דצמבר 2020

רופא/ה, רוקח/ת נכבדים,

הריני להודיעכם על עדכונים בהתוויה, משטר המינון ושינויים נוספים בעלון של התכשירים:

Zejula 100 mg זג'ולה 100 מ"ג

Hard Capsule

Per os

Niraparib (as tosylate monohydrate) 100 mg :מרכיב פעיל

-התוויה מאושרת

4.1 Therapeutic indications

Zejula is indicated:

- As monotherapy for the maintenance treatment of adult patients with advanced epithelial (FIGO Stages III and IV) high-grade ovarian, fallopian tube or primary peritoneal cancer who are in response (complete or partial) following completion of first-line platinum-based chemotherapy.

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

– עדכון משטר מינון

First-line ovarian cancer maintenance treatment

The recommended starting dose of Zejula is 200 mg (two 100-mg capsules), taken once daily. However, for those patients who weigh ≥ 77 kg and have baseline platelet count ≥ 150,000/µL, the recommended starting dose of Zejula is 300 mg (three 100-mg capsules), taken once daily. (see section 4.4 and 4.8).

Recurrent Ovarian Cancer *maintenance treatment*

The dose is three 100 mg hard capsules once daily, equivalent to a total daily dose of 300 mg.

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

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

Missing dose

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

Dose adjustments for adverse reactions

The recommended dose modifications~~Recommendations~~ for ~~the management of~~ adverse reactions are listed~~provided~~ in Tables~~Table~~ 1, 2 and 3.

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

~~Dose reductions may be implemented based on adverse reactions. The recommended dose reductions are first from three hard capsules daily (300 mg) to two hard capsules daily (200 mg). If further dose reduction is needed, a second dose reduction from two hard capsules daily (200 mg) to one capsule daily (100 mg) may be implemented.~~

~~The recommended dose modifications for adverse reactions are listed in Tables 1 and 2.~~

Table 1: Recommended ~~Dose~~ dose ~~Modifications~~ modifications for Adverse Reactionsi		
Starting dose level	**200 mg**	**300 mg**
First dose reduction	**100 mg/day~~a~~**	**200 mg/day (two 100-mg capsules)**
Second dose reduction	**Discontinue medication.**	**100 mg/day~~a~~ (one 100-mg capsule)**

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

Table 2: Dose modifications for non-haematologic adverse reactions

Non-haematologic CTCAE* ≥ Grade 3 treatment-related adverse reaction where prophylaxis is not considered feasible or adverse reaction persists despite treatment	First occurrence: • Withhold Zejula for a maximum of 28 days or until resolution of adverse reaction. • Resume Zejula at a reduced dose level per Table 1 ~~(200 mg/day).~~
	Second occurrence: • Withhold Zejula for a maximum of 28 days or until resolution of adverse reaction. • Resume Zejula at a reduced dose • Or discontinue per tablet 1 • ~~(100 mg/day).~~
CTCAE ≥ Grade 3 treatment-related adverse reaction lasting more than 28 days while patient is administered Zejula 100 mg/day	Discontinue treatment.

*CTCAE=Common Terminology Criteria for Adverse Events

Table 3: ~~2:~~ Dose modifications for haematologic adverse reactions	
Haematologic adverse reactions have been observed during the treatment with Zejula especially during the initial phase of the treatment. It is therefore recommended to monitor complete blood counts (CBCs) weekly during the first month of treatment and modify the dose as needed. After the first month, it is recommended to monitor CBCs monthly and periodically after this time (see section 4.4). Based on individual laboratory values, weekly monitoring for the second month may be warranted.	
Haematologic adverse reaction requiring transfusion or haematopoietic growth factor support	• For patients with platelet count ≤ 10,000/µL, platelet transfusion should be considered. If there are other risk factors for bleeding such as co-administration of anticoagulation or antiplatelet medicinal products, consider interrupting these substances and/or transfusion at a higher platelet count. • Resume Zejula at a reduced dose.
Platelet count < 100,000/µL	First occurrence: • Withhold Zejula for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥ 100,000/µL. • Resume Zejula at same or reduced dose per Table 1

Table 3: ~~2:~~ Dose modifications for haematologic adverse reactions	
	based on clinical evaluation. • If platelet count is < 75,000/µL at any time, resume at a reduced dose per Table 1.
	Second occurrence: • Withhold Zejula for a maximum of 28 days and monitor blood counts weekly until platelet counts return to ≥ 100,000/µL. • Resume Zejula at a reduced dose per Table 1. • Discontinue Zejula if the platelet count has not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Neutrophil < 1,000/µL or Haemoglobin < 8 g/dL	• Withhold Zejula for a maximum of 28 days and monitor blood counts weekly until neutrophil counts return to ≥ 1,500/µL or haemoglobin returns to ≥ 9 g/dL. • Resume Zejula at a reduced dose per Table 1. • Discontinue Zejula if neutrophils and/or haemoglobin have not returned to acceptable levels within 28 days of the dose interruption period, or if the patient has already undergone dose reduction to 100 mg QD.
Confirmed diagnosis of myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML)	• Permanently discontinue Zejula.

Patients with low body weight in recurrent ovarian cancer maintenance treatment

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

עדכונים נוספים:

Special warnings and precautions for use

Haematologic adverse reactions

~~In the NOVA study, patients eligible for Zejula therapy had the following baseline haematologic parameters: absolute neutrophil count (ANC) ≥ 1,500 cells/µL; platelets ≥ 100,000 cells/µL and haemoglobin ≥ 9 g/dL prior to therapy.~~ Haematologic adverse reactions (thrombocytopenia, anaemia, neutropenia) have been reported in patients treated with Zejula (see section 4.8). Patients with lower body weight or lower baseline platelet count may be at increased risk of Grade 3+ thrombocytopenia

(see section 4.2).

~~In the NOVA study, 48 of 367 (13 %) of patients experienced bleeding with concurrent thrombocytopenia; all bleeding events concurrent with thrombocytopenia were Grade 1 or 2 in severity except for one event of Grade 3 petechiae and haematoma observed concurrently with a serious adverse event of pancytopenia. Thrombocytopenia occurred more commonly in patients whose baseline platelet count was less than 180 × 10^9/L. Approximately 76 % of patients with lower baseline platelets (< 180 × 10^9/L) who received Zejula experienced thrombocytopenia of any grade, and 45 % of the patients experienced Grade 3/4 thrombocytopenia. Pancytopenia has been observed in < 1 % of patients receiving niraparib. If a patient develops severe persistent haematologic toxicity including pancytopenia that does not resolve within 28 days following interruption, Zejula should be discontinued.~~

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

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

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

Myelodysplastic syndrome/acute myeloid leukaemia

Cases of myelodysplastic syndrome/acute myeloid leukemia (MDS/AML) have been observed in patients treated with Zejula monotherapy or combination therapy in clinical trials and postmarketing.

~~Myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML), including cases with fatal outcome, have been reported in a small number of patients who received Zejula or placebo. In the pivotal Phase 3 international trial (ENGOT-OV16), the incidence of MDS/AML in patients who received niraparib (1.4 %) was similar to that in patients who received placebo (1.1 %). Overall, MDS/AML has been reported in 7 out of 751 (0.9 %) patients treated with Zejula in clinical studies.~~

The duration of Zejula treatment in patients prior to developing MDS/AML varied from 0.5 months~~1 month~~ to > 4.9~~2~~ years. The cases were typical of secondary, cancer therapy-related MDS/AML. All patients had received multiple platinum-containing chemotherapy regimens and many had also received other DNA damaging agents and radiotherapy. Some of the patients had a history of bone marrow dysplasia.

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

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Hypertension, including hypertensive crisis

Hypertension, including hypertensive crisis, has been reported with the use of Zejula (see section 4.8).~~.~~ Pre-existing hypertension should be adequately controlled before starting Zejula treatment~~. Blood pressure should be monitored monthly for the first year and periodically thereafter during treatment with Zejula.~~

Blood pressure should be monitored at least weekly for two months, monitored monthly afterwards for the first year and periodically thereafter during treatment with Zejula. Home blood pressure monitoring may be considered for appropriate patients with instruction to contact their health care provider in case of rise in blood pressure.

Hypertension should be medically managed with antihypertensive medicinal products as well as adjustment of the Zejula dose (see section 4.2), 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). Zejula should be discontinued in case of hypertensive crisis or if medically significant hypertension cannot be adequately controlled with antihypertensive therapy.

Posterior Reversible Encephalopathy Syndrome (PRES)

There have been reports of Posterior Reversible Encephalopathy Syndrome (PRES) in patients receiving Zejula (see section 4.8). PRES is a rare, reversible, neurological disorder which can present with rapidly evolving symptoms including seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI).

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

[…]

Effect of other medicinal products on niraparib

[…]

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

[…]

Inhibition of UDP-glucuronosyltransferases (UGTs)

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

[…]

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

4.8 Undesirable effects

Summary of the safety profile

Adverse~~In the pivotal ENGOT-OV16 study, adverse~~ reactions (ADRs) of all grades occurring in ≥ 10 % of the 851 patients receiving Zejula monotherapy in the pooled PRIMA (either 200 mg or 300 mg starting dose) and NOVA trials were nausea, anaemia, thrombocytopenia, fatigue, ~~/asthenia, anaemia,~~ constipation, vomiting, headache, insomnia, platelet count decreased, neutropenia, abdominal pain, ~~neutropenia, insomnia, headache,~~ decreased appetite, ~~nasopharyngitis,~~ diarrhoea, dyspnoea~~dyspnea~~, hypertension, asthenia, ~~dyspepsia, back pain,~~ dizziness, neutrophil count decreased, cough, ~~urinary tract infection,~~ arthralgia, back pain, white blood cell count decreased, and hot flush~~palpitations, and dysgeusia~~.

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

Tabulated list of adverse reactions

The following adverse reactions have been identified based on pooled data generated from ~~in~~ the PRIMA and NOVA clinical trials ~~ENGOT-OV16 study~~ in patients receiving Zejula monotherapy (see Table ~~43~~).

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); and very rare (< 1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table ~~43~~: Adverse drug reactions reported in patients treated with a fixed starting dose of 300 mg/day of Zejula (PRIMA and NOVA trial pool)[ii]~~: frequencies based on all causality adverse events*~~

System Organ Class	Frequency of all CTCAE* grades	Frequency of CTCAE* grade 3 or 4
Infections and infestations	**Very common** Urinary tract infection **Common** Bronchitis, conjunctivitis	**Uncommon** Urinary tract infection, bronchitis
Blood and lymphatic system disorders	**Very common** Thrombocytopenia, anaemia, neutropenia, leukopenia ~~**Common**~~ ~~Leukopenia~~ **Uncommon** Pancytopenia, febrile neutropenia	**Very common** Thrombocytopenia, anaemia, neutropenia **Common** Leukopenia **Uncommon** Pancytopenia, febrile neutropenia
Immune system disorders	**Common** Hypersensitivity†	**Uncommon** Hypersensitivity
Metabolism and nutrition disorders	**Very common** Decreased appetite **Common** Hypokalemia	**Common** Hypokalemia **Uncommon** Decreased appetite
Psychiatric disorders	**Very common** Insomnia **Common** Anxiety, depression **Uncommon** Confusional state	**Uncommon** Insomnia, anxiety, depression confusional state
Nervous system disorders	**Very common** Headache, dizziness ~~, dysgeusia~~**Common**	**Uncommon** Headache

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System Organ Class	Frequency of all CTCAE* grades	Frequency of CTCAE* grade 3 or 4
	Dysgeusia **Rare** Posterior Reversible Encephalopathy Syndrome (PRES)**	
Cardiac disorders	**Very common** Palpitations **Common** Tachycardia	
Vascular disorders	**Very common** Hypertension **Rare** Hypertensive crisis	**Common** Hypertension
Respiratory, thoracic and mediastinal disorders	**Very common** Dyspnoea~~Dyspnea~~, cough, nasopharyngitis **Common** Epistaxis **Uncommon** Pneumonitis	~~Common~~**Uncommon** Dyspnoea, epistaxis ~~Dyspnea~~ pneumonitis
Gastrointestinal disorders	**Very common** Nausea, constipation, vomiting, abdominal pain, diarrhoea, dyspepsia **Common** Dry mouth, abdominal distension, mucosal inflammation, ~~(including mucositis),~~ stomatitis	**Common** Nausea, vomiting, abdominal pain **Uncommon** Diarrhoea, constipation, mucosal inflammation, ~~(including mucositis),~~ stomatitis, dry mouth

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System Organ Class	Frequency of all CTCAE* grades	Frequency of CTCAE* grade 3 or 4
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, ~~ALT increased,~~ blood alkaline phosphatase increased ~~**Common**~~ ~~Gamma-glutamyl transferase increased~~

*CTCAE= ~~Frequencies are based on percent~~Common Terminology Criteria for Adverse Events version 4.02

** Based on niraparib clinical trial data. This is not limited to pivotal ENGOT-OV16 monotherapy study.

† Includes hypersensitivity, drug hypersensitivity, anaphylactoid reaction, drug eruption, angioedema, and urticaria.

The adverse reactions noted in the group of patients who were administered a 200 mg starting dose of

Zejula based on baseline weight or platelet count were of similar or lesser frequency compared to the group administered a fixed starting dose of 300 mg (Table 4).

-See ~~section~~ below for specific information regarding frequency of thrombocytopenia, anaemia and neutropenia~~using all-causality adverse events~~.

Description of selected adverse reactions

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

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

In the clinical programme, haematologic adverse reactions were managed with laboratory monitoring and dose modifications (see section 4.2).

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

Thrombocytopenia

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

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

23 days, and the median duration of Grade 3/4 thrombocytopenia was 10 days. Patients treated with Zejula who develop thrombocytopenia might have an increased risk of haemorrhage. In the clinical programme, thrombocytopenia was managed with laboratory monitoring, dose modification and platelet transfusion where appropriate (see section 4.2). 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 180×10^9/L. Approximately 76 % of patients with lower baseline platelets ($< 180 \times 10^9$/L) who received Zejula experienced thrombocytopenia of any grade, and 45 % of the patients experienced Grade 3/4 thrombocytopenia. Pancytopenia has been observed in < 1 % of patients receiving niraparib.

Anaemia

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

In NOVA, approximately~~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), and where appropriate with red blood cell transfusions. Discontinuation due to anaemia occurred in 1 % of patients.

Neutropenia

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

In NOVA, approximately~~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).~~ In addition, Granulocyte-Colony Stimulating Factor (G-CSF) was administered to approximately 6 % of patients treated with niraparib as concomitant therapy for neutropenia. Discontinuation due to neutropenia events occurred in 2 % of patients.

Hypertension

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

In NOVA, hypertension~~Hypertension, including hypertensive crisis, has been reported with Zejula therapy. Hypertension~~ of any grade occurred in 19.3 % of patients treated with Zejula. Grade 3/4 hypertension occurred in 8.2 % of patients. Hypertension~~In the clinical programme, hypertension~~ was readily managed with anti-hypertensive medicinal products. Discontinuation due to hypertension occurred in < 1 % of patients.

5.1 Pharmacodynamic properties

[…]

Clinical efficacy and safety

First-line ovarian cancer maintenance treatment

PRIMA was a Phase 3 double-blind, placebo-controlled trial in which patients (n=733) in complete or partial response to first-line platinum-based chemotherapy were randomised 2:1 to Zejula or matched placebo. PRIMA was initiated with a starting dose of 300 mg QD in 475 patients (whereof 317 was randomised to the niraparib arm vs. 158 in the placebo arm) in continuous 28-day cycles. The starting dose in PRIMA was changed with Amendment 2 of the Protocol. From that point forward, patients with a baseline body weight ≥77 kg and baseline platelet count ≥150,000/µL were administered Zejula 300 mg (3×100 mg capsules) (n=34) or placebo (3 capsules) daily (n=21) while patients with a baseline body weight <77 kg or baseline platelet count <150,000/µL were administered Zejula 200 mg (2×100 mg capsules) (n=122) or placebo (2 capsules) daily (n=61).

Patients were randomised post completion of first-line platinum-based chemotherapy plus/minus surgery. Subjects were randomized within 12 weeks of the first day of the last cycle of chemotherapy.

Subjects had ≥6 and ≤9 cycles of platinum-based therapy. Following interval debulking surgery subjects had ≥2 post-operative cycles of platinum-based therapy. Patients who had received bevacizumab with chemotherapy but could not receive bevacizumab as maintenance therapy were not excluded from the study. Patients could not have received prior PARP inhibitor therapy, including Zejula. Patients who had neoadjuvant chemotherapy followed by interval debulking surgery could have visible residual or no

residual disease. Patients with Stage III disease who had complete cytoreduction (i.e., no visible residual disease) after primary debulking surgery were excluded. Randomisation was stratified by best response during the front-line platinum regimen (complete response vs partial response), neoadjuvant chemotherapy (NACT) (Yes vs No); and homologous recombination deficiency (HRD) status [positive (HR deficient) vs negative (HR proficient) or not determined]. Testing for HRD was performed using the HRD test on tumour tissue obtained at the time of initial diagnosis. The CA-125 levels should be in the normal range (or a CA-125 decrease by > 90 %) during the patient's front-line therapy, and be stable for at least 7 days.

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

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

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

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

~~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.*~~

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

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

*At the time of primary PFS analysis, an estimated survival at two years after randomization of 84% for patients receiving Zejula, as compared to 77% for patients receiving placebo in the overall population.

Data of PFS2 and OS are currently not mature.

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

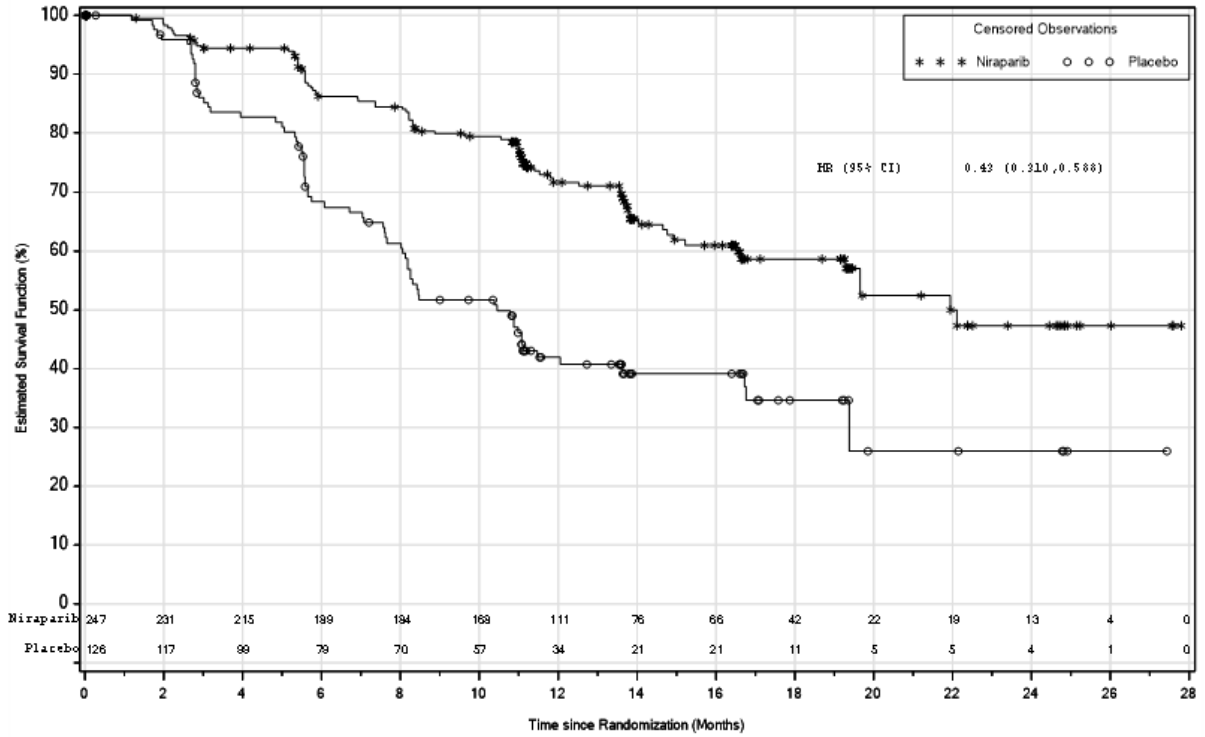

Figure 2: Progression-free survival in the overall population (ITT population, N=733)

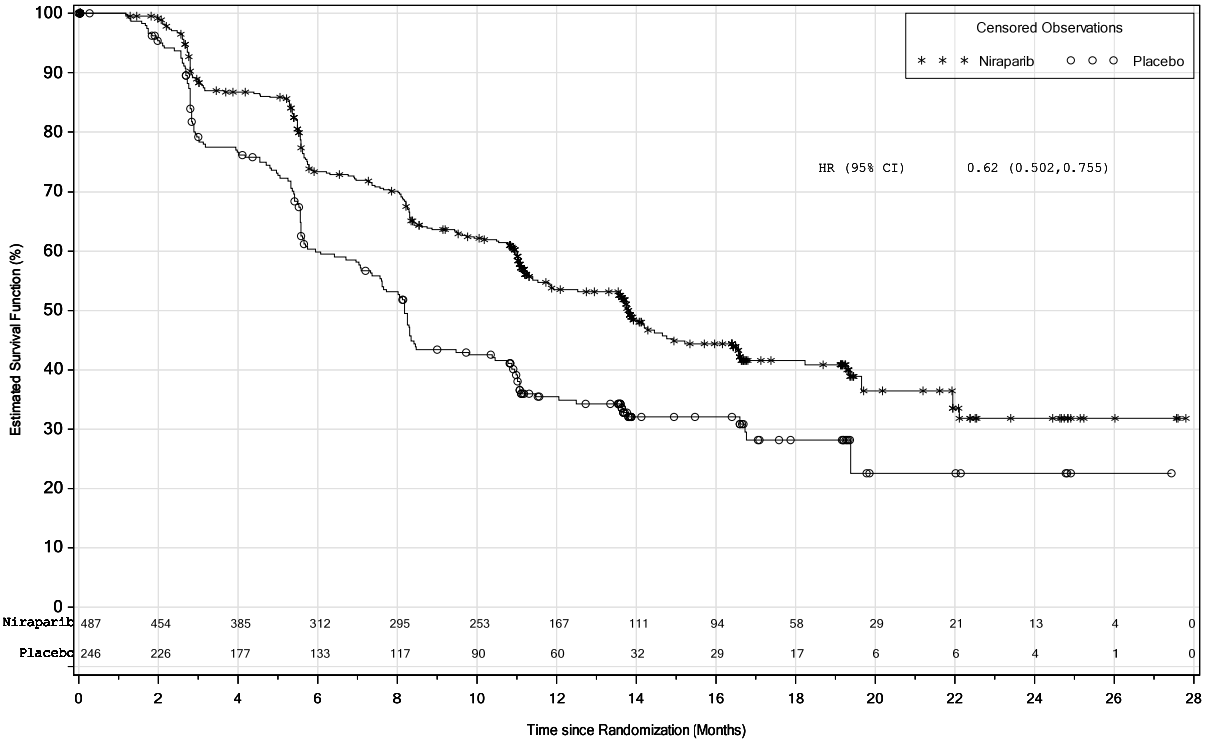

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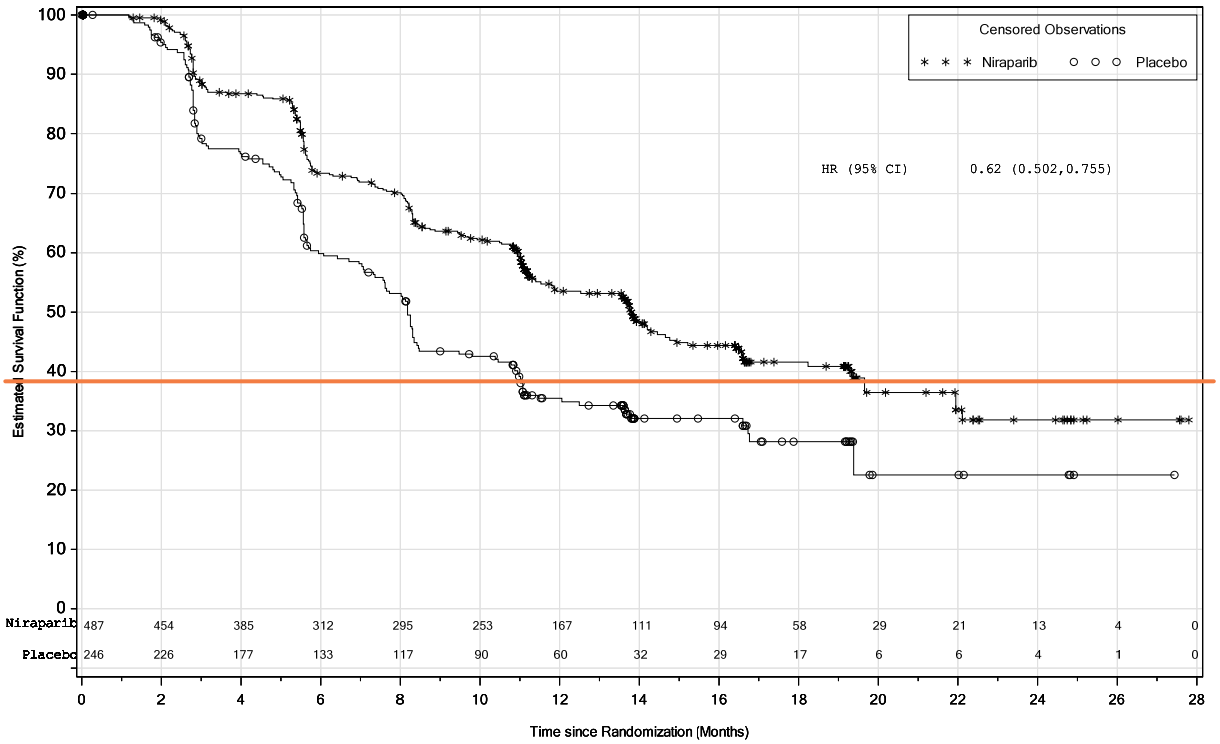
Figure 1: Progression-free survival in patients with HR deficient tumours (ITT population, N=373)[vi]

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



Subgroup analyses

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

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

[…]

5.2 Pharmacokinetic properties

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[…]

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

A concomitant high-fat meal did not significantly affect the pharmacokinetics of niraparib after administration of 300 mg of niraparib.

Distribution

Niraparib was moderately protein bound in human plasma (83.0 %), mainly with serum albumin. In a population pharmacokinetic analysis of niraparib, the apparent volume of distribution V_d/F was 1,311 L (based on a 70 kg patient) ~~1,074 L (based on a 70 kg patient)~~ in cancer patients, (CV 116%), indicating extensive tissue distribution of 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).~~

Renal impairment

In the population pharmacokinetic analysis, patients with mild (creatinine clearance 60-90 ml/min) and moderate (30-60 mL/min) renal impairment had mildly reduced niraparib clearance compared to individuals with normal renal function (7-17% higher exposure in mild and 17-38% higher exposure in moderate renal impairment). The difference in exposure is not considered to warrant dose adjustment. No patients with pre-existing severe renal impairment or end-stage renal disease undergoing hemodialysis were identified in clinical studies (see section 4.2).

Hepatic impairment

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

~~*Age, weight and race*~~

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

Weight, age and race

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

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

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

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

Preclinical safety data

~~Secondary~~ Safety pharmacology

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

Repeat-dose toxicity

~~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.~~

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

[...]...

בעלון לצרכן עודכנו הסעיפים:

1. למה מיועדת התרופה?
למה מיועדת זג'ולה?

זג'ולה מיועדת כמונותרפיה לטיפול אחזקתי בחולים מבוגרים עם:

- סרטן מתקדם מדרגה גבוהה מסוג שחלה אפיתליאלי (FIGO Stages III and IV) או סרטן חצוצרות או סרטן פריטוניאלי ראשוני, לאחר השגת תגובה מלאה או חלקית לכימותרפיה מבוססת פלטינום בקו טיפול הראשון.

- סרטן נשנה אפיטליאלי בדרגה גבוהה רגיש לפלטינום, של השחלות, חצוצרות (חלק ממערכת הרבייה הנשית המחבר את השחלות לרחם) או סרטן ראשוני של הצפק (הקרום המרפד את הבטן), שהגיב (באופן חלקי או מלא) לטיפול קודם בכימותרפיה על בסיס פלטינום.

כיצד תשתמשי בתרופה?

יש להשתמש בתכשיר תמיד בהתאם להוראות הרופא. קחי תרופה זו תמיד כפי שהורה לך הרופא המטפל או הרוקח. עלייך לבדוק עם הרופא או הרוקח אם אינך בטוחה בנוגע למינון ואופן הטיפול בתכשיר. המינון ואופן הטיפול יקבעו על ידי הרופא בלבד.

לסרטן שחלה אשר הגיב לטיפול ראשוני ~~ל~~בכימותרפיה מבוססת פלטינום-

המינון ההתחלתי המומלץ בדרך כלל הוא 200 מ"ג (שתי ~~כ~~קפסולות של 100 מ"ג), הנלקחות ביחד פעם ביום, עם או ללא מזון. במידה ואת שוקלת ≤ 77 ק"ג וספירת הטסיות בדם lμ/ 150,000 לפני תחילת הטיפול , המינון ההתחלתי המומלץ בדרך כלל הוא 300 מ"ג (שלוש ~~כ~~קפסולות של 100 מ"ג), הנלקחות ביחד פעם ביום, עם או ללא מזון.

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הישנות מחלה לסרטן שחלה

המינון ההתחלתי המומלץ בדרך כלל הוא 300 מ"ג ~~3~~ (3 ~~כמוסות~~ קפסולות של 100 מ"ג) הנלקחות יחד~~.~~, פעם ביום (~~מינון יומי כולל של 300 מ"ג~~), עם או ללא מזון.

...

4. תופעות לוואי

תופעות לוואי שכיחות מאוד - תופעות שמופיעות ביותר ממשתמש אחד מתוך עשרה

- חבלות או דימום הנמשכים מעבר לרגיל אם נפצעת – אלה יכולים להיות סימנים לספירת טסיות נמוכה (טרומבוציטופניה).
- קוצר נשימה, תחושת עייפות רבה, עור חיוור, או דופק מהיר – אלה יכולים להיות סימנים של ספירה נמוכה של תאי דם אדומים (אנמיה).
- חום או זיהום – ספירה נמוכה של תאי דם לבנים (נויטרופניה) יכולה להגביר את הסיכון לזיהום. הסימנים עשויים לכלול חום, צמרמורת, הרגשת חולשה או בלבול, שיעול, כאב או תחושת צריבה בעת מתן שתן. זיהומים מסוימים יכולים להיות חמורים ועלולים להוביל למוות.
-
- ירידה במספר תאי דם לבנים (לויקופניה)
-

~~מתן שתן. זיהומים מסוימים יכולים להיות חמורים ועלולים להוביל למוות.~~

תופעות לוואי שכיחות - תופעות שמופיעות ב- 1-10 משתמשים מתוך 100

- ~~ירידה במספר תאי דם לבנים (לויקופניה)~~
- תגובה אלרגית (כולל תגובה תגובה אלרגית חמורה אשר עשויה להיות מסכנת חיים). הסימנים כוללים פריחה מורמת ומגרדת (סרפדת) ונפיחות -שלעיתים תופיע בפנים או בפה (אנגיואדמה), הגורמת לקשיי נשימה, והתמוטטות או איבוד הכרה.

תופעות לוואי נדירות - תופעות שמופיעות ב 1-10 משתמשים מתוך 10,000

- מצב חירום רפואי שעלול להוביל לנזק באיברים או להיות מסכן חיים, כתוצאה מעלייה פתאומית בלחץ הדם.
- מצב חירום רפואי העשוי להוביל לנזק באיברים או להיות מסכן חיים כתוצאה ממצב מוחי הכולל את התסמינים פרכוס, כאב ראש, בלבול ושינויים בראייה (תסמונת אנצפלופתיה אחורית הפיכה [PRES]).

פני לרופא אם יש לך תופעות לוואי אחרות. הן יכולות לכלול:

תופעות לוואי שכיחות מאוד - תופעות שמופיעות ביותר ממשתמש אחד מתוך עשר

- תחושת חולי (בחילה)
- צרבת
- ירידה במספר תאי דם לבנים בדם
- ירידה במספר טסיות בדם

- ירידה במספר תאי דם אדומים (אנמיה) בדם
- תחושת עייפות
- תחושת חולשה
- עצירות
- הקאה
- כאב בטן
- אי יכולת לישון
- כאב ראש
- ~~איבוד~~ ירידה בתיאבון
- נזלת או גודש באף
- שלשול
- קוצר נשימה
- כאב מפרקים~~שרירים~~
- כאב גב
- לחץ דם גבוה
- הפרעות עיכול
- סחרחורת
- שיעול
- זיהום בדרכי השתן
- פלפיטציות (תחושה שהלב מדלג על פעימות או פועם חזק מהרגיל)
- ~~טעם חריג בפה~~

תופעות לוואי שכיחות - תופעות שמופיעות ב - 1-10משתמשים מתוך 100

- תגובות דמויות כוויית שמש לאחר חשיפה לאור
- נפיחות בכפות הרגליים, בקרסוליים, ברגליים ו/או בידיים
- רמות נמוכות של אשלגן בדם
- דלקת או נפיחות של דרכי האוויר בין הפה והאף והריאות, דלקת הסמפונות (ברונכיט)
- נפיחות בבטן
- תחושות של דאגה, עצבנות, או אי-נוחות
- תחושות של עצב, דיכאון
- דימום מהאף
- ירידה במשקל
- ~~כאב שרירים~~ כאב שרירים
- ~~כאב גב~~
- ~~כאב מפרקים~~
- דלקת הלחמית
- קצב לב מהיר העלול לגרום לסחרחורת, כאב בחזה או קוצר נשימה
- יובש בפה
- דלקת של הפה ו/או מערכת העיכול
- פריחה
- ערכים גבוהים בבדיקות הדם
- ערכים חריגים בבדיקות הדם
- טעם חריג בפה

תופעות לוואי שאינן שכיחות - תופעות שמופיעות ב- 1-10 משתמשות מתוך 1,000

- ירידה במספר תאי הדם האדומים, תאי הדם הלבנים והטסיות
- בלבול

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- דלקת בריאות העשויה לגרום לקוצר וקשיי נשימה. (דלקת ריאות שאינה זיהומית- פנאומוניטיס)

העלון לרופא והעלון לצרכן נמצאים בקישור וכן מפורסמים במאגר התרופות באתר משרד הבריאות, וניתן לקבלם מודפסים על ידי פניה לבעל הרישום.

בברכה,
מדיסון פארמה בע"מ

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