אוגוסט 2020

רופא/ה, רוקח/ת נכבדים,

הריני להודיעכם כי העלון של התכשיר עודכן:

Zejula 100 mg זג'ולה 100 מ"ג

Hard Capsule

Per os

מרכיב פעיל: Niraparib (as tosylate monohydrate) 100 mg

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

בעלון לרופא עודכנו הסעיפים הבאים:

4.4 Special warnings and precautions for use
[…]

Hypertension, including hypertensive crisis

Hypertension, including hypertensive crisis, has been reported with the use of Zejula. Pre-existing hypertension should be adequately controlled before starting Zejula treatment. Blood pressure should be monitored 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

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including hypertension. The safety of reinitiating Zejula therapy in patients previously experiencing PRES is not known.
[…]

4.5 Interaction with other medicinal products and other forms of interaction
[…]

Pharmacokinetic interactions

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

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

Niraparib is not a substrate of bile salt export pump (BSEP), or multidrug resistance-associated protein 2 (MRP2). The major primary metabolite M1 is not a substrate of P-gp, BCRP, 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.
[…]

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

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

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

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4.8 Undesirable effects

[…]

Tabulated list of adverse reactions

The following adverse reactions have been identified in the ENGOT-OV16 study in patients receiving Zejula monotherapy (see Table 3).

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

System Organ Class	Frequency of all CTCAE grades	Frequency of CTCAE grade 3 or 4
Infections and infestations	**Very common** Urinary tract infection **Common** Bronchitis, conjunctivitis	**Uncommon** Urinary tract infection, bronchitis
Blood and lymphatic system disorders	**Very common** Thrombocytopenia, anaemia, neutropenia **Common** Leukopenia **Uncommon** Pancytopenia, febrile neutropenia	**Very common** Thrombocytopenia, anaemia, neutropenia **Common** Leukopenia **Uncommon** Pancytopenia, febrile neutropenia
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 **Rare** Posterior Reversible Encephalopathy Syndrome (PRES)**	**Uncommon** Headache
Cardiac disorders	**Very common** Palpitations **Common**	

System Organ Class	Frequency of all CTCAE grades	Frequency of CTCAE grade 3 or 4
	Tachycardia	
Vascular disorders	**Very common** Hypertension **Rare** Hypertensive crisis	**Common** Hypertension
Respiratory, thoracic and mediastinal disorders	**Very common** Dyspnea, cough, nasopharyngitis **Common** Epistaxis **Uncommon** Pneumonitis	**Common** Dyspnea **Uncommon** 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
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	**Uncommon** AST increased, ALT increased, blood alkaline phosphatase increased **Common** Gamma-glutamyl transferase increased

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

5.3 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~~ Decreased spermatogenesis was observed ~~seen~~ in ~~both species~~ rats and dogs~~.~~ ~~These findings occurred~~ at exposure levels below those seen clinically~~,~~ and ~~were~~ was largely reversible within 4 weeks of cessation of dosing.
[…]

בעלון לצרכן עודכנו הסעיפים הבאים:

2. לפני השימוש בתרופה
[...]

לחץ דם גבוה
זג'ולה יכולה לגרום ללחץ דם גבוה, שבמקרים מסוימים יכול להיות חמור. הרופא עשוי גם לתת לך תרופה לטיפול בלחץ דם גבוה ולשנות את המינון של זג'ולה במידת הצורך. הרופא עשוי להמליץ לך על מעקב אחר לחץ הדם בבית, ולהנחות אותך מתי ליצור עימו קשר במקרה של עלייה בלחץ הדם.

תסמונת אנצפלופתיה אחורית הפיכה (PRES)
PRES, תופעת לוואי נוירולוגית נדירה, נמצאה ~~מקושרת~~קשורה לטיפול עם Zejula. במידה ואתה חווה כאב ראש, שינויים בראייה, בלבול או ~~ב~~פרכוס עם או ללא עלייה בלחץ הדם, פנה אל הרופא המטפל.
[...]

4. תופעות לוואי
[...]

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 שאינן שכיחות - תופעות שמופיעות ב- 1-10 ~~משתמשת~~ משתמשים מתוך 1,000
- ירידה במספר תאי הדם האדומים, תאי הדם הלבנים והטסיות
- בלבול
- דלקת בריאות העשויה לגרום לקוצר וקשיי נשימה. (דלקת ריאות שאינה זיהומית- פנאומוניטיס)

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.

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- 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]).

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

בברכה,

שרון עמיר
רוקחת ממונה

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