1]

Important Safety Information (continued)

Maintenance Recurrent Ovarian Cancer

Most common adverse reactions (Grades 1-4) in ≥10% of patients who received ZEJULA in NOVA were nausea (74%), thrombocytopenia (61%), fatigue/asthenia (57%), anemia (50%), constipation (40%), vomiting (34%), neutropenia (30%), insomnia (27%), headache (26%), decreased appetite (25%), nasopharyngitis (23%), rash (21%), hypertension (20%), dyspnea (20%), mucositis/stomatitis (20%), dizziness (18%), back pain (18%), dyspepsia (18%), leukopenia (17%), cough (16%), urinary tract infection (13%), anxiety (11%), dry mouth (10%), AST/ALT elevation (10%), dysgeusia (10%), palpitations (10%).

Common lab abnormalities (Grades 1-4) in ≥25% of patients who received ZEJULA in NOVA included: decrease in hemoglobin (85%), decrease in platelet count (72%), decrease in white blood cell count (66%), decrease in absolute neutrophil count (53%), increase in AST (36%), and increase in ALT (28%).

Treatment of Advanced HRD+ Ovarian Cancer

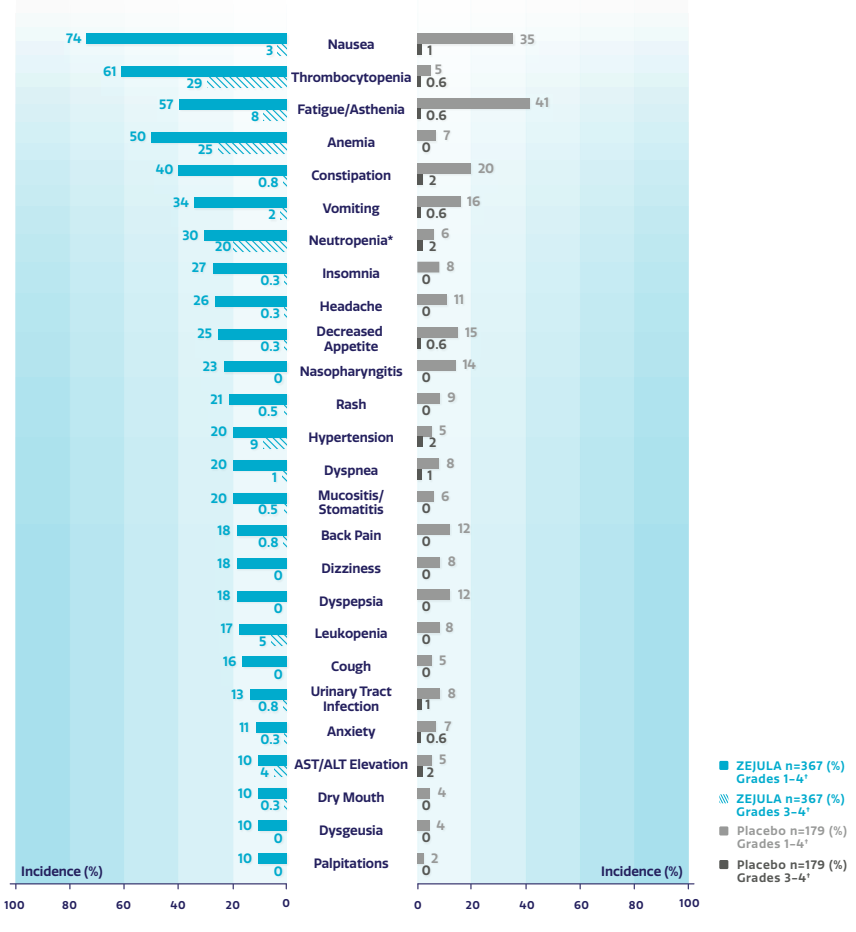
Most common adverse reactions (Grades 1-4) in ≥10% of patients who received ZEJULA in QUADRA were nausea (67%), fatigue (56%), thrombocytopenia (52%), anemia (51%), vomiting (44%), constipation (36%), abdominal pain (34%), musculoskeletal pain (29%), decreased appetite (27%), dyspnea (22%), insomnia (21%), neutropenia (20%), headache (19%), diarrhea (17%), acute kidney injury (17%), urinary tract infection (15%), hypertension (14%), cough (13%), dizziness (11%), AST/ALT elevation (11%), blood alkaline phosphatase increased (11%).

Common lab abnormalities (Grades 1-4) in ≥25% of patients who received ZEJULA in QUADRA included: decreased hemoglobin (83%), increased glucose (66%), decreased platelets (60%), decreased lymphocytes (57%), decreased leukocytes (53%), decreased magnesium (46%), increased alkaline phosphatase (40%), increased gamma glutamyl transferase (40%), increased creatinine (36%), decreased sodium (34%), decreased neutrophils (34%), increased aspartate aminotransferase (29%), and decreased albumin (27%).

Please see additional Important Safety Information throughout, as well as the Prescribing Information.

The side effect profile of ZEJULA is well characterized[1]

Adverse Reactions Reported in ≥10% of All Patients Receiving ZEJULA in NOVA: Grades 1-4 (N=546)[1]



*Includes preferred terms of neutropenic infection, neutropenic sepsis, and febrile neutropenia.
†Common Terminology Criteria for Adverse Events version 4.02.

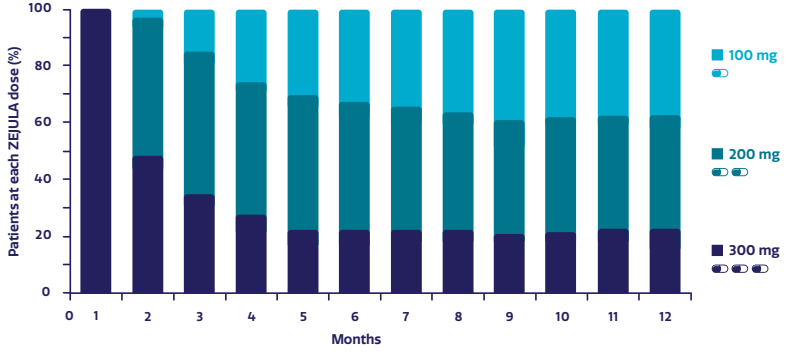
- In NOVA, adverse events led to dose reduction or interruption in 69% of patients, most frequently from thrombocytopenia (41%) and anemia (20%)[1]
- No on-treatment deaths were reported during the study[8]

2L = second-line; ALT = alanine transaminase; AST = aspartate transaminase; PARP = poly (ADP-ribose) polymerase.

After dose modification, 200 mg was the most commonly administered dose in NOVA[10,11]

Dose reductions primarily occurred within the first few months of NOVA[10]

ZEJULA Dose Level by Month on Treatment in the NOVA Trial



The approved starting dose for maintenance treatment of patients with recurrent ovarian cancer is 300 mg once daily. For patients with moderate hepatic impairment, reduce the starting dosage of ZEJULA to 200 mg once daily. Monitor patients for hematologic toxicity and reduce the dose further, if needed.[1]

Important Safety Information (continued)

Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), including some fatal cases, was reported in 15 patients (0.8%) out of 1785 patients treated with ZEJULA monotherapy in clinical trials. The duration of therapy in patients who developed secondary MDS/cancer therapy-related AML varied from 0.5 months to 4.9 years. These patients had received prior chemotherapy with platinum agents and/or other DNA-damaging agents including radiotherapy. Discontinue ZEJULA if MDS/AML is confirmed.

Hematologic adverse reactions (thrombocytopenia, anemia, neutropenia, and/or pancytopenia) have been reported in patients receiving ZEJULA. The overall incidence of Grade ≥3 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 39%, 31%, and 21% of patients receiving ZEJULA in PRIMA; 29%, 25%, and 20% of patients receiving ZEJULA in NOVA; and 28%, 27%, and 13% of patients receiving ZEJULA in QUADRA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 4%, 2%, and 2% of patients in PRIMA; 3%, 1%, and 2% of patients in NOVA; and 4%, 2%, and 1% of patients in QUADRA. In patients who were administered a starting dose of ZEJULA based on baseline weight or platelet count in PRIMA, Grade ≥3 thrombocytopenia, anemia, and neutropenia were reported, respectively, in 22%, 23%, and 15% of patients receiving ZEJULA. Discontinuation due to thrombocytopenia, anemia, and neutropenia occurred, respectively, in 3%, 3%, and 2% of patients. Do not start ZEJULA until patients have recovered from hematological toxicity caused by prior chemotherapy (≤Grade 1). Monitor complete blood counts weekly for the first month, monthly for the next 11 months, and periodically thereafter. If hematological toxicities do not resolve within 28 days following interruption, discontinue ZEJULA, and refer the patient to a hematologist for further investigations.

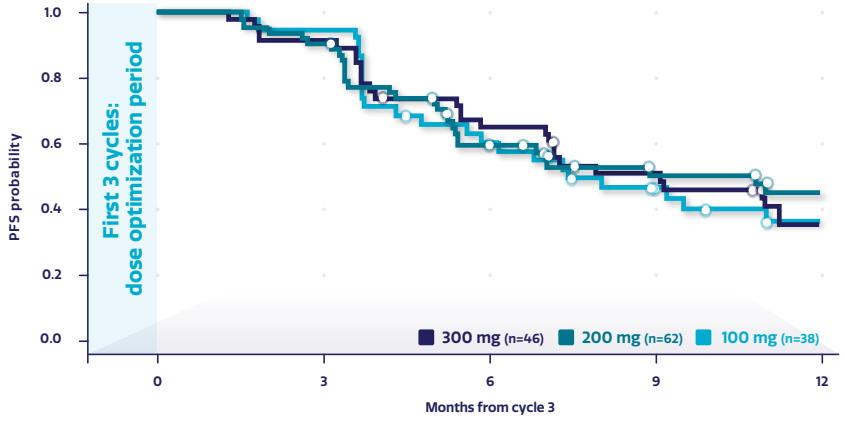
An exploratory subgroup analysis of NOVA suggested that efficacy was not compromised by dose reduction[12]

1 DAILY DOSE
Zejula niraparib capsules 100 mg

Estimated PFS probability by dose level measured after cycle 3 in *BRCA*wt subgroup[12]*

This analysis is exploratory in nature; it does not control for type 1 error and is not powered to determine treatment effect in any subgroup

PFS by Dose Level



- Confidence intervals for efficacy by dose curves are overlapping
- Interrupt and reduce dose at the first sign of unacceptable toxicity[1]

*Censored subjects are indicated by circles.

Important Safety Information (continued)

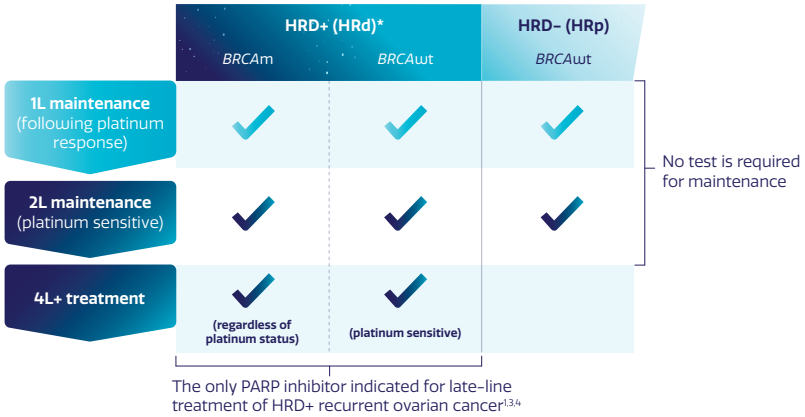
Hypertension and hypertensive crisis have been reported in patients receiving ZEJULA. Grade 3-4 hypertension occurred in 6% of patients receiving ZEJULA vs 1% of patients receiving placebo in PRIMA, with no reported discontinuations. Grade 3-4 hypertension occurred in 9% of patients receiving ZEJULA vs 2% of patients receiving placebo in NOVA, with discontinuation occurring in <1% of patients. Grade 3-4 hypertension occurred in 5% of ZEJULA-treated patients in QUADRA, with discontinuation occurring in <0.2% of patients. Monitor blood pressure and heart rate at least weekly for the first two months, then monthly for the first year, and periodically thereafter during treatment with ZEJULA. Closely monitor patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension. Manage hypertension with antihypertensive medications and adjustment of the ZEJULA dose if necessary.

Please see additional Important Safety Information throughout, as well as the Prescribing Information.

2L = second-line; *BRCA* = breast cancer susceptibility gene; *BRCA*wt = *BRCA* wild type; PFS = progression-free survival.

THE ONLY PARP INHIBITOR INDICATED FOR LATE-LINE TREATMENT OF HRD+ ADVANCED OVARIAN CANCER[1,3,4]

FDA-approved indications for ZEJULA[1]



*In QUADRA, HRD-positive status (HRD+) was determined using the Myriad myChoice® CDx as either t*BRCA*m and/or GIS+ (genomic instability score [GIS] ≥42).[1]

Important Safety Information (continued)

Posterior reversible encephalopathy syndrome (PRES) occurred in 0.1% of 2,165 patients treated with ZEJULA in clinical trials and has also been described in postmarketing reports. Monitor all patients for signs and symptoms of PRES, which include seizure, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Diagnosis requires confirmation by brain imaging. If suspected, promptly discontinue ZEJULA and administer appropriate treatment. The safety of reinitiating ZEJULA is unknown.

Embryo-fetal toxicity and lactation: Based on its mechanism of action, ZEJULA can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months after receiving their final dose of ZEJULA. Because of the potential for serious adverse reactions from ZEJULA in breastfed infants, advise lactating women to not breastfeed during treatment with ZEJULA and for 1 month after receiving the final dose.

4L+ TREATMENT FOR ADVANCED HRD+ OVARIAN CANCER

1 DAILY DOSE

Zejula niraparib capsules 100 mg

MEDIAN DURATION OF RESPONSE

8.3 months

in the indicated population[1]:
(95% CI, 6.5-NE) n=98

OBJECTIVE RESPONSE RATE

24%

(95% CI, 16-34) n=98[1]

ZEJULA is indicated for the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either:

- a deleterious or suspected deleterious *BRCA* mutation, or
- genomic instability and who have progressed more than 6 months after response to the last platinum-based chemotherapy

Select patients for therapy based on an FDA-approved companion diagnostic for ZEJULA.

Study Design: QUADRA, a single-arm, phase 2 trial of patients (N=463) with advanced ovarian cancer who have been treated with 3 or more prior lines of chemotherapy. The FDA-indicated population is for HRD+ patients with either *BRCA*m tumors, regardless of platinum status, or *BRCA*wt tumors with genomic instability (GIS+) and who had progressed more than 6 months after the last platinum-based chemotherapy. Those with prior exposure to PARP inhibitors were excluded. Patients received ZEJULA 300 mg once daily continuously for 28-day cycles until disease progression or unacceptable toxicity.[1,13]

Important Safety Information (continued)

Allergic reactions to FD&C Yellow No. 5 (tartrazine): ZEJULA capsules contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

Please see additional Important Safety Information throughout, as well as the Prescribing Information.

1L = first-line; 2L = second-line; 4L = fourth-line; *BRCA* = breast cancer susceptibility gene; *BRCA*m = *BRCA*-mutated; *BRCA*wt = *BRCA* wild type; CI = confidence interval; HRd = homologous recombination deficient; HRp = homologous recombination proficient; NE = not estimable; PARP = poly (ADP-ribose) polymerase; t*BRCA*m = tumor *BRCA*-mutated.

ZEJULA (niraparib) is the only once-daily PARP inhibitor for ovarian cancer[1,3,4]

The approved starting dose of ZEJULA for 4L+ treatment of advanced ovarian cancer is 300 mg once daily[1]

ZEJULA Recommended Dose Modifications for Adverse Reactions[1]

STARTING DOSE:	FIRST DOSE REDUCTION:	SECOND DOSE REDUCTION:	THIRD DOSE REDUCTION:
300 mg/day	200 mg/day	100 mg/day	discontinue

For patients with moderate hepatic impairment, reduce the starting dosage of ZEJULA to 200 mg once daily. Monitor patients for hematologic toxicity and reduce the dose further, if needed.[1]

Important Safety Information (continued)

First-line Maintenance Advanced Ovarian Cancer

Most common adverse reactions (Grades 1-4) in ≥10% of all patients who received ZEJULA in PRIMA were thrombocytopenia (66%), anemia (64%), nausea (57%), fatigue (51%), neutropenia (42%), constipation (40%), musculoskeletal pain (39%), leukopenia (28%), headache (26%), insomnia (25%), vomiting (22%), dyspnea (22%), decreased appetite (19%), dizziness (19%), cough (18%), hypertension (18%), AST/ALT elevation (14%), and acute kidney injury (12%).

Common lab abnormalities (Grades 1-4) in ≥25% of all patients who received ZEJULA in PRIMA included: decreased hemoglobin (87%), decreased platelets (74%), decreased leukocytes (71%), increased glucose (66%), decreased neutrophils (66%), decreased lymphocytes (51%), increased alkaline phosphatase (46%), increased creatinine (40%), decreased magnesium (36%), increased AST (35%) and increased ALT (29%).

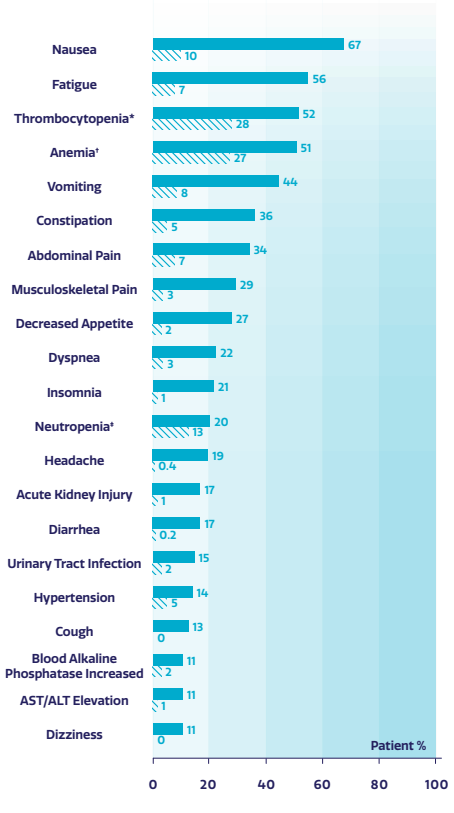
Maintenance Recurrent Ovarian Cancer

Most common adverse reactions (Grades 1-4) in ≥10% of patients who received ZEJULA in NOVA were nausea (74%), thrombocytopenia (61%), fatigue/asthenia (57%), anemia (50%), constipation (40%), vomiting (34%), neutropenia (30%), insomnia (27%), headache (26%), decreased appetite (25%), nasopharyngitis (23%), rash (21%), hypertension (20%), dyspnea (20%), mucositis/stomatitis (20%), dizziness (18%), back pain (18%), dyspepsia (18%), leukopenia (17%), cough (16%), urinary tract infection (13%), anxiety (11%), dry mouth (10%), AST/ALT elevation (10%), dysgeusia (10%), palpitations (10%).

Adverse reactions in QUADRA were consistent with previous clinical findings in NOVA[1]

1 DAILY DOSE
Zejula niraparib capsules 100 mg

Adverse Reactions Reported in ≥10% of Patients Receiving ZEJULA in QUADRA: Grades 1-4 (N=463) [1]



Adverse reactions led to dose reduction or interruption in 73% of patients receiving ZEJULA.

The most common adverse reactions (≥5%) resulting in dose reduction or interruption of ZEJULA were thrombocytopenia (40%), anemia (21%), nausea (13%), neutropenia (11%), vomiting (11%), fatigue (9%), and abdominal pain (5%).[1]

*Thrombocytopenia includes events with preferred terms of thrombocytopenia and platelet count decreased.

†Anemia includes events with preferred terms of anemia, hemoglobin decreased, anemia macrocytic, aplastic anemia, and normochromic normocytic anemia.

‡Neutropenia includes events with preferred terms of neutropenia, neutrophil count decreased, neutropenic infection, and neutropenic sepsis.

§Common Terminology Criteria for Adverse Events version 4.02.

Please see additional Important Safety Information throughout, as well as the Prescribing Information.

4L = fourth-line; ALT = alanine transaminase; AST = aspartate transaminase; PARP = poly (ADP-ribose) polymerase.

ZEJULA dose modifications to manage adverse reactions[1]

Dose Adjustments for Adverse Reactions[1]

Non-hematologic

- CTCAE ≥Grade 3 adverse reaction that persists despite medical management

Hematologic

- Hematologic ARs requiring transfusion
- Thrombocytopenia: platelet count <100,000/µL
- Grade ≥3 neutrophil count <1,000/µL
- Grade ≥3 hemoglobin count <8 g/dL

Interrupt treatment for up to 28 days*

Resume at reduced dose following resolution

Obtain CBC weekly

Resume at same† or reduced dose following resolution

Continue CBC weekly for an additional 4 weeks

Monitoring complete blood counts, blood pressure, and heart rate helps identify the need to dose modify[1]

BLOOD COUNTS
1X a week: 1st month
1X a month: Rest of year
1X every 2-3 months: After year 1‡

BLOOD PRESSURE AND HEART RATE
1X a week: 1st and 2nd month
1X a month: Rest of year
1X every 2-3 months: After year 1‡

*If hematological toxicities do not resolve within 28 days following interruption, discontinue ZEJULA and refer the patient to a hematologist for further investigation. †Resume at the same dose only for the first occurrence of thrombocytopenia if platelets are >75,000/µL. ‡Monitor periodically. Schedule provided as an example.

Important Safety Information (continued)

Common lab abnormalities (Grades 1-4) in ≥25% of patients who received ZEJULA in NOVA included: decrease in hemoglobin (85%), decrease in platelet count (72%), decrease in white blood cell count (66%), decrease in absolute neutrophil count (53%), increase in AST (36%), and increase in ALT (28%).

Treatment of Advanced HRD+ Ovarian Cancer

Most common adverse reactions (Grades 1-4) in ≥10% of patients who received ZEJULA in QUADRA were nausea (67%), fatigue (56%), thrombocytopenia (52%), anemia (51%), vomiting (44%), constipation (36%), abdominal pain (34%), musculoskeletal pain (29%), decreased appetite (27%),

Please see additional Important Safety Information throughout, as well as the Prescribing Information.

No starting dose adjustment necessary for most special populations or conditions[1]

1 DAILY DOSE Zejula niraparib capsules 100 mg

Dose adjustment

FOR MODERATE HEPATIC IMPAIRMENT§

Total bilirubin ≥1.5 x ULN to 3.0 x ULN and any AST level[1]

For patients with moderate hepatic impairment, reduce the starting dosage of ZEJULA to 200 mg once daily.[1]

Monitor patients for hematologic toxicity and reduce the dose further, if needed.

No dose adjustment necessary[1]

FOR FOOD

Food does not significantly affect the absorption of niraparib

FOR MILD/MODERATE RENAL IMPAIRMENT ||

Mild: CLcr 60-89 mL/min
Moderate: CLcr 30-59 mL/min

FOR MILD HEPATIC IMPAIRMENT

Total bilirubin <1.5 x ULN and any AST level
OR
bilirubin ≤ULN and AST >ULN[1]

FOR AGE

≥65

≥65 years

ZEJULA: once-daily oral dosing[1]

TAKEN ANY TIME OF THE DAY

Bedtime administration may be a potential method for managing nausea

ZEJULA should be taken at approximately the same time each day.

DRUG-DRUG INTERACTIONS

No specific drug-drug interactions have been reported¶

STORAGE REQUIREMENT

68-77°F

Store at room temperature (68-77 °F)

Important Safety Information (continued)

dyspnea (22%), insomnia (21%), neutropenia (20%), headache (19%), diarrhea (17%), acute kidney injury (17%), urinary tract infection (15%), hypertension (14%), cough (13%), dizziness (11%), AST/ALT elevation (11%), blood alkaline phosphatase increased (11%).

AR = adverse reaction; AST = aspartate transaminase; CBC = complete blood count; CLcr = creatinine clearance; CTCAE = Common Terminology Criteria for Adverse Events; ULN = upper limit of normal.

§There are no data in patients with severe hepatic impairment.

||There are no data in patients with severe renal impairment or end-stage renal disease undergoing hemodialysis.

¶No clinical drug interaction studies have been performed with ZEJULA.

CONSIDER ZEJULA FOR YOUR ELIGIBLE PATIENTS

Convenient, once-daily, oral monotherapy[1]
- The only once-daily PARPi monotherapy available for HRd patients[1-4]

Low discontinuation rates due to adverse reactions were observed with ZEJULA as maintenance treatment[1]

In 1L maintenance, lower rates of select Grade 3–4 hematologic adverse reactions were observed with an individualized starting dose compared to the overall study population[1,6]

Visit **ZEJULAHCP.COM** to explore more dosing information.

Important Safety Information (continued)

Common lab abnormalities (Grades 1-4) in ≥25% of patients who received ZEJULA in QUADRA included: decreased hemoglobin (83%), increased glucose (66%), decreased platelets (60%), decreased lymphocytes (57%), decreased leukocytes (53%), decreased magnesium (46%), increased alkaline phosphatase (40%), increased gamma glutamyl transferase (40%), increased creatinine (36%), decreased sodium (34%), decreased neutrophils (34%), increased aspartate aminotransferase (29%), and decreased albumin (27%).

Please see additional Important Safety Information throughout, as well as the Prescribing Information.

1L = first-line; PARPi = poly (ADP-ribose) polymerase inhibitor.

References: 1. ZEJULA (niraparib). Prescribing Information. GlaxoSmithKline; 2021. **2.** González-Martín A, Pothuri B, Vergote I, et al; PRIMA/ENGOT-OV26/GOG-3012 Investigators. Niraparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med*. 2019;381(25):2391-2402. doi:10.1056/NEJMoa1910962 **3.** Lynparza (olaparib). Prescribing Information. AstraZeneca Pharmaceuticals LP; 2021. **4.** Rubraca (rucaparib). Prescribing Information. Clovis Oncology, Inc; 2020. **5.** González-Martín A, Pothuri B, Vergote I, et al; PRIMA/ENGOT-OV26/GOG-3012 Investigators. Niraparib in patients with newly diagnosed advanced ovarian cancer [supplementary appendix]. *N Engl J Med*. 2019;381(25):1-42. doi:10.1056/NEJMoa1910962 **6.** Mirza MR, González-Martín A, Graybill W, et al. Evaluation of an individualized starting dose of niraparib in the PRIMA/ENGOT-OV26/GOG-3012 study. Poster presented at: American Society of Clinical Oncology Congress; May 29-31, 2020; virtual. **7.** Korach J, Graybill W, Redondo A, et al. Niraparib in patients with newly diagnosed advanced ovarian BRCAm cancer: a post hoc analysis of the PRIMA/ENGOT-OV26/GOG-3012 trial. *Int J Gynecol Cancer*. 2020;30(suppl 4):A125-A126. doi:10.1136/ijgc-2020-ESGO.220 **8.** Mirza MR, Monk BJ, Herrstedt J, et al; ENGOT-OV16/NOVA Investigators. Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer. *N Engl J Med*. 2016;375(22):2154-2164. doi:10.1056/NEJMoa1611310 **9.** Mirza MR, Monk BJ, Oza AM, et al. ENGOT-OV16/NOVA trial: niraparib maintenance therapy in patients with recurrent ovarian cancer. Presented at: 41st European Society for Medical Oncology Congress; October 7-11, 2016; Copenhagen, Denmark. **10.** Berek JS, Matulonis UA, Peen U, et al. Safety and dose modification for patients receiving niraparib. *Ann Oncol*. 2018;29(8):1784-1792. doi:10.1093/annonc/mdy181 **11.** Data on file. GlaxoSmithKline. **12.** Wang J, Zhang Z-Y, Mirza MR, et al. The exposure-response relationship of niraparib in patients with g*BRCA*mut and non-g*BRCA*mut: results from the ENGOT-OV16/NOVA trial. Poster presented at: Annual Congress of the European Society for Medical Oncology; September 8-12, 2017; Madrid, Spain. **13.** Moore KN, Secord AA, Geller MA, et al. Niraparib monotherapy for late-line treatment of ovarian cancer (QUADRA): a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol*. 2019;20(5):636-648. doi:10.1016/S1470-2045(19)30029-4

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1 DAILY DOSE
Zejula
niraparib
capsules 100 mg